RESEARCH AGENDA FOR HEALTH ECONOMIC EVALUATION

Health Economic Evidence Review

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Contents

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Abbreviations

AAP	Atypical antipsychotics
A&E	Advise and Exercise
ABI	Ankle brachial index
ACBT	Active cycle of breathing techniques
ACE	Angiotensin-converting-enzyme
ACR	Albumin-to-creatinin ratio
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ARB	Angiotensin II receptor blockers
ARI	Acute respiratory illness
AUSDRISK	Australian Type 2 Diabetes Risk Assessment Tool
BGA	Behavioural graded activity
BMI	Body Mass Index
BMS	Bare Metal Stent
BP	Bisphosphonates
BP	Blood pressure
BSC	Best supportive care
CABG	Coronary Aftery Bypass Graft
CAD	Coronary Artery Disease
CAS	Carotid artery stenting
CBT	Cognitive behavioral therapy
CCT	Circuit class training
CEA	Carotid endarterectomy
CECC	Conventional extracorporeal circulation
CHEC	Consensus on Health Economic Criteria
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disorder
CT	Computerized tomography
CT	Cognitive Therapy
CV	Cardiovascular
CVE	Cardiovascular event
DALY	Disability Adjusted Life Year
DBP	Diastolic blood pressure
DCB	Drug-coated balloon
DES	Drug Eluting Stent
DM	Diabetes mellitus
DMP	Disease Management Programme
DPP	Diabetes Prevention Programme
DTx	Definitive treatment
DVT	Deep Vein Thrombosis
EC/IC	Extracranial-to-intracranial
ECT	Electroconvulsive therapy
EECP	Enhanced External Counterpulsation
EHSD	Early Home-Supported Discharge
EQ-5D	EuroQol 5D
ER	Extended-release

ESD	Early supported discharge
ESRD	End-stage renal disease
EU	European Union
FBSS	Failed back surgery syndrome
FPG	Fasting plasma glucose
FRA	Fructosamine
GBD	Global Burden of Disease study
GI	Gastro-Intestinal
GLP1	Glucagon-like Peptide 1
GP	General Practitioner
HEE	Health Economic Evaluation
HDL	High-density lipoprotein
HMO	Health Maintenance Organization
HR	Hazard ratio
HRT	Hormone replacement therapy
HT	Hypertension
IABP	Intra-aortic balloon pump
ICER	Incremental Cost-Effectiveness Ratio
ICS	Inhaled corticosteroids
IDET	Intradiscal Electrothermal Therapy
IFT	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IHD	Ischaemic Heart Disease
IMV	Invasive mechanical ventilation
IPT	Interpersonal Therapy
ISDN	Isosorbide Dinitrate
ISMO	Isosorbide Mononitrate
ICD-10	International Classification of Disease version 10
IV	Intravenous
LABA	Long-acting beta2-agonists
LAGB	Laparoscopic adjustable gastric banding
LAMA	Long acting muscarinic antagonists
LC	Lung cancer
LMP	Lifestyle Modification Programme
LSI	Lifestyle Intervention
LVH	Left ventricular hypertrophy
LVRS	Lung volume reduction surgery
LY	Life year
LYG	Life years gained
LYS	Life years saved
MACE	Major adverse cardiovascular events
MECC	Minimal extracorporeal circulation
MCP	Manual chest physiotherapy
mDPP	Modified Diabetes Prevention Programme
MeSH	Medical Subject Headings
MI	Mycardial Infarction
MPS	Myocardial Perfusion Scintigraphy
MSD	Musculoskeletal disorder
MTU	Utrecht School of Manual Therapy
NCD	Non-communicable disease
NERS	National Exercise Referral Scheme

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	Non-insulin-dependent diabetes mellitus
NNT	Number needed to treat
NPPV	Non-invasive positive pressure ventilation
NRT	Nicotine replacement therapy
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NDTx	Non-definitive treatment
OA	Osteoarthritis
OAD	Oral antidiabetic
OEF	Oxygen extraction fraction
OGTT	Oral glucose tolerance test
OR	Oral Rapamycin
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PBA	Plain balloon angioplasty
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCT	Preventive cognitive therapy
PCT	Primary Care Trusts
PD	Parkinson's Disease
PDE-4	Phosphodiesterase-4
pDRS	pre Diabetic Risk Score
PEP	Psychoeducational prevention program
PET	Positron emission tomography
PIRFT	Percutaneous Intradiscal Radio-Frequency Thermocoagulation
PMR	Percutaneous Myocardial Laser Revascularization
PPCI	Primary Percutaneous Coronary Intervention
PPI	Proton Pump Inhibitor
PRA	Platelet Reactivity Assay
PSA	Probabilistic sensitivity analysis
PSWD	Pulsed Short Wave Diathermy
PT	Physical therapy
PTCA	Percutaneous transluminal coronary angioplasty
PVAD	Percutaneous ventricular assist device
QALY	Quality Adjusted Life Year
RCT	Randomized Control Trial
REBT	Rational emotional behavioral therapy
RPG	Random Plasma Glucose
RR	Repeat revascularization
rTMS	Repetitive transcranial magnetic stimulation
RYGB	Roux-en-Y gastric bypass
SABA	Short acting beta agonists
SAMA	Short acting muscarinic antagonists
SCD	Sickle cell disease
SCLC	Small cell lung cancer
SCS	Spinal Cord Stimulation
SGRQ	St George's Respiratory Questionnaire
SHI	Statutory Health Insurance
SLT	Speech and Language Therapy

SMC	Scottish Medicines Consortium
SMT	Spinal manipulation therapy
SNRI	Serotonin-Norepinephrine Reuptake Inihibitors
SPLC	Second primary lung cancer
SSRI	Selective Serotonin Re-uptake Inhibitor
SUC	Stroke Unit Care
SWC	Standard wound care
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCA	Tricyclic Antidepressants
TCD	Transcranial Doppler
TL	Thrombolysis
TMLR	Transmyocardial Laser Revascularization
TNP	Topical negative pressure
tPA	Tissue Plasminogen Activator
TVR	Target Vessel Revascularization
UFH	Unfractioned Heparin
UK	United Kingdom
WHO	World Health Organization
WS	Work Style
WTP	Willingness To Pay

1 Health economic evidence for 10 highest burden conditions in the EU

1.1 Introduction

The financial sustainability of publicly funded universal access health systems in Europe is currently endangered by the combined forces of among other things population ageing, technological progress and limited financial resources (Pammolli, Riccaboni & Magazzini, 2012), with chronic and non-communicable disease driving a significant proportion of costs (Busse et al., 2010). These developments raise increased demands on the effectiveness and cost-effectiveness of EU health systems, which must respond to both increasing health challenges and a more restricted budgetary context(EC, 2010).

In the Tallin Charter, adopted at the WHO European Ministerial Conference on Health and Health Systems in 2008, member states of the World Health Organization Regional Office for Europe (WHO/Europe) committed to improving population health by strengthening health systems and addressing major health challenges in the context of epidemiological and demographic change, widening socioeconomic disparity, limited resources, technological development and rising expectations (WHO, 2008). In the 2013 follow-up meeting, Health systems for Health and Wealth in the Context of Health 2020, member states commitment to the Charter was reaffirmed (WHO, 2013).

The RAHEE project aims to outline a future research agenda for the EU on health economic evaluation, based on both gaps in the available evidence and the application of health economic evidence in practice. The main objectives are 1) to prepare an overview of the state of health economic evidence for a selection of high burden conditions in the European Union, based on a systematic assessment of the scientific literature, complemented by cross-cutting observations on methodological or other weaknesses that reduce the applicability of health economic evidence in practice; and 2) to identify difficulties in the translation of existing evidence on preventive public health interventions based on case studies in selected countries. A High Level Expert Panel consisting of public health officials, health economists and policymakers will formulate research recommendations for the EU based on this research.

The present report outlines the health economic evidence base for the 10 highest burden conditions in the EU. Chapter 1 outlines the methodology employed for the identification of health economic evidence, how it is mapped to the clinical reality, and how relevant experts have been identified for consultation. It briefly outlines the limitations of the approach described, and gives an overview of the search that was implemented. The subsequent chapters, 2 to 16, each report the search results for individual conditions and for preventive studies for selected conditions with significant modifiable risk factors. For ease of reference, separate bibliographies are included for all chapters.

1.2 Methodology

1.2.1 Identification of 10 highest burden conditions in the EU

The 10 conditions representing the highest burden of disease in the European Union (EU) were selected based on Disability Adjusted Life Years (DALY's) from the Global Burden of Disease (GBD) study (Murray et al., 2012)[1].

One disease category identified with this approach, "Other Musculoskeletal Disorders", was an aggregate of 62 discrete conditions with separate International Classification of Disease (ICD) 10 codes (Appendix I). For the present review, the most significant single condition from the list of 62 was identified based on expert opinion, and in addition the most significant single musculoskeletal disorder (MSD) from the main GBD list, ie. outside the "Other Musculoskeletal Disorder" category, was selected for inclusion.

1.2.2 Clinical pathways

Stratifications of the clinical management of each of the 10 study conditions were produced as a framework for considering the economic evidence. For each condition, the Up-to-Date database (http://www.uptodate.com/home) was searched for clinical guidelines and expert opinions, which were synthesised in a flow chart. Primary references for the clinical management are given in Appendix II.

1.2.3 Literature search

Primary peer-reviewed literature and literature reviews were identified using PubMed/MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) with search terms derived from the Medical Subject Headings (MeSH) controlled vocabulary. Full details on the selection of MeSH terms for specific conditions are given in Appendix III. For all searches, studies with health economic content were included with the terms:

- *Health Care Economics and Organizations [N03] > Economics [N03.219] > Costs and Cost Analysis [N03.219.151] > Cost-Benefit Analysis [N03.219.151.125]*
- *Health Care Economics and Organizations [N03] > Economics [N03.219] > Economics, Pharmaceutical [N03.219.390]*
- *Health Care Economics and Organizations [N03] > Technology Assessment, Biomedical [N03.880]*
    - *Includes Technology Assessment, Biomedical [N03.880] > Technology, High-Cost [N03.880.502]*

In addition, irrelevant publication types were excluded with the following terms:

- *NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])*

Studies reporting a full economic evaluation (cost-benefit, cost-effectiveness incl. cost-utility) with an English abstract were included. Studies without an effectiveness component (ie. cost or economic

[1] List of high burden conditions for European Union+EFTA was derived from http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-arrow-diagram

burden of illness, cost of treatment, cost-consequence etc.) were excluded. A cut-off year was not enforced for primary studies, however reviews were only included in the analysis if published in 2009 or later. All searches were conducted in July-August 2014, except for the category "Other Musculoskeletal Disorders" which were conducted in November 2014.

All primary studies and reviews identified in the present search which met the inclusion criteria were associated with the relevant clinical management branch. Economic evaluations that met the inclusion criteria but could not be mapped to a specific clinical management strategy (for example: organisation of care, different criteria for diagnosis, implementation of guidelines etc.) were included in a residual category of evidence ("other evidence"). A narrative review was produced based on the identified literature, using recently published reviews (2009 onwards) when available. When no recently published reviews were available, the present review was conducted based on the primary studies identified.

1.2.4 Identification of health economic experts

Experts in the health economics of the ten high-burden conditions of the RAHEE project were identified by a systematic assessment of the published peer-reviewed literature, focusing on the volume of research produced by individual researchers in their respective fields. The analysis was carried out with the PubReMiner tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi) using a set of basic search terms given in Table 1.1. The 10 highest ranking authors were analysed and three for each disease category were shortlisted. Authors from outside Europe were not considered for inclusion, due to significant differences in European vs other health systems. Apart from technical coverage, candidates of approximately equal technical strength were considered based on nationality and gender to improve representation.

Table 1.1 Search terms for PubReMiner expert search

Condition	PubReMiner search term
Other Musculoskeletal	(cost-benefit OR cost-utility OR cost-effectiveness) AND osteoporosis (cost-benefit OR cost-utility OR cost-effectiveness) AND osteoarthritis[1]
Low back pain	(cost-benefit OR cost-utility OR cost-effectiveness) AND (low back pain)
Neck pain	(cost-benefit OR cost-utility OR cost-effectiveness) AND (Neck pain)
Diabetes	(cost-benefit OR cost-utility OR cost-effectiveness) AND diabetes
Stroke	(cost-benefit OR cost-utility OR cost-effectiveness) AND stroke
Ischemic heart disease	(cost-benefit OR cost-utility OR cost-effectiveness) AND (angina pectoris OR myocardial infarction OR (heart failure AND ischemic))
Major depressive disorder	(cost-benefit OR cost-utility OR cost-effectiveness) AND (major depressive disorder)
Lung cancer	(cost-benefit OR cost-utility OR cost-effectiveness) AND (lung cancer)
Falls	(cost-benefit OR cost-utility OR cost-effectiveness) AND falls
COPD	(cost-benefit OR cost-utility OR cost-effectiveness) AND COPD

[1] *For "Other Musculoskeletal", two separate searches were run and overlapping candidates were identified*

1.3 Limitations

Several databases collect references and metadata on health economic literature according to different inclusion criteria and with different scope (Aguiar-Ibáñez et al., 2005). Though such databases are intended to be relatively comprehensive in coverage, it has been shown that not all relevant economic evaluations are included. In addition, when reviewing evidence from the past 3-5 years, it is suggested to supplement health economic database searches with other database searches due to an inherent delay in indexing (Sassi, Archard, & McDaid, 2002). For these reasons, a broader search strategy was chosen based on the MEDLINE database as detailed in Methods (section 1.2.3). Although a more exhaustive strategy is possible, such as the inclusion of EMBASE, Web of Science etc., within the limitations of the project it was not considered feasible to cover all sources. Additionally, the present review is intended to provide an adequate snapshot of the available health-economic literature, rather than a fully inclusive and in-depth review. To avoid exclusion of key studies, the expert panel (section 1.2.4) was consulted for feedback on individual sections and comments were incorporated.

1.4 Search overview

1.4.1 List of priority conditions

The list of high burden conditions in the European Union (EU) as defined by the Global Burden of Disease study (Murray et al., 2012a) for the years 1990 and 2010 is given in Table 1.2. Comparison between the years reveals that little has changed in terms of the top-10 causes of morbidity and mortality between 1990 and 2010, with the categories Other Musculoskeletal and Neck Pain displacing Road Injury and Self-Harm.

Table 1.2 Ten conditions responsible for the highest burden of disease in the European Union 1990 and 2010

Rank #	1990	2010
1	Ischemic Heart Disease	Ischemic Heart Disease
2	Stroke	Low Back Pain
3	Low Back Pain	Stroke
4	Lung Cancer	Major Depressive Disorder
5	Road Injury	Lung Cancer
6	Major Depressive Disorder	Falls
7	COPD	COPD
8	Falls	Diabetes
9	Diabetes	Other Musculoskeletal
10	Self-harm	Neck pain

The GBD (2010) consists of a hierarchy of 291 diseases and injuries across four levels of detail (Murray et al., 2012b) as illustrated in Figure 1.1 where the 10 conditions selected for analysis in the present report are indicated in dark colours. As shown, nine out of the ten conditions fall under the umbrella of non-communicable diseases (NCD's) with falls being the only exception.

The category of "Other Musculoskeletal" disorders is an aggregate of 62 discrete conditions with separate ICD10 codes as detailed in Appendix I (Lozano et al., 2012). As these 62 conditions only form a

significant burden of disease in combination, it was deemed appropriate to select one condition from the "Other Musculoskeletal" category for analysis, supplemented with the single musculoskeletal disorder (MSD) with the highest burden of disease from the entire GBD ranking. Consequently, the present analysis focuses on osteoporosis, which is part of the "Other Musculoskeletal" category, and osteoarthritis, which ranks 23rd in the overall GBD for 2010.

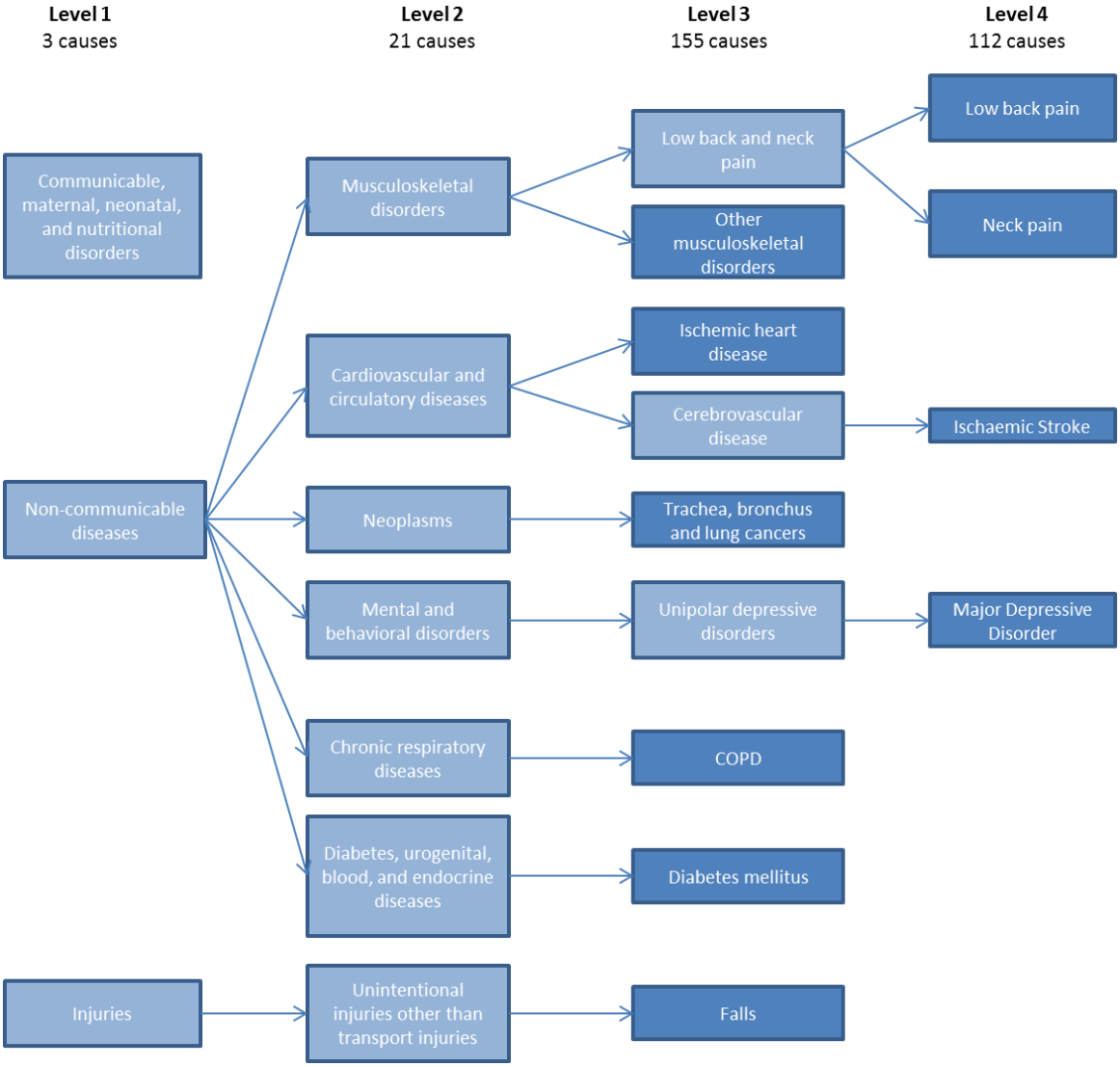

Figure 1.1 Excerpts from the causes of death and disability hierarchy of the Global Burden of Disease study. Based on (Murray et al., 2012b)**.**

The 11 conditions examined in the present work were mapped to the controlled vocabulary of the MEDLINE database, Medical Subject Headings (MeSH) terms, as shown in Table 1.3 and detailed further in Appendix III.

1.4.2 Expert panel

A total of ten condition-specific experts were identified covering all topics of the project (Table 1.4). Experts were consulted for comments on the narrative reviews of the evidence within their expertise (sections 2 to 16), and all comments were incorporated.

Table 1.3 Mapping between GBD and MEDLINE MeSH terms

GBD condition	MeSH term(s)
Ischemic Heart Disease	"Myocardial Ischemia"[MeSH Terms]
Low Back Pain	"Low Back Pain"[MeSH Terms]
Stroke	"Stroke"[MeSH Terms]
Major Depressive Disorder	"Depressive Disorder, Major"[MeSH Terms] OR "Depressive Disorder, Treatment-Resistant"[MeSH Terms]
Lung Cancer	"Lung Neoplasms"[MeSH Terms]
Falls	"Accidental falls"[MeSH Terms] OR "Accident Prevention"[MeSH Terms:noexp]
COPD	"Pulmonary Disease, Chronic Obstructive"[MeSH Terms]
Diabetes	"Diabetes Mellitus"[MeSH Terms] NOT ("Diabetes Mellitus, Experimental"[MeSH Terms] NOT "Diabetes, Gestational"[MeSH Terms] NOT "Donohue Syndrome"[MeSH Terms] NOT "Prediabetic State" [MeSH Terms] NOT "Diabetes Complications"[MeSH Terms])
Other Musculoskeletal	"Osteoporosis"[MeSH Terms]
	"Osteoarthritis"[MeSH Terms]
Neck pain	"Neck Pain"[MeSH Terms]

1.4.3 Public consultation

The condition-specific reviews were open for public consultation between November 25th 2014 and December 29th 2014. The consultation was announced on the RAHEE website[2], disseminated through the Steering Committee and authors of recent reviews on the RAHEE subjects were invited directly. Comments received through the public consultation were incorporated in the reviews.

[2] http://www.euro.who.int/en/about-us/organization/office-locations/who-representation-to-the-european-union,-brussels,-belgium/research-agenda-for-health-economic-evaluation-rahee-project/technical-consultations-on-conditions

Table 1.4 Experts identified for the High Level Expert Panel

Condition	Name	Affiliation	Country
Lower back pain + neck pain	Hanneke van Dongen	EMGO, VU University Medical Centre	Netherlands
Diabetes	Norman Waugh	University of Aberdeen	UK
Ischemic heart disease	Bengt Jonsson	Stockholm School of Economics	Sweden
Lung cancer	Christos Chouaid	Centre Hospitalier Intercommunal Creteil	France
Falls	Tracey Sach	Norwich Medical School	UK
COPD	Maureen Rutten-van Molken	Erasmus Medical Centre, Rotterdam	Netherlands
Mental health	Pim Cuijpers	Vrije Universiteit Amsterdam	Netherlands
Osteoporosis and osteoarthritis	Jean-Yves Reginster	University of Liège	France
Stroke	Anita Patel	Kings College, London	UK

[1]*Osteoporosis is part of the "other musculoskeletal disorders" Global Burden of Disease category, and osteoarthritis is the single highest burden musculoskeletal disorder. However "other musculoskeletal disorders" contains 61 additional conditions (appendix I) where input from a generalist is appropriate*

1.5 References

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Health Economic Evidence Analysis: Management of ischemic heart disease

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2 Ischemic heart disease

2.1 Bibliometrics

A total of 283 economic studies were mapped to the clinical model for ischemic heart disease (Table 2.1 and Figure 2.1) with the majority[1] of studies published since 2005. Of the 41 reviews identified, 8 were published between 2009 and 2014.

Table 2.1 Bibliometric data for ischemic heart disease

PubMed/MEDLINE	
Search term	"Myocardial Ischemia"[MeSH Terms] ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	283
Included as "other"	236
Reviews	41
Excluded	1258
Total	1818
Additional studies suggested by reviewers	
Total	0

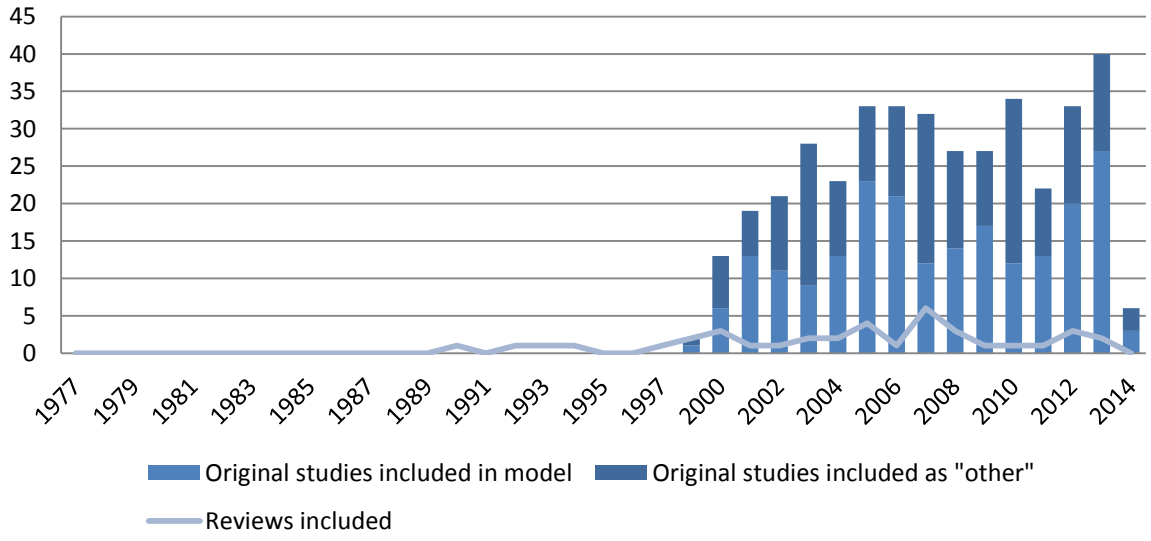

Figure 2.1 Bibliometric data for ischemic heart disease by year

[1] 75% of studies or more

2.2 Review coverage

The clinical model for ischemic heart disease (IHD) consists of 30 treatment modalities. Of these, seven treatments (23%) were addressed by one of the nine reviews published between 2009 and 2014 (Table 2.2). The remaining 23 treatments (77%) were not associated with any health economic reviews, though primary studies were available in several cases (Table 2.4 to Table 2.6 and described in sections 2.3.1 to 2.3.3).

Table 2.2 Table of reviews for ischemic heart disease and associated treatments

Title and reference	Year	Treatments covered
"*Cost-effectiveness of ticagrelor in acute coronary syndromes*" (Henriksson and Janzon 2013)	2013	The antiplatelet ticagrelor
"*Cost effectiveness of anticoagulation in acute coronary syndromes*" (Latour-Pérez and de-Miguel-Balsa 2012)	2012	Low-molecular-weight heparin, bivalirudin, fondaparinux and enoxaparin in acute coronary syndrome
"*Economic evidence of interventions for acute myocardial infarction: a review of the literature*" (Callea, Tarricone, and Lara 2012)	2012	Primary angioplasty and thrombolysis for acute myocardial infarction
"*A systematic review of economic evaluations of cardiac rehabilitation*" (Wong et al. 2012)	2012	Cardiac rehabilitation: exercise, risk factor reduction and psychosocial intervention for patients following myocardial infarction or heart failure
"*Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis*" (Greenhalgh et al. 2011)	2011	Clopidogrel and modified-release dipyridamole (MRD) in the prevention of occlusive vascular events
"*Fondaparinux: a pharmacoeconomic review of its use in the management of non-ST-segment elevation acute coronary syndrome*" (McKeage and Lyseng-Williamson 2010)	2010	Fondaparinux in non-ST-segment elevation acute coronary syndrome (NSTE-ACS)
"*Cost-effectiveness of alternative approaches to the management of chronic obstructive coronary artery disease*" (Amin and Cohen 2009)	2009	Percutaneous coronary intervention in the management of chronic obstructive coronary artery disease

2.3 Evidence analysis

2.3.1 Treatment of acute coronary syndrome

Acute coronary syndrome is managed pharmacologically with anti-platelets, anti-coagulants or fibrinolysis, or surgically through reperfusion with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), as shown in Table 2.3.

Table 2.3 Treatment of acute coronary syndrome

Acute management of unstable angina & acute non-ST elevation myocardial infarction, acute MI with ST elevation	Studies	Reviews
Antithrombotic therapy		
Anti-platelets	23	1
Anti-coagulants: heparin, Enoxaparin, bivalirudin , Fondaparinux	12	2
Thrombolysis: Alteplase, Reteplase, Tenecteplase	24	1
Reperfusion		
Coronary Artery Bypass Graft and Percutaneous coronary intervention [PCI]: baloon angioplasty, drug eluting stent placement, bare metal stent placement	19	1

2.3.1.1 Antithrombotic therapy

2.3.1.1.1 Antiplatelets

One review covered the use of the anti-platelet ticagrelor in antithrombotic therapy (Henriksson and Janzon 2013). Economic data collected alongside the PLATO trial of ticagrelor against clopidogrel over 12 months showed that total treatment costs, excluding drugs, was higher in the clopidogrel group. When drug costs were included, the ticagrelor group incurred higher total costs resulting in an ICER of EUR 2,800/QALY. The cost-effectiveness model of the PLATO study was subsequently adapted to the Mexican, Polish and Brazilian contexts, incurring ICER's of USD 7,500; PLN 23,000 (approx.. EUR 5,400) and USD 9,000 per QALY. A Canadian model from the payer perspective, based on sources external to the PLATO study, estimated an ICER of CA$ 500/QALY for ticagrelor, although this study used branded clopidogrel as the comparator. A Dutch study estimated an ICER of EUR 8,000/QALY.

Henriksson and Janzon also review a genotype driven treatment strategy, where the CYP2C19 genotype determines whether clopidogrel or ticagrelor is appropriate. Over a 5-year horizon from the US Medicare perspective, the ICER for universal ticagrelor over the genotyping strategy was USD 10,000.

The review authors note "*the cost-effectiveness results of ticagrelor summarized above indicate that the cost per QALY gained with ticagrelor compared with clopidogrel is in line with other treatments that are currently perceived as standard of care in the CV field*". These observations were based on results from 10 primary studies.

Apart from this review, the present search identified 23 primary studies on anti-platelets. Of these, eight were published in 2009 or later. Three studies assessed clopidogrel prior to its patent expiry and are not considered since the higher pharmaceutical cost applied would not give correct ICER's at present prices.

Prasugrel was compared with (hypothetically generic) clopidogrel for the prevention of cardiovascular events in patients with ACS and planned PCI in a clinical trial, resulting in an ICER of USD 9,727 per LYG (Mahoney et al. 2010).

The CYP2C19 genotype was also used to guide treatment with prasugrel or clopidogrel in patients with ACS in New Zealand from the health system perspective. The authors reported actual hospital-based adverse event rates were higher than in the clinical trial setting, especially for Maoris and Pacific Islanders compared with other ethnic groups studied. Using the genetic test to select between drugs was cost-effective at NZ$ 8,702/QALY and $NZ 24,617/QALY for hospital and trial incidence of adverse events, respectively, compared with universal clopidogrel (Panattoni et al. 2012). Assays monitoring P2Y12 platelet reactivity (PRA) can also be used to predict clopidogrel response. One study assessed the cost-effectiveness of using PRA to guide anti-platelet therapy using a Markov model of four strategies: universal clopidogrel, ticagrelor, prasugrel or PRA-driven ticagrelor or prasugrel. 5-year costs and outcomes were modelled. PRA-driven ticagrelor and prasugrel were cost-effective compared with universal clopidogrel with ICERs of USD 40,100 and USD 49,143 per QALY, respectively, though universal ticagrelor and prasugrel incurred ICER's higher than normally considered cost-effective (USD 61,651 and USD 96,261 per QALY, respectively) (Coleman and Limone 2013).

Finally, in an observational study of patients with ST-elevation MI undergoing PCI, abciximab was given as bolus plus subsequent infusion (standard strategy) or bolus only followed by infusion if indicated in combination with a higher loading dose of clopidogrel (modified strategy). At 30 days there was a trend towards lower composite death, re-infarction and target vessel revascularization in the modified strategy, but this was not significant. The rate of stent thrombosis was lower in the modified strategy, as were mean total medical costs, both statistically significant. The authors conclude that in primary PCI with a loading dose of 600 mg clopidogrel it appears safe and cost-saving to give abciximab bolus with optional infusion (Berglund, Nilsson, and Janzon 2013)

Main findings:

- Ticagrelor appears to be cost-effective compared with generic clopidogrel at less than EUR 10,000 per QALY gained
- Prasugrel appears to be cost-effective over clopidogrel in preventing cardiovascular events following PCI at USD 9,727/LYG (one study)
- Using CYP2C19 genotyping guided prasugrel/clopidogrel appears to be cost-effective over universal clopidogrel (one study)
- P2Y12 platelet reactivity assay (PRA) guided ticagrelor and prasugrel therapy appears to be more cost-effective than universal clopidogrel (one study)
- In primary PCI with a high loading dose of clopidogrel it appears to be cost-saving to give abciximab bolus with optional infusion (one study)

2.3.1.1.2 Anti-coagulants

Two reviews addressed anti-coagulants in antithrombotic therapy. The most recently published review included studies published until May 2010 and considered all relevant anticoagulants (Latour-Pérez and de-Miguel-Balsa 2012) while the second review included studies until June 2010 and considered only fondaparinux (McKeage and Lyseng-Williamson 2010).

The review by Latour-Perez and de-Miguel Balsa included 21 studies based on randomized controlled trials (RCT's) and used a modified Evers checklist for quality appraisal. The review contains four sections as outlined below. Of the 12 studies identified in the present review, three were not covered by Latour-Perez and de-Miguel Balsa: one study was excluded by for being a deferred randomization study (Janzon, Levin, and Swahn 2003), and two studies were published around or after the cut-off date of the review. The remaining nine studies identified in the present review were covered by Latour-Perez and de-Miguel Balsa.

Indirect thrombin inhibitors

In Non-ST Elevation ACS, six of the 10 economic studies identified by the review authors were cost-analyses showing enoxaparin was more expensive than unfractioned heparin (UFH) in acquisition costs, but resulted in reduced healthcare utilisation costs for catheterisation and revascularisation which more than offset the additional cost of enoxaparin. Four studies addressed cost-effectiveness of enoxaparin vs UFH. Enoxaparin was dominant in the base case of all four studies, but not necessarily in the worst-case scenario.

In ST-Elevation ACS, four economic studies compared enoxaparin with UFH. In the US setting, enoxaparin was dominant over UFH in 80% of cases at 30 days and 71% of cases at 1 year. In three other studies from the US, Canada and UK over a lifetime horizon, the cost of enoxaparin treatment was higher but with an ICER "*within the limits usually accepted as cost-effective*" (USD 50,000).

Direct thrombin inhibitors

Latour-Perez and de-Miguel Balsa note that "economic studies available are limited to the use of bivalirudin in Non-ST Elevation ACS managed invasively. Two studies were identified. A US costing study found total costs were lower in bivalirudin monotherapy patients compared with UFH due to decreased rates of major and minor bleeding, while there were no differences in ischemic events. A cost-utility study of bivalirudin monotherapy vs heparin plus GPIIb/IIIa inhibitor resulted in an ICER of GBP 9,906-12,276 from the UK NHS perspective.

Selective Factor Xa Inhibitors

This part of the review by Latour-Perez and de-Miguel Balsa considers only fondaparinux, consequently it is considered together with the review by McKeage and Lyseng-Williamson. Latour-Perez and de-Miguel Balsa identify three cost-utility analyses of fondaparinux on non-ST Elevation ACS. Fondaparinux was compared with enoxaparin from the French health system perspective, and was slightly cost-saving in the short term but very cost-effective in the long term at EUR 2,758/QALY. In a study from the US perspective, fondaparinux was found to be dominant in most scenarios, despite assuming the differences in effectiveness disappeared after 16 days. A third study from the Spanish perspective compared fondaparinux with enoxaparin plus a GPIIb/IIIa inhibitor in patients managed with an early invasive strategy. In the long term, fondaparinux was dominant.

McKeage and Lyseng-Williamson review the same three studies as Latour-Perez and de-Miguel Balsa. The authors note the analyses of fondaparinux were "*generally well conducted*" and that "*trial data from OASIS-5, which was used in all of these analyses, provided current data on head-to-head comparisons of fondaparinux and enoxaparin in a large, well designed study*" although it was also noted cost and utility data were not collected alongside the OASIS-5 trial but retrieved from the literature. The authors state that two of the studies were funded by the manufacturer of fondaparinux (McKeage and Lyseng-Williamson 2010).

Multiple comparisons

Latour-Perez and de-Miguel Balsa review two studies comparing more than two anticoagulants. One study reporting a clinical trial from India compared enoxaparin, nadroparin and dalteparin but was not sufficiently powered and did not report conclusive results. A second study of Non-ST Elevation ACS compared UFH plus GPIIb/IIIa inhibitor; enoxaparin plus GPIIb/IIIa inhibitor; bivalirudin monotherapy; and fondaparinux plus GPIIb/IIIa inhibitor. In the base case, bivalirudin monotherapy dominated the UFH and enoxaparin strategies, and was cost-effective over fondaparinux. However the review authors note "*differences in the profiles of patients included in each of the alternatives (obtained from trials with different inclusion criteria) and the difficult interpretation of the terminal nodes (which assigns equal weight to a death and to a minor haemorrhage) seriously limit the usefulness of these results for decision making*" (Latour-Pérez and de-Miguel-Balsa 2012)

Main findings:

- Indirect thrombin inhibitors appear to be mostly dominant in Non-ST Elevation ACS (four studies) but incur additional costs at an acceptable ICER in ST-Elevation ACS (four studies)
- Limited evidence was reviewed on direct thrombin inhibitors, with only one study assessing bivalirudin. Against unfractioned heparin, bivalirudin monotherapy was found to be cost-effective in invasive Non-ST Elevation ACS
- Fondaparinux is cost-saving or very cost-effective in non-ST Elevation ACS over enoxaparin with or without GPIIb/IIIa (three studies)

2.3.1.1.3 Thrombolysis

Thrombolysis was covered in one review by Callea et al. comparing primary PCI (PPCI) with thrombolysis (TL). As the review focused on PPCI, it is described in section 2.3.1.2.1 below. Key findings were that of 14 studies reviewed, nine reported PPCI to be cost-effective compared with TL, three reported PPCI to be cost-saving, and two studies reported cost-neutrality between the two treatments or that there was no statistically significant difference (Callea, Tarricone, and Lara 2012).

Of the primary studies identified in the present review, the majority (20 of 24) were published prior to year 2000. Only one study was published more recently than 2009, examining early vs late PCI following thrombolysis in acute myocardial infarction (AMI) in Norway. This study reported a slight increase in QALY's in the early intervention group at 12-months, at an ICER of EUR 69,750 (Bøhmer et al. 2011).

Main findings:

- All economic evidence assessing thrombolysis in acute myocardial infarction was published prior to 2000 with the exception of two studies from 2005. One study from 2009 found the cost of a marginal benefit associated with early vs late PCI following thrombolysis to be relatively high.

2.3.1.2 Reperfusion

2.3.1.2.1 Percutaneous coronary intervention and coronary artery bypass graft

Several studies published earlier than 2009 considered eg. early vs late "invasive intervention" consisting of either PCI or CABG, but did not differentiate between the two interventions. Consequently no recent economic evidence comparing PCI with CABG in the acute setting was identified.

Percutaneous coronary intervention (PCI) was covered in one review by Callea et al. comparing primary PCI (PPCI) with thrombolysis (TL). The review included 14 studies published between 1980 and 2011, of which nine reported PPCI to be cost-effective compared with TL, three reported PPCI to be cost-saving, and two studies reported cost-neutrality between the two treatments or that there was no statistically significant difference. Comparators used were tPA (reteplase, alteplase, tenecteplase) , prourokinase and streptokinase. The review authors note that sensitivity analysis was carried out in eight of the 14 studies, while QALY's were estimated in only four studies.

Callea et al. note that these cost-effectiveness studies are based on clinical evidence from established catheter laboratories specializing in PPCI, rather than real world evidence, and that cost-effectiveness may therefore differ in practice. Indirect and carer's costs were also excluded in the reviewed studies because patients were at or near retirement age, however the authors note an increasing retirement age in Europe may have implications for this practice. Finally the authors note "*none of the cost-effectiveness analyses have taken account of the costs for implementing a network for treating AMI. It would be advisable that future research fills this gap since implementing these networks might be a prerequisite to improving patient's access to treatment and to guaranteeing a timely reperfusion strategy according to international guidelines"* (Callea, Tarricone, and Lara 2012).

Of the 19 primary studies identified in the present review, five were reviewed by Callea et al. Three primary studies published in 2009 or later with non-thrombolytic comparators were identified. Two of these reported on drug-eluting stents (DES) in AMI. In a French subgroup of patients in the TYPHOON multicenter clinical trial, patients with AMI with ST-segment elevation received PCI with either a sirolimus coated DES or a bare metal stent (BMS) and followed for one year. There was no difference in rate of death, recurrent myocardial infarction or stent thrombosis after 1 year, but target vessel revascularization (TVR) was lower in the DES group. The ICER was EUR 7,321 per TVR avoided (Canoui-Poitrine et al. 2009). From a German sickness fund perspective, the ICER of DES vs BMS was negative EUR 718,709 per life saved, and the authors conclude treatment with DES for AMI is less cost-effective than BMS (Bäumler et al. 2012).

The third study published since 2009 estimated the cost-effectiveness of guiding antiplatelet treatment in patients undergoing PCI according to CYP2C19 genotype. A Markov model from the US Medicare perspective compared three strategies: CYP2C19 guided antiplatelet treatment, vs. empiric clopidogrel or prasugrel. The genetic testing strategy dominated the two empiric strategies (Lala et al. 2013).

Main findings:

- The majority of studies (12/14) reviewed by Callea et al. find primary PCI to be cost-effective or dominant compared with thrombolysis, however this is based on access to clinics specializing in PPCI procedures. Real-world effectiveness may differ, and the cost of making acute myocardial infarction treatment broadly available is not taken into account.
- Only two recent studies compared drug eluting vs bare metal stents. These studies do not report cost/QALY but only cost per target vessel revascularization avoided or per life saved.
- A single study indicated genetically guided antiplatelet therapy is dominant over empirically selected clopidogrel or prasugrel

2.3.2 Treatment of Angina

The various treatments used for the management of angina are summarized together with identified economic evidence in Table 2.4.

Table 2.4 Economic evidence for the treatment of angina

Treatment of Angina	Studies	Reviews
Medical Therapies		
Sub-lingual nitroglycerine	1	0
Beta blockers: Propranolol, Atenolol, Metoprolol, Nadolol, Pindolol and acebutolol, Carvedilol, Felodipine	0	0
Ca channel blockers: nifedipine, verapamil, diltiazem, amlodipine, nicardipine, diltiazem, amlodipine	3	0
Fatty acid oxidation inhibitors: Trimetazidine, Ranolazine, Perhexilin	2	0
K channel blocker: Nicorandil	0	0
Xanthine oxidase inhibitor: Allopurinol	0	0
Endothelin receptor blockers: Ivabradine, Fasudil	0	0
High-dose statin therapy	1	0
Mechanical Therapies		
Enhanced external counterpulsation	1	0
Spinal cord stimulation	6	0
Surgical Therapies		
Transmyocardial laser revascularization	2	0
Percutaneous coronary intervention [PCI]: baloon angioplasty, drug eluting stent placement, bare metal stent placement	55	1
Coronary artery bypass graft surgery [CABG]: on pump or off pump	14	0

2.3.2.1 Medical therapies for angina

Overall the level of evidence for medical management of angina was low (Table 2.4). No evidence was identified for the use of beta blockers, potassium channel blockers, xanthine oxidase inhibitors or endothelin receptor blockers.

2.3.2.1.1 Sub-lingual nitroglycerine for angina

A single study was identified for the use of sub-lingual nitroglycerine for the treatment of angina. This study compared isosorbide dinitrate (ISDN), isosorbide mononitrate (ISMO) and nitroglycerin patches in a hypothetical cohort of 45-55 year old male patients with acute angina from the payer perspective. ISMO was associated with greater patient tolerance and less frequent need for titration, and was less expensive annually than the alternatives (Larrat 1994).

Main findings:

- According to a single study from 1994, isosorbide mononitrate is more cost-effective than isosorbide dinitrate and nitroglycerin patches from the US payer perspective.

2.3.2.1.2 Calcium channel blockers for angina

Three primary studies were identified on the use of the calcium channel blocker amlodipine for angina. An Italian study assessed amlodipine vs usual care including direct costs of pharmaceuticals and hospitalisations over 36 months for patients with coronary artery disease. Patients receiving amlodipine experienced decreased incidence of unstable angina events and revascularization procedures, translating to an incremental cost of EUR 1,780 per patient remaining free of any vascular event (De Portu et al. 2006). A similar model in the Swedish context, comparing amlodipine with placebo over 36 months, estimated savings in total costs with amlodipine attributable to decreased rates of angina, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, congestive heart failure, and myocardial infarction (Doyle et al. 2002).

For patients undergoing angioplasty procedures in Norway and Canada, amlodipine was modelled over 4 months following the procedure. Amlodipine decreased rates of myocardial infarction, repeat angioplasty, coronary artery bypass graft and all-cause mortality, and reduced total costs of care in both countries (Thaulow et al. 2002)

Main findings:

- Two studies show amlodipine to be cost-effective (slightly cost-saving) in patients with coronary artery disease in preventing angina and other cardiovascular events. In patients undergoing angioplasty (one study), amlodipine was also slightly cost-saving.

2.3.2.1.3 Fatty acid oxidation inhibitors for angina

Two primary studies were identified for the use of fatty acid oxidation inhibitors in angina treatment. An American claims-based study found patients taking ranolazine were less likely to require revascularization procedures, and incurred lower total costs compared to patients taking long-acting nitrates, beta blockers or calcium channel blockers (Phelps, Buysman, and Gomez Rey 2012). In patients

with stable coronary disease experiencing 3 attacks per week or more, an American Markov model from a societal perspective showed adding ranolazine to standard therapy incurred an additional USD32,682 per QALY. The ICER remained under USD50,000 when indirect costs were excluded (Kohn et al. 2014).

Main findings:

- Ranolazine is cost-saving or cost-effective according to two American studies in the treatment of patients with angina

2.3.2.1.4 High-dose statin therapy for angina

High-dose vs conventional-dose statin therapy reduces risk of cardiovascular events in patients with acute coronary syndrome (ACS) and stable coronary artery disease (CAD). A Markov model estimated the cost-effectiveness of high- vs. conventional-dose statins in 60 year old patients with ACS or stable CAD. In ACS patients, the high-dose regimen was cost-effective at less than USD 30,000 per QALY under all assumptions examined, whereas for CAD patients the QALY gain was lower and the price differential between the two regimens could not exceed USD 1,70 daily for the ICER to remain under USD50,000 per QALY (Chan et al. 2007).

- Cost-effectiveness of high-dose statins was less pronounced in coronary artery disease than in acute coronary syndrome. Difference in daily cost of therapy must be less than USD 1,70 for high-dose to be cost-effective over low-dose statin therapy in CAD patients (one study).

2.3.2.2 Mechanical therapies

2.3.2.2.1 Enhanced external counterpulsation for angina

A single economic study assessed enhanced external counterpulsation (EECP) for the treatment of angina in the UK. The model compared EECP plus usual care against usual care alone from the healthcare perspective over a lifetime horizon, resulting in GBP 18,643. The authors note the effectiveness estimates are based on a single clinical trial and not considered “firm evidence” (McKenna et al. 2010).

- Enhanced external counterpulsation appears to be cost-effective in the UK (one study), though this conclusion is based on limited clinical evidence.

2.3.2.2.2 Spinal cord stimulation for angina

Six primary studies were identified for spinal cord stimulation (SCS) in the management of angina. Five of these studies considered SCS in patients who were unsuited for coronary revascularisation (refractory or intractable angina). One study reported on the Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris (ESBY) trial, which enrolled 104 patients with increased surgical risk and no prognostic benefit from revascularisation. Compared with coronary artery bypass graft (CABG), SCS was associated with fewer hospitalization days related to the primary intervention or to cardiac events. The interventions did not differ regarding causes of death (Andréll et al. 2003).

These observations were borne out in three economic evaluations. Using patient-level data, a Polish study estimated cost of treatment of angina patients two years before and after SCS. Costs of treatment

were 46% lower in angina patients following SCS, and quality of life was improved according to SF-36 (Harat et al. 2012). A similar study in 8 patients in New Zealand collected cost data 12 months before and after SCS. In six of the eight patients with successful implantation, subsequent healthcare resource use and days of hospitalization were reduced. The authors calculated the cost of the intervention would be recouped over 15 months due to reduced healthcare costs (Merry et al. 2001). Comparable findings were reported from Sweden, where SCS implantation resulted in fewer angina attacks, reduced nitroglycerin use, and hospitalization days. The total cost of the SCS procedure was recovered 16 months after implantation due to reduced hospitalization costs (Yu et al. 2004).

Additionally, a 20-year Markov model of SCS vs usual care from the Canadian Ministry of Health perspective estimated an ICER of CA$ 9,984 per QALY gained, in a study assessing SCS for refractory angina, failed back surgery syndrome, complex regional pain syndrome and peripheral arterial disease (Kumar and Rizvi 2013).

Finally, a pilot clinical trial (Refractory Angina Spinal Cord stimulation and usuAL care, RASCAL) is underway to "*assess the feasibility of a definitive trial to assess if addition of spinal cord stimulation (SCS) to usual care is clinically superior and more cost-effective than usual care alone in patients with refractory angina*". The trial also assesses cost-effectiveness, however the perspective and methods are not stated. Resource utilization and health-related quality of life are collected (Eldabe et al. 2013).

Main findings:

- Three studies of patient-level resource use reported reductions in hospitalization days following a spinal cord stimulation intervention, leading the cost of the intervention to be recouped within 15-16 months. Reduction of hospitalization days was initially reported in a clinical trial of SCS versus CABG.
- A pilot clinical trial is underway to assess whether a large-scale trial of SCS should be undertaken to determine clinical and cost-effectiveness.

2.3.2.3 Surgical therapies for angina

2.3.2.3.1 Transmyocardial laser revascularization

Two studies reported on clinical trials of transmyocardial laser revascularization (TMLR) or percutaneous myocardial laser revascularization (PMR) versus usual care in the UK. From the national health service perspective, over a 12-month horizon post-intervention, TMLR was associated with an ICER of GBP 228,000 per QALY (H E Campbell et al. 2001). Similarly for percutaneous myocardial laser revascularization (PMR) from the UK NHS perspective over 12 months, the ICER was GBP 50,873 (Helen E Campbell et al. 2005). These results were both based on relatively small clinical trials of 188 and 73 patients, respectively.

Main findings:

- Single studies show transmyocardial/percutaneous myocardial laser revascularization to be relatively cost-ineffective therapies at GBP 228,000 and GBP 50,873 per QALY gained, respectively. These findings were based on single clinical trials.

2.3.2.3.2 Percutaneous coronary intervention

The use of percutaneous coronary intervention (PCI) was addressed in 56 primary studies and a single review. The review by Amin and Cohen was published in 2009 but did not state the search methodology or inclusion dates (Amin and Cohen 2009). This review identified nine studies assessing percutaneous transluminal coronary angioplasty (PTCA, balloon angioplasty) against CABG. While treatment costs were reported in all nine studies, an ICER was reported only for two, describing the same trial at different follow-up times. The ICER for CABG over PTCA was USD 26,000 per LYG at 5 years and USD 14,300 at 12 years in the Bypass Angioplasty Revascularization Investigation trial (BARI). The use of drug-eluting stents in PCI was also discussed by Amin and Cohen, who note that compared with CABG, PCI plus paclitaxel eluting stents is less costly and yielded improved quality-adjusted life expectancy at 1-year follow-up. The authors also note that 1-year follow-up is too short to form valid conclusions (Amin and Cohen 2009).

Among the primary evidence identified in the present search, a significant proportion (22 of 56, 38%) are published in 2009 or later. In the interest of clarity, we restrict the analysis to these recent studies.

Three studies addressed PCI as the main intervention against medical management. In patients with abnormal fractional flow reserve in the US, from the Medicare perspective, the ICER at 1-year follow-up was USD 36,000 per QALY over medical therapy (Fearon et al. 2013). In a US modelling study of patients with stable angina, the ICER of PCI over medical treatment was USD 9,505/QALY (Gada, Whitlow, and Marwick 2012). The incremental cost per patient achieving “significant clinical improvement” from PCI over medical care ranged from USD 80,000 to >USD3,000,000 from highest to lowest severity of angina, showing significant variation in benefit according to severity groups (Zugui Zhang et al. 2011).

A significant body of evidence addressed the use of bare metal or drug eluting stents, in total 12 studies since 2009. An overview is provided in Table 2.5. A brief examination reveals that ICER’s span a significant range, from PCI+DES being a dominant intervention (Wisløff, Atar, and Sønbø Kristiansen 2013) to incurring over USD 1,000,000 per QALY (Bischof et al. 2009).

Table 2.5 Primary studies assessing drug eluting and bare metal stents

	Patients	Interventions	Model	ICER of comparator 1 over comparator 2
(Wijeysundera et al. 2013)	Stable CAD	PCI+DES, PCI+BMS, OMT	Markov model, Canada, lifetime extrapolation	PCI+BMS vs OMT: USD13,271/QALY PCI+BMS vs PCI+DES: PCI+BMS dominant
(Magnuson et al. 2013)	Diabetes mellitus and multivessel CAD	PCI+DES, CABG	Clinical trial, US health system, lifetime extrapolation	CABG vs PCI+DES: <USD10,000/QALY

(Amin et al. 2012)	Moderate to high risk of stenosis	PCI+DES (everolimus), PCI+DES (paclitaxel)	Clinical trial, US health system, 2 year followup	Probability of everolimus vs paclitaxel stent ICER <USD 50,000: 85.7%
(Cohen et al. 2012)	Patients with three-vessel or left main CAD	PCI+DES (paclitaxel), CABG	Clinical trial, US health system, 1 year followup	PCI+DES dominant overall, but varied according to angiographic complexity
(Wisløff, Atar, and Sønbø Kristiansen 2013)	CAD	PCI+DES (sirolimus), PCI+DES (paclitaxel) PCI+BMS	Markov model, lifetime horizon	PCI+DES (sirolimus) vs BMS: PCI+DES dominant PCI+DES (paclitaxel) vs PCI+DES (sirolimus): USD21,400/LYG
(Schafer et al. 2011)	N/A	PCI+DES, PCI+BMS	US payer perspective, 3 years	PCI+DES vs PCI+BMS: incremental cost per repeat target revascularization avoided USD 6,379
(Hung et al. 2011)	Stable angina	PCI+DES, PCI+BMS	Taiwan payer perspective, 2 years	PCI+DES vs PCI+BMS: incremental cost per repeat target revascularization avoided NT$ 546,444 (EUR 14,000)
(Ferreira et al. 2010)	Uniarterial coronariopathy	PCI+DES, PCI+BMS	Brasil payer perspective, 4 years	PCI+DES vs PCI+BMS: incremental cost per prevented restenosis R$ 131,647 (EUR 42,000)
(Remak et al. 2010)	De novo native coronary artery lesions	PCI+DES (zotarolimus), PCI+BMS	Model, 4 years	PCI+DES vs PCI+BMS: GBP 3,757/QALY
(Eisenstein, Leon, et al. 2009)	N/A	PCI+DES (zotarolimus), PCI+DES (sirolimus)	Model, US Medicare perspective, 3 years	PCI+DES (zotarolimus) vs PCI+DES (sirolimus): USD 57,002/QALY
(Eisenstein, Wijns, et al. 2009)	N/A	PCI+DES (zotarolimus), PCI+BMS	Model, US Medicare perspective, 4 years	No difference in quality-adjusted survival days or total costs
(Bischof et al. 2009)	Chronic CAD	PCI+DES (sirolimus), PCI+DES (paclitaxel),	Markov model, Medicare/Medicaid perspective, 3 years	PCI+DES (sirolimus) vs BMS: >USD1,000,000/QALY PCI+DES (paclitaxel)

		PCI+BMS		vs BMS: BMS dominant
(Goeree et al. 2009)	All stent procedures in Ontario province	PCI+DES, PCI+BMS	Prospective Cohort study, Canada, 2 years	PCI+DES vs PCI+BMS: CA$419,000 in the most favorable risk group

OMT = Optimal medical therapy; DES = Drug Eluting Stents; BMS = Bare Metal Stents; N/A = not specified or ambiguous

Three studies assessed the use of oral drugs as adjuvants to bare metal stents. Oral rapamycin (OR, sirolimus) plus BMS was compared against a DES in a clinical trial of 200 patients over 5 years. OR+BMS resulted in lower costs, lower incidence of death, myocardial infarction and cerebrovascular events and was thus considered dominant at 5 years (Rodriguez et al. 2014). The same trial reporting at 3 years found differences in clinical outcomes were not significant, although costs were lower in the OR+BMS arm (Rodriguez et al. 2012). A Markov model described addition of eptifibatide to BMS for high risk patients, from a hospital and third-party payer perspective. For both perspectives, addition of eptifibatide was a dominant intervention due to avoided repeat procedures and cardiovascular events (Dewilde et al. 2012).

Two Markov model studies assessed paclitaxel-coated balloon angioplasty in restenosis after stenting. In patients with restenosis after BMS, drug-coated balloon (DCB) was compared with DES placement from the payer perspective. DCB was found to result in more life-years gained at a lower cost than DES over 12 months (Bonaventura et al. 2012). In patients with restenosis after DES, plain balloon angioplasty (PBA) and repeat DES was compared with DCB in a Markov model from the German payer perspective over 6 months. DCB was less costly and more effective than both PBA and repeated DES (Dorenkamp et al. 2013).

Finally, a percutaneous ventricular assist device (PVAD) to prevent hemodynamic collapse during high-risk PCI was assessed against intra-aortic balloon pump (IABP) in a Markov model from the German payer perspective over a 10-year horizon. The ICER over IABP was EUR 31,727-38,069 per QALY depending on the source of short-term clinical data (Roos et al. 2013).

Main findings:

- Compared with medical management, the ICER of PCI is within ranges normally considered cost-effective (two studies). The cost-effectiveness of PCI improves with more severe angina (one study)
- The significant range of ICERs observed for PCI with drug eluting or bare metal stents precludes clear conclusions about their cost-effectiveness.
- A clinical trial over 5 years and a modelling study both found addition of drugs (sirolimus, an antiproliferative; or eptifibatide, an antiplatelet) to BMS procedures was a dominant strategy over DES.
- For in-stent restenosis, drug-coated balloon angioplasty is a dominant strategy over plain balloon angioplasty and DES placement (two studies)

- A percutaneous ventricular assist device (PVAD) to prevent hemodynamic collapse during high-risk PCI was considered cost-effective over intra-aortic balloon pump at <EUR 40,000/QALY (one study)

2.3.2.3.3 Coronary artery bypass graft

The use of coronary artery bypass graft (CABG) surgery was addressed in 14 primary studies, no reviews were identified. The studies addressed a variety of aspects relating to CABG.

Two studies assessed on-pump vs off-pump CABG. In the US, a large clinical trial (2,203 patients) comparing the two modes of CABG found neither costs nor quality of life was different between the groups (T. H. Wagner et al. 2013). In Danish patients above 70 years, off-pump surgery was marginally less expensive than on-pump, at no change in QALY's. The authors considered off-pump surgery to be more cost-effective than on-pump, but call for comparisons over longer time-horizons than the 6 months examined (Houlind et al. 2013).

One study assessed different approaches to CABG surgery. A comparison of minimal versus conventional extracorporeal circulation (MECC vs CECC). Total costs were found to be lower with MECC in the study countries (Greece, Germany, Netherlands and Switzerland), and life-years gained were slightly higher for MECC, leading the authors to conclude it may be dominant (Anastasiadis et al. 2013).

Two early studies assessed cost-effectiveness of CABG alone. In one, costs included surgery, medical management of angina and treatment of future myocardial infarctions. CABG was found to increase quality-adjusted life expectancy, at a cost of USD 3,800 (left main disease) to USD 30,000 (one-vessel disease) per QALY (Weinstein and Stason 1982). A decision model of 14 hypothetical patients estimated a cost of USD1,500 to $32,000 per QALY gained for patients in which surgery was considered the optimal treatment (Pliskin et al. 1981).

Nine studies compared CABG with other treatments, of which six compared CABG with percutaneous coronary intervention (PCI). Early work in this area was inconclusive regarding their relative cost-effectiveness using a "multiple indicator multiple cause" model in a simultaneous equation system (Lee et al. 1997). In 2003 a Markov model determined surgical revascularisation (CABG) was less costly and more effective than catheter-based interventions (PCI) (Yock et al. 2003). In contrast a Veterans Affairs clinical study in the US compared urgent PCI with CABG in high-risk patients from the 3rd party payer perspective. At 3 and 5 years, PCI was less costly and associated with higher survival than CABG (Stroupe et al. 2006). In patients with multivessel coronary artery disease, CABG was compared with PCI or medical treatment alone over 5 years. CABG yielded longer event-free and event plus angina-free survival than the comparators. However the event-free costs where higher for PCI and CABG than medical management. Medical management was concluded to be more cost-effective than PCI and CABG, and CABG more cost-effective than PCI (Vieira et al. 2012).

An Armenian study evaluated PCI plus drug-eluting stents (DES) versus CABG in preventing a composite outcome of myocardial infarction (MI), repeat revascularization (RR) and death over 4 years in patients with IHD. CABG patients had significantly longer event-free survival and incurred lower medical costs (Perikhanyan 2011). A prospective observational study from the UK NHS perspective, comparing CABG,

PCI and medical management found CABG cost GBP22,000 per additional QALY over PCI in patients only eligible for CABG, and GBP19,000 per additional QALY over medical management in patients eligible for both types of surgery. PCI was not found to be cost-effective under any circumstances, and in patients only eligible for PCI the ICER over medical management was GBP 47,000 per QALY. The authors concluded CABG was cost-effective and PCI was not (Griffin et al. 2007).

Addition of abciximab to a CABG intervention was compared with CABG alone for high risk patients in a retrospective matched cohort study from the US payer perspective. At 6 months abciximab was associated with a lower but statistically insignificant incidence of ischemic events at an incremental cost of USD 21,789 per event avoided (Reed, Mullins, and Magder 2000). Compared with medical management alone in elderly patients with chronic angina, at one year follow-up the higher costs of surgery were found to be almost offset by increased practitioner visits and symptom-driven late revascularization in the medical management group. The incremental cost of preventing one major event by CABG was CHF 10,100. The authors consider CABG in elderly patients with chronic angina to be cost-effective (Claude et al. 2004). Finally, an Irish study compared various interventions related to coronary heart disease in terms of cost per LYG. Revascularisation for chronic angina was the least cost-effective intervention compared with antiplatelets, beta-blockers, ACE inhibitors, spironolactone, warfarin and statins, but still considered cost-effective at EUR 12,000-20,000 per LYG (Bennett et al. 2009).

Main findings:

- Two studies suggest there is little or no difference in cost-effectiveness between on- and off-pump CABG
- CABG yields longer event-free survival than PCI with or without DES (two studies). CABG was consistently considered more cost-effective than PCI in 4 studies, while one study reported the opposite.
- Abciximab in addition to CABG may reduce incidence of ischemic events but at added cost. The findings from this single study were statistically insignificant.
- Early CABG may be considered cost-effective in elderly patients with chronic angina, due to costs associated with medical management and symptom-driven late CABG (one study)
- CABG is the least cost-effective way to manage coronary heart disease compared with antiplatelets, beta-blockers, ACE inhibitors, spironolactone, warfarin and statins (one study)

2.3.3 Prevention of disease progression: secondary prevention

An overview of economic studies identified for the prevention of disease progression, secondary prevention, is given in Table 2.6.

Table 2.6 Economic evidence for the prevention of disease progression

Prevention of Disease Progression	Studies	Reviews
Pharmaceuticals		
Antiplatelet Therapy: asprin, clopidogrel, dipyridamole, ticlopidine, cilostazol, triflusal, ticagrelor	28	1

Gastroprotection	3	0
Influenza vaccine	0	0
Reduction of risk factors		
Blood Pressure Management: lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products, medications: diuretics, beta blockers, calcium channel blockers, ace-i, angiotensin receptor blockers, aldosterone antagonists.	5	0
smoking cessation: behavioral counseling, pharmacological therapies (bupropion, or varenicline),	4	0
Lipid Management: Statins (should be started before hospital discharge for MI), Bile Acid Sequesterant (2nd line)	32	0
weight loss: lifestyle modification, structured exercise, decreasing caloric intake, and formal behavioral program	0	0
glycemic control if diabetic	1	0
Life style		
Exercise: cardiac rehab, physician directed, home based programs	5	1
Screening and Treatment of Comorbid Depression: therapy, anti-depressants	3	0
Decrease Alcohol consumption	0	0
Avoiding Exposure to Air Pollution	0	0
Stress Management	0	0

2.3.3.1 Pharmaceuticals

Pharmaceuticals for the prevention of angina, or more generally acute coronary syndrome (ACS), include antiplatelets such as aspirin, clopidogrel and more recent drugs including ticagrelor and prasugrel. For long term aspirin therapy, proton pump inhibitors (PPI) are sometimes considered for the reduction of gastrointestinal side-effects. Influenza vaccine can be considered in patients more likely to develop complications from infection, which includes patients with chronic heart disease. However no economic evidence was identified for the use of influenza vaccine in this scenario.

2.3.3.1.1 Antiplatelet therapy

The use of antiplatelets in the prevention of angina disease progression was relatively well studied with 28 primary studies. Ticagrelor, clopidogrel and prasugrel accounted for the majority of studies. In the interest of clarity we review the 13 studies (46%) published in 2009 or later.

Of these, ten studies assessed combinations of prasugrel, clopidogrel and ticagrelor (Table 2.7). Compared with clopidogrel, addition of ticagrelor or prasugrel to aspirin is generally cost-effective at less than EUR 10,000/QALY gained. In some cases the newer drugs are dominant (Gasche et al. 2013; Mauskopf et al. 2012; Theidel et al. 2013). Prior to its patent expiration, clopidogrel against aspirin incurred an additional USD 10,691/LYG, which is likely to be an over-estimate compared to time of

writing. Recent studies used generic clopidogrel as comparator (Chin et al. 2013; A Davies et al. 2013; Gasche et al. 2013; Nikolic et al. 2013)

Table 2.7 Economic evidence for the use of prasugrel, clopidogrel and ticagrelor in prevention of angina progression

	Patients	Interventions	Model	ICER of comparator 1 over comparator 2
(Nikolic et al. 2013)	Acute coronary syndrome	Ticagrelor, clopidogrel	Decision model, healthcare perspective, lifetime horizon	Ticagrelor vs clopidogrel: EUR 2,753
(Gasche et al. 2013)	Acute coronary syndrome	Ticagrelor+aspirin, clopidogrel+aspirin	Decision model, payer perspective, 5 years or lifetime horizon	Ticagrelor+Aspirin vs Clopidogrel+Aspirin, lifetime: CHF 1,536/QALY (EUR 1,270) Ticagrelor+Aspirin vs Clopidogrel+Aspirin, 5y: Ticagrelor dominant
(A Davies et al. 2013)	Acute coronary syndrome undergoing PCI	Prasugrel, clopidogrel	Markov model, lifetime horizon	Prasugrel vs clopidogrel: EUR 9,489/QALY
(Liew et al. 2013)	Acute coronary syndrome	Ticagrelor+aspirin, clopidogrel+aspirin	Markov model, Australian context, healthcare perspective, 10 year horizon	Ticagrelor+aspirin vs clopidogrel+aspirin: AU$ 9,031 (EUR 6,250)
(Chin et al. 2013)	Acute coronary syndrome	Ticagrelor+aspirin, clopidogrel+aspirin	Markov model, Singapore healthcare perspective, lifetime horizon	Ticagrelor+aspirin vs clopidogrel+aspirin: SGD 10,136/QALY (EUR 6,300)
(Theidel et al. 2013)	Acute coronary syndrome	Ticagrelor+aspirin, clopidogrel+aspirin	Markov model, German healthcare perspective , lifetime horizon	Ticagrelor+aspirin vs clopidogrel+aspirin: Ticagrelor dominant to EUR 2,728/QALY
(Andrew Davies et al. 2013)	Acute coronary syndrome undergoing PCI	Prasugrel, clopidogrel	Markov model, German, Swedish, Dutch, Turkish healthcare perspective, lifetime horizon	Prasugrel vs clopidogrel: EUR 6,520 to 14,350/QALY
(Zefeng Zhang et al. 2009)	ST-elevated myocardial infarction	Clopidogrel+aspirin, placebo+aspirin	Decision model, US Medicare perspective, lifetime horizon	Clopidogrel+aspirin vs placebo+aspirin: USD 10,691/LYG

(Logman et al. 2010)	High-risk atherosclerotic patients (pre-existing symptomatic atherosclerotic disease)	Clopidogrel, aspirin	Markov model, Swedish societal perspective, lifetime perspective	Clopidogrel vs aspirin: SEK 38,153/QALY (EUR 4,100) Probability of being cost-effective: 81% at SEK100,000; 98% at SEK500,000 per QALY
(Mauskopf et al. 2012)	Acute coronary syndrome undergoing PCI	Prasugrel+aspirin, clopidogrel+aspirin	Economic model, US Managed Care Organisation perspective, 15 month horizon	Prasugrel+aspirin vs clopidogrel+aspirin: Prasugrel+aspirin dominant. Prasugrel+aspirin vs lower price generic clopidogrel: USD 6,643-13,906/QALY

Three studies assessed the use of genotyping to guide clopidogrel vs ticagrelor choice in acute coronary syndrome patients. In Australia, three strategies were compared: universal ticagrelor, universal clopidogrel, or selection based on sensitive genotypes. A Markov model over a lifetime horizon showed genotyping was more effective and cost-effective than universal clopidogrel, but universal ticagrelor was the most effective strategy with acceptable ICER over the genotyping strategy (Sorich et al. 2013). A comparable model over 15 months found genotyping to be dominant over universal prasugrel (when generic clopidogrel was modelled), but cost savings were not observed compared with universal generic clopidogrel (Reese et al. 2012). From the US Medicare perspective, a Markov model compared genotype-driven treatment with universal ticagrelor over 5 years, and found universal ticagrelor incurred USD 10,059/QALY over genotype-driven treatment (Crespin et al. 2011).

Main findings:

- Addition of ticagrelor or prasugrel to aspirin is generally cost-effective at less than EUR 10,000/QALY gained against generic clopidogrel
- Three studies assess genotype-driven selection between ticagrelor, prasugrel and clopidogrel. Mixed results are reported, but suggest genotyping is beneficial over universal prasugrel, while universal ticagrelor is preferable over genotyping.

2.3.3.1.2 Gastroprotection

Three primary studies were identified for gastroprotective pharmaceuticals administered alongside aspirin. One study compared aspirin alone, aspirin+proton pump inhibitor (PPI) combination therapy and fixed combination of aspirin/PPI. In primary prevention of acute coronary syndrome no medications were superior to aspirin monotherapy. In secondary prevention, aspirin+PPI combination therapy was cost-effective (EUR 563/QALY), while fixed combination therapy only exhibited an ICER less than EUR

20,000/QALY in a populations with elevated risk of upper gastrointestinal (GI) bleeding or moderate PPI compliance. PPI use lowered the overall risk of acute coronary syndrome (de Groot et al. 2013).

A Markov model over a lifetime horizon assessed aspirin plus PPI in primary prevention of coronary heart disease (CHD) in men aged 45 at different risks of CHD and GI bleeding. Compared with aspirin, aspirin plus PPI was associated with an ICER of USD 447,077/QALY, though the authors note PPI addition may be cost-effective in patients at increased risk of GI bleeding (Earnshaw et al. 2011).

In secondary prevention, aspirin monotherapy was also compared with aspirin+PPI in a Markov model of patients aged 50+ in the US setting. Here the ICER was USD40,090 per LYG at "over-the-counter cost" (generic), and >USD100,000 at "prescription cost" (on-patent) (Saini et al. 2008)

Main findings:

- Proton pump inhibitors (PPI) reduce the risk of acute coronary syndrome in aspirin primary and secondary prevention.
- In primary prevention, aspirin monotherapy appears to be the most cost-effective option (two studies), while for secondary prevention, aspirin plus a (generic) PPI can be cost-effective, though the ICER varied significantly over the two studies.

2.3.3.2 Reduction of risk factors

Several risk factors are addressed in the following sections, incl. blood pressure, smoking, lipid management, weightloss and glycemic control in diabetics. Some interventions do not address single risk factors but address "life style modification" more broadly. This includes an American Medicare-sponsored study of two intensive lifestyle modification programmes (LMP) in patients who had had acute myocardial infarction or a cardiac procedure within the preceding 12 months, or had stable angina pectoris. The 1-year intervention included exercise, diet, small-group support and stress reduction. The two programmes yielded reductions in total hospitalization rates, and programme costs were offset by reductions in health care utilization (Zeng et al. 2013).

Patients with preclinical or established CAD have been enrolled in a clinical trial of a comprehensive lifestyle modification programme, which uses positron emission tomography for risk stratification and offers educational and motivational therapy for participants (Langabeer et al. 2012). An economic analysis of the trial suggested the cost of the trial in present value terms was USD 7,058 per patient, however no cost-effectiveness analysis has been reported (Delgado et al. 2014).

A model was developed to assess the potential cost-effectiveness of optimizing cardiovascular prevention in patients with coronary heart disease. The Framingham risk of individual participants was assessed and any suboptimal areas of prevention were identified. The effects of optimizing prevention (incl. smoking cessation, diet and exercise improvement, blood pressure and lipid control) was then estimated. The cost-effectiveness analysis, which covered Belgium, Bulgaria, Croatia, Finland, France, Italy, Poland and the UK, demonstrated an average ICER of EUR 12,484/QALY. Only in patients with very low baseline risk of events was the intervention not cost-effective (De Smedt et al. 2012).

Nutrition was specifically addressed in one study which estimated the cost-effectiveness of adopting a Mediterranean diet following MI. The study reported a Markov model based on the Lyon Diet Heart Study, and estimated an ICER of AU$ 1,013/QALY for the Mediterranean diet over a "prudent Western diet" which included increased costs of food as well as healthcare utilisation (Dalziel, Segal, and de Lorgeril 2006).

2.3.3.2.1 Blood pressure management

Five primary studies were identified for blood pressure management with ACE inhibitors, all of which studied patients with prior myocardial infarction.

A decision model based on the Survival and Ventricular Enlargement (SAVE) trial assessed cost-effectiveness of captopril in 50-80 year old myocardial infarction (MI) survivors. If treatment effect was assumed beyond 4 years, ICER's ranged from USD3,700 to USD10,400/QALY with high age associated with lower ICER's. Assuming no effect beyond 4 years the ICER's were USD3,600 to USD60,800/QALY (Tsevat et al. 1995). Captopril was also modelled in Italy based on the SAVE trial, where the ICER was estimated at USD9,619/LYG for patients matching the entry criteria to the SAVE trial (Mantovani, Belisari, and Szucs 1998).

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI-3) trial assessed the efficacy of early treatment with an ACE inhibitor (lisinopril) for 6 weeks following MI. The cost per additional survivor was estimated at USD 2,080 (Franzosi et al. 1998).

One study assessed the cost-effectiveness of three treatment strategies following myocardial infarction: high risk, intermediate risk and initial treatment of all patients followed by long-term treatment according to high or intermediate risk. The cost per LYG over 10 years was GBP 1,752 and GBP 2,962 for the first two strategies respectively; the third strategy raised these costs to GBP 2,017 and 3,110 per LYG, respectively. The authors conclude, if a low cost ACE inhibitor is used, that "*initial treatment of relatively unselected patients followed by long-term treatment of those at high and medium risk maximizes benefit at an acceptable cost*" (McMurray et al. 1997).

A more recent study compared valsartan in post-MI patients with left ventricular systolic dysfunction and/or heart failure, who are not suitable for treatment with ACE inhibitors, with placebo. A Markov model over 10 years resulted in an ICER of GBP 5,338/QALY gained (Taylor et al. 2009).

Main findings:

- The use of ACE inhibitors following acute myocardial infarction appears to be cost-effective, but may be sensitive to the timeframe of the benefit.
- Selecting ACE inhibitor treatment strategy based on risk may provide slightly improved costs per LYG (one study)
- In patients who are not suitable for treatment with ACE inhibitors, valsartan may be a cost-effective alterantive (one study)

2.3.3.2.2 Smoking cessation

Studies assessed the cost-effectiveness of smoking cessation in patients with existing coronary heart disease. One study was addressed in section 2.3.3.2 as an intervention to improve preventive measures according to individual patients risk profile, resulting in an average ICER of EUR 12,484/QALY (De Smedt et al. 2012).

A protocol for a clinical trial in the Netherlands assessing two smoking cessation interventions that "suit nursing practice" has been reported. The intervention combines nicotine replacement therapy and face-to-face or telephone counselling (Berndt et al. 2012). To date no follow-up reports have been published.

A Monte Carlo simulation model in the US setting was based on a meta-analysis of clinical trials of smoking cessation studies, and was used to assess the impact of routine care (advice to quit smoking) with routine care plus supportive follow-up, consisting of telephone calls from a nurse after discharge. The cost-effectiveness was estimated to be USD5,050 per QALY from the societal perspective (Ladapo et al. 2011). An earlier study of a nurse-led smoking cessation intervention after myocardial infarction reported a cost-effectiveness of USD220/LYG (Krumholz et al. 1993).

Main findings:

- Available evidence (two studies) suggests smoking cessation as an isolated intervention is cost-effective in patients with myocardial infarction. An ongoing clinical trial will provide evidence on the cost-effectiveness of telephone vs. face-to-face nurse coaching following hospital discharge.

2.3.3.2.3 Lipid management

A total of 32 studies were identified for lipid management in secondary prevention for patients with existing ischemic heart disease. We restrict the analysis to studies published in 2009 or later (5 of 32), but note that the majority of older studies (26 of 27) address cost-effectiveness of various statin therapies, while the last study addresses gemfibrozil in raising high-density lipoprotein (HDL) cholesterol and lowering triglyceride levels (Nyman et al. 2002).

Of the five recent studies, one was addressed in section 2.3.3.2 (De Smedt et al. 2012) and is not discussed further. One study reported a Markov model estimating the lifetime costs and benefits for acute coronary syndrome patients in the UK setting of ezetimibe+simvastatin over double statin doses, which incurred an ICER of GBP 11,571/QALY. The ICER was slightly lower in patients on a higher statin dose prior to treatment switch (Reckless et al. 2010). Double simvastatin doses were also studied in a clinical trial over 4.8 years in Canada including patients with previous myocardial infarction (MI). A Markov model from the societal perspective extrapolated results to a lifetime horizon, resulting in CA$ 26,795/QALY compared with standard dose, or CA$ 38,834 when only direct costs were considered (M. Wagner et al. 2009).

An Indian study estimated the incremental cost per major coronary event averted at IR 2,000,000 (EUR 25,800) and per CHD death averted at IR 5,240,000 (EUR 67,600) for statin therapy in secondary prevention (Sanmukhani and Shah 2010). Finally an Australian study reported a Markov model estimating the cost-effectiveness of increasing the statin coverage in secondary prevention from 82%

(actual situation) to 100% with generic statins. Considering direct medical costs including costs of the programme, an ICER of AU$ 29,717 per LYG was reported (Ademi et al. 2011).

Main findings:

- Recent literature on statins in secondary prevention finds double-dose statin therapy is cost-effective following myocardial infarction (one study), however ezetimibe/simvastatin is also cost-effective over double-dose statins (one study).
- Increasing the coverage of statin therapy in secondary prevention, where this is currently sub-optimal, may be a cost-effective intervention (one study)

2.3.3.2.4 Glycemic control if diabetic

A single clinical trial was identified addressing coronary artery disease and diabetes comorbidity, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) (Hlatky, Melsop, and Boothroyd 2006). In this study, patients with type 2 diabetes and stable coronary disease received either prompt revascularization or medical therapy with delayed revascularization as needed to relieve symptoms. Based on 4-year data, cost-effectiveness analysis favored medical therapy over prompt revascularization, with lifetime extrapolations suggesting an ICER of USD 600/LYG (Hlatky et al. 2009).

- In diabetic patients, medical management with delayed revascularization as needed appears to be cost-effective over prompt revascularization (on clinical study)

2.3.3.3 Life style

Life style interventions in the prevention of disease progression include exercise (cardiac rehabilitation), management of comorbid depression, decreased alcohol consumption, avoiding exposure to air pollution and stress management. Economic evidence was only identified for exercise and comorbid depression management.

2.3.3.3.1 Exercise

Five primary studies were identified for cardiac rehabilitation following coronary events. An early evaluation from Canada randomized patients with acute myocardial infarction (AMI) to an 8-week rehabilitation programme or usual care with 12 month follow-up. Included patients also suffered from mild to moderate anxiety and/or depression. The study reported an ICER of CA$ 9,200/QALY gained (Oldridge et al. 1993). Subsequent work from the US was based on modelling and reported a cost/LYG of USD 2,130 compared with usual care (Ades, Pashkow, and Nestor 1997).

More recently a clinical trial in Australia assessed "*18 sessions of comprehensive exercise-based outpatient cardiac rehabilitation*" against conventional care following an acute coronary syndrome. Direct costs were considered over 1 year, resulting in an ICER of USD 42,535 (Briffa et al. 2005). In a Canadian clinical trial, patients with CAD were randomized to a 3-month or 12-month programme and followed over 24 months. The analysis found the 3-month programme to be more cost-effective for patients at high risk, with previous coronary artery bypass graft and for male patients. The 12-month programme was more cost-effective for patients with lower risk of disease progression and for female patients (Papadakis et al. 2008).

The topic of peripheral arterial disease (PAD), which can hinder cardiac rehabilitation programmes, was addressed in one study. Three strategies were compared: cardiac rehabilitation only; ankle brachial index (ABI) if cardiac rehabilitation fails followed by diagnostic work-up and revascularization for PAD if needed; ABI prior to cardiac rehabilitation followed by diagnostic work-up and revascularization for PAD if needed. The second strategy (ABI if cardiac rehabilitation fails) was found to be most cost-effective at USD 44,251/QALY over cardiac rehabilitation only (Spronk et al. 2008).

Main findings:

- Cardiac rehabilitation compared with no rehabilitation is cost-effective (three studies)
- Depending on risk factors and patient characteristics, different types of programmes may be more cost-effective, eg. shorter vs. longer interventions (one study)
- Management of peripheral arterial disease may improve the cost-effectiveness of cardiac rehabilitation (one study)

2.3.3.3.2 Screening and treatment of comorbid depression

Three primary studies addressed treatment of depression as a comorbidity of IHD. Based on direct medical costs and clinical results from the Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART), a placebo-controlled safety trial of 24 weeks of treatment with sertraline after acute coronary syndrome, calculations from the Italian healthcare perspective showed average total costs were lower in patients receiving sertraline, though the difference was not statistically significant. The results suggested antidepressive treatment may provide improved outcomes at lower costs (Lattanzio et al. 2008). From the US payer perspective, a similar study also concluded no significant differences in per-patient average costs between sertraline and placebo. The authors noted a trend toward fewer psychiatric or cardiovascular hospitalizations in the sertraline group (O'Connor, Glassman, and Harrison 2005).

An ongoing clinical trial in the Netherlands is assessing the cost-effectiveness of a nurse-led stepped-care programme to prevent major depression in patients with type II diabetes and/or coronary heart disease in primary care, who also have subthreshold depressive symptoms. Costs will be assessed from the societal perspective measured at 3, 6, 9 and 12 months (van Dijk et al. 2013). To date no follow-up has been reported.

- Antidepressive therapy with sertraline following acute coronary syndrome appears to reduce subsequent healthcare usage and may be cost-saving, however no statistically significant results have been reported (two studies)
- An ongoing clinical trial in the Netherlands will assess the cost-effectiveness of a nurse-led stepped-care program in preventing progression from subthreshold depression in patients with type II diabetes and/or coronary heart disease (one study)

2.4 Evidence gaps in ischemic heart disease

Observations from published studies

- Guiding treatment with CYP2C19 or P2Y12 genotyping for prasugrel/clopidogrel or ticagrelor/prasugrel appears to be cost-effective compared with universal treatment in antithrombotic therapy, though only two studies are published on the topic.
- No updated economic evidence was identified for thrombolysis in acute myocardial infarction, with the majority of studies published prior to year 2000.
- Primary Percutaneous Coronary Intervention (PCI) was well studied against thrombolysis, however these studies assume access to clinics specializing in such operative interventions, which may not be the case in practice.
- The level of economic evidence for pharmacological treatment of acute angina was relatively low with three studies or less underpinning each treatment. The majority of these studies (except fatty acid oxidation inhibitors) was published in or before 2007.
- A wide range of literature on percutaneous coronary intervention (PCI) with drug eluting and (DES) bare metal stents (BMS) presents a wide range of ICER's. Adding pharmacotherapy to BMS treatment appears to be dominant over DES.
- Coronary artery bypass graft (CABG) was found to be more cost-effective than percutaneous coronary intervention (PCI) in four out of five studies. It appears early CABG is also cost-effective in elderly patients compared with conservative management, due to costs associated with medical management and symptom-driven late CABG, however only a single study supported this finding.
- Proton pump inhibitors (PPI) used for gastroprotection in combination with antiplatelets for primary or secondary prevention lower overall risk of acute coronary syndrome, however some studies suggest the ICER is excessively high.
- Risk factor interventions for the prevention of disease progression, including blood pressure management, smoking cessation, lipid management and glycemic control (for diabetics) are all cost-effective, though there is little evidence on how to best deliver these services, eg. telephone vs. face-to-face coaching for smoking cessation, and a significant portion of the blood pressure management literature was published prior to year 2000.
- Life style interventions, including cardiac rehabilitation and the early management of depressive symptoms following acute coronary syndrome, appear to be cost-effective. Anti-depressive treatment trended towards lower healthcare utilization and costs, though this was not statistically significant. An ongoing clinical trial for nurse-led preventive care may shed some light on this, though this trial is focused on patients with type II diabetes and/or coronary heart disease with existing subthreshold depressive symptoms.

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Health Economic Evidence Analysis: Treatment of Low Back Pain

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3. Low back pain

3.1 Bibliometrics

A total of 63 economic studies were mapped to the clinical model for low back pain (Table 3.1 and Figure 3.1) with the majority[1] of studies published since 2005. Of the 11 reviews identified, five were published between 2009 and 2014.

Table 3.1 Bibliometric data for low back pain

PubMed/MEDLINE	
Search term	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Low Back Pain"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	63
Included as "other"	47
Reviews	11
Excluded	69
Total	190
Additional references from reviewers	
Total	2

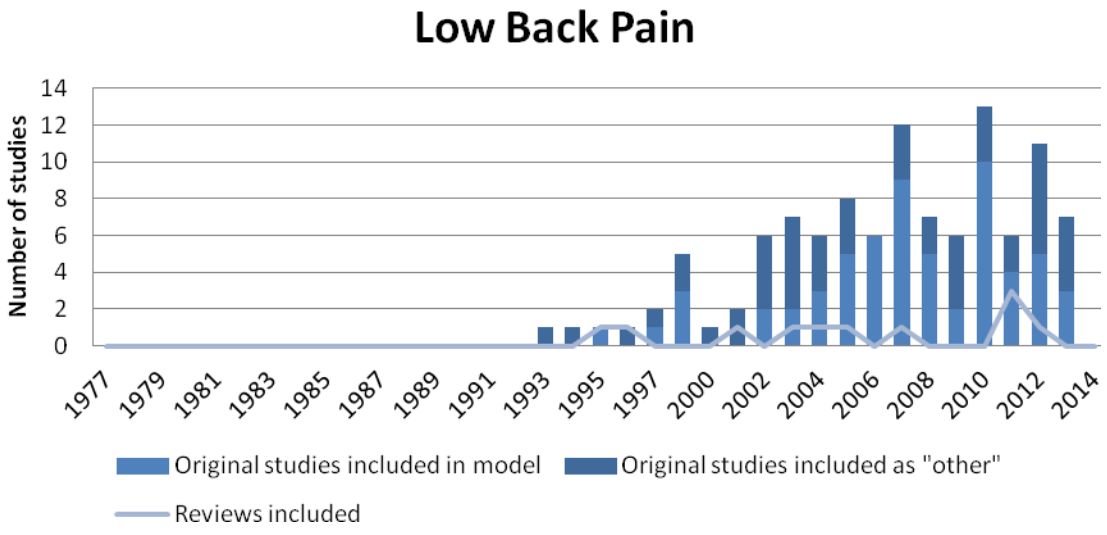

Figure 3.1 Bibliometric data for low back pain by year

[1] 75% of studies or more

3.2 Review coverage

The clinical model for low back pain consists of 63 treatment modalities. Of these, 11 treatments (17%) were addressed by at least one of the five reviews published between 2009 and 2014 (Table 3.2). The remaining 52 treatments (83%) were not associated with any health economic reviews, though primary studies were available in several cases (Table 3.3, Table 3.4 and described in sections 3.3.1.1 to 3.3.2.8). No reviews were identified for the treatment of acute LBP.

Table 3.2 Table of reviews for low back pain and associated treatments

Title and reference	Year	Treatments covered
"*Value-based care in the management of spinal disorders: a systematic review of cost-utility analysis*" (Indrakanti et al., 2012)	2012	**Sub-acute/chronic low back pain:** Exercise therapy/physical therapy Back schools Spinal manipulation Acupuncture Cognitive-Behavioral Therapy Transcutaneous Electrical Nerve Stimulation Percutaneous Electrical Nerve Stimulation Spinal fusion Standard open discectomy Microdiscectomy
"Spinal manipulation epidemiology: Systematic review of cost effectiveness studies" (Michaleff et al., 2012)	2012	**Sub-acute/chronic low back pain:** Cost-effectiveness of spinal manipulation therapy for patients with spinal pain of any duration
"*The efficacy, safety, effectiveness, and cost-effectiveness of ultrasound and shock wave therapies for low back pain: a systematic review*" (Seco, Kovacs & Urrutia, 2011)	2011	*The authors searched for Randomised Controlled Trials of ultrasound and shockwave therapies which included cost-effectiveness evaluation, but found none*
"*Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review*" (Lin et al., 2011a)	2011	**Sub-acute/chronic low back pain:** Exercise therapy/physical therapy Back schools Spinal manipulation Acupuncture Cognitive-Behavioral Therapy Spinal fusion
"*Cost-effectiveness of general practice care for low back pain: a systematic review*" (Lin et al., 2011b)	2011	**Sub-acute/chronic low back pain:** Exercise therapy/physical therapy Back schools Spinal manipulation Acupuncture Cognitive-Behavioral Therapy

3.3 Evidence analysis

The following sections present information gathered from recent (2009-2014) reviews when available, and from essential information on primary evidence where no reviews are available. Acute and sub-acute/chronic LBP are considered in turn.

3.3.1 Acute low back pain

The evidence identified for acute LBP is summarized in Table 3.3. No reviews specifically covering cost-effectiveness of treatments for acute LBP were identified. One review (Lin et al., 2011a) identified a single cost-minimisation analysis for spinal manipulation in acute LBP. In addition the review by Michaleff et al identified a single study which evaluated the cost-effectiveness of GP care plus spinal manipulation in a mixed population of patients with both neck and low back pain of between 2 – 12 weeks. These are described in section below.

Table 3.3 Primary evidence and reviews identified for cost-effectiveness of treatments for acute low back pain

Acute Low Back Pain Treatment Options	Primary studies	Reviews
Pharmacology		
Non-steroidal anti-inflammatory drugs (NSAIDS): ketorolac, meperidine, ibuprofen, naproxen	1	0
Acetaminophen	1	
Muscle Relaxants	0	0
Opioids	0	0
Activity and Physical Treatments		
Physical therapy / exercise program	2	0
Spinal manipulation	1	2
Massage	0	0
Yoga	0	0
Acupuncture	1	0
Cold/heat (heat wrap)	1	0
Traction	0	0
Corsets/braces	0	0
Mattress recommendations	0	0
Injections into trigger points, epidural space, facet joint or sacroiliac joint		
Local anesthetics	0	0
Proliferant-sclerosing solutions (known as prolotherapy or sclerotherapy)	0	0
Botulinum toxin	0	0
Oxygen-ozone mixtures	0	0
TNF-alpha inhibitors	0	0

3.3.1.1 Pharmacology

A placebo controlled randomized controlled trial (RCT) was performed for acetominophen (paracetamol) in acute low back pain with plans for an economic evaluation from "*health sector and societal perspectives*" including a cost-utility analysis (Williams et al., 2010). However the trial found no differences in efficacy between paracetamol (regular or as-needed) and placebo, measured in median time to recovery (Williams et al., 2014) and consequently no economic evaluation was performed.

Paracetamol was compared with a branded heat wrap (ThermaCare) and ibuprofen in a cost-effectiveness modelling study reporting cost per successful treatment but no utility measures. The prescription costs per successful treatment were GBP 2.37 for heat wrap, GBP 1.00 for paracetamol and GBP 1.55 for ibuprofen. When costs of health care utilization were included, taking into account failed treatment, the cost per successful treatment was lower with heat wrap (GBP 48.72) than with paracetamol (GBP 131.63) and ibuprofen (GBP 200.24). The study was funded by the manufacturer of ThermaCare (Lloyd et al., 2004).

Main findings:

- No differences in efficacy were found between paracetamol and placebo in one clinical trial, consequently no follow-up cost-effectiveness studies have been published.
- There is a lack of evidence on the cost-effectiveness of heat wrap therapy with only a single manufacturer sponsored study published in 2004. The study does not take into account all available evidence on the effectiveness of heat wrap therapy, which currently numbers 3-4 clinical trials

3.3.1.2 Physical treatments

No economic evidence was identified for massage, yoga or mattress recommendations.

Spinal manipulation for acute LBP was addressed by two reviews (Lin et al., 2011a; Michaleff et al., 2012) with each review only identifying one primary study. Lin et al. identified a single study, which was also identified in the present search, reporting a cost-minimisation analysis of spinal manipulation, GP care or an intensive training programme in a study population of 180 patients with acute LBP. These three treatments were found to be equally effective in terms of impairment, pain, functional disability and socio-economic disability (Seferlis, Lindholm & Németh, 2000). The differences in cost between the three options appeared small (SEK 45,423 for training programme to 50,834 for GP care) however no formal statistical comparison was performed, and incomplete costs were identified with only study treatment, investigations and operations collected as direct costs (Lin et al., 2011a). Michaleff et al. identified one clinical trial which included patients with both neck and low back pain of 2-12 weeks duration (acute/sub-acute). In this study population, from a UK healthcare perspective, SMT plus GP care was found to be cost-effective over GP care alone with an ICER of GBP 3,560/QALY (also discussed in section 3.3.2.2).

Two studies were related to physical therapy/exercise specifically of acute LBP, and both assessed the economic benefits of early intervention: One study evaluated cost-utility from a societal perspective of a multidisciplinary early intervention for acute LBP patients considered at risk of chronic pain,

randomizing 121 patients to treatment as usual or an early intervention with cognitive behavioral therapy and physical therapy. From a societal perspective, the early intervention was found to be less costly and more effective (Rogerson, Gatchel & Bierner, 2010). A randomized trial of an early intervention focused on a range of musculoskeletal disorders resulting in temporary work disability, of which back pain accounted for approximately 1/3rd of all enrolled patients. The intervention consisted of an education programme including instructions on mobilization of painful regions, ergonomic care, physical activity etc. provided by a rheumatologist. According to need, patients were escalated through three tiers of intensified care. The study found median duration of work disability was significantly shorter in the intervention arm compared with usual care. A cost-benefit analysis showed a positive net benefit, and the cost-benefit was estimated at USD 8 to USD 11 per USD 1 invested (Abásolo, 2005)

A study protocol for an RCT of acupuncture in 340 patients with a cost-effectiveness element was reported (Vas et al., 2006) but no efficacy data or economic analyses have been published to date (ISRCTN, 2008). Cost-effectiveness of heat wrap therapy was reported by a single study as described in section 3.3.1.1, briefly this study found heat wrap therapy to be more cost-effective by cost per successful treatment than paracetamol and ibuprofen when healthcare utilization was taken into account.

Main findings:

- Early intervention with a targeted approach is cost-saving or associated with positive net benefit according to two clinical trials.
- There is a lack of evidence on the cost-effectiveness of heat wrap therapy with only a single manufacturer sponsored study published in 2004. The study does not take into account all available evidence on the effectiveness of heat wrap therapy, which currently numbers 3-4 clinical trials.
- In a small clinical trial of 180 patients, no differences in outcomes were reported between spinal manipulation, GP care and an intensive training programme. Costs were relatively similar, with training being marginally cheaper and GP care the most expensive, however the study was limited by a small sample size and a limited array of direct costs included. In addition, SMT plus GP care was found to be cost-effective compared with GP care alone however this study recruited patients with both low back pain and neck pain of between 2-12 weeks duration. These conclusions are based on the findings of single studies. Additional studies are required to strengthen the conclusions that can be made as to the cost-effectiveness of spinal manipulative therapy in patients with acute low back pain.

3.3.1.3 Injections into trigger points, epidural space, facet joint or sacroiliac joint

No evidence was identified on the topic of injections into trigger points, epidural space, facet joint or sacroiliac joint.

3.3.2 Sub-acute and chronic low back pain

The economic evidence identified for sub-acute and chronic back pain is given in Table 3.4.

Table 3.4 Primary evidence and reviews identified for sub-acute and chronic low back pain

Sub-Acute/ Chronic Low Back Pain Treatment Options	Primary studies	Reviews
Pharmacology		
Non-steroidal anti-inflammatory drugs (NSAIDS): acetaminophen, ketorolac, meperidine, ibuprofen, naproxen	1	0
Muscle Relaxants: cyclobenzaprine, flupirtine, tolperisone, carisoprodol, meprobamate	1	0
Opioids: tramadol, codeine/acetaminophen	2	0
Steroids: methylpredniosone	0	0
Local Anesthetics: lidocaine patches	0	0
Anti-depressants: trazadone, duloxetine, tricyclic antidepressants	2	0
Benzodiazipines: tetrazepam	0	0
Anti-epileptics: gabapentin, pregabalin, topirimate	0	0
Glucosamine	0	0
Herbal Therapies:Harpagophytym procumbens (Devil's claw), Salix alba (White willow bark), and topical Sapsicum frutescens (cayenne)	0	0
Anti-TNF-Alpha Therapy	0	0
Activity and Physical Treatments		
Exercise Therapy/ Physical Therapy	22	3
Back Schools	2	3
Spinal Manipulation	5	4
Acupuncture	8	3
Massage	1	1
Yoga	1	0
Traction/corsets/braces	3	0
Psychological and Multi-Disciplinary Interventions		
Cognitive-Behavioral Therapy	15	3
Interdisciplinary Rehabilitation	0	0
Functional Restoration	0	0
Physical Modalities		
Interferential Therapy	0	0
Low-level Laser Therapy	0	0
Ultrasound	0	0
Short-wave Diatherapy	0	0
Traction	0	0
Transcutaneous or Percutaneous Electrial Nerve Stimulation	2	1
Interventional Diagnostic Procedures		

Sub-Acute/ Chronic Low Back Pain Treatment Options	Primary studies	Reviews
Discography	0	0
Diagnostic Nerve Root Blocks	0	0
Facet Joint Blocks	1	0
Sacroiliac Joint Blocks	0	0
Injections		
Epidural: glucocorticoids, etanercept	0	0
Intradiscal: glucocorticoids, etanercept, chemonucleolysis, methylene blue	0	0
Local or Trigger Point: glucocorticoids, etanercept	0	0
Facet Joint: glucocorticoids, etanercept	0	0
Medial Branch Block: glucocorticoids, etanercept	0	0
Sacroiliac Joint: glucocorticoids, etanercept	0	0
Piriformis Syndrome: glucocorticoids	0	0
Paravertrebal: Boutulinum Toxin	0	0
Electrothermal and Radiofrequency Therapies		
Intradiscal Therapy: Intradiscal Electrothermal Therapy (IDET) and Percutaneous Intradiscal Radio-Frequency Thermocoagulation (PIRFT)	1	0
Radiofrequency Denervation	2	0
Prolotherapy	0	0
Surgical Treatment		
Spinal fusion	7	2
Lumbar disc replacement	2	0
Standard open discectomey	2	1
Microdiscectomey	2	1

3.3.2.1 Pharmacology

No reviews were identified specifically for pharmacological treatment in chronic LBP. One review (Lin et al., 2011a) searched for pharmacological studies but identified none.

Limited primary evidence was identified for NSAIDS, muscle relaxants and anti-depressants (in total three unique studies published subsequent to the review of Lin et al. in 2011). A clinical trial of 200 patients compared chiropractic treatment with "multidisciplinary integrative care" in chronic LBP, in which medications (NSAIDS, analgesics and/or muscle relaxants) were prescribed according to individual patient needs along with several other interventions including chiropractic treatment, cognitive behavioral therapy (CBT), exercise etc. The economic evaluation was reported to be performed from a societal perspective and would include cost-utility analysis (Westrom et al., 2010). The study was estimated for completion in December 2013 but no results have been reported to date (ClinicalTrials, 2014).

Antidepressants are described in two studies, both of duloxetine and both reporting incremental cost-effectiveness ratios (ICER's) from an American private payer perspective (Wielage et al., 2013b) and a Canadian societal perspective (Wielage et al., 2013a) respectively. ICER's for duloxetine were estimated at USD59,473/QALY over naproxen, less than USD30,000/QALY over NSAIDS while duloxetine was dominant over all strong opioids from an American private payer perspective (Wielage et al., 2013b). From a Canadian societal perspective, the ICER of duloxetine over naproxen was USD43,437/QALY and comparators other than celecoxib and naproxen were dominated by duloxetine (Wielage et al., 2013a). Both studies report an adaptation of a Markov model produced by the National Institute of Health and Care Excellence (NICE) to a different country context, and are produced largely by the same authors who are employed by the manufacturer of duloxetine or are commercial consultants.

Main findings:

- An ongoing RCT of multidisciplinary integrative care (pharmacology, chiropractic treatment, cognitive behavioral therapy, exercise, etc.) is reported to include a cost-utility analysis from a societal perspective, which is not yet published. However this study will not provide cost-effectiveness data on pharmacology as an isolated intervention, only as part of the multidisciplinary programme.
- The antidepressant duloxetine was studied in the context of Canada and USA using adaptations of the same Markov model from NICE for chronic LBP. Duloxetine was more effective at a higher cost than naproxen (ICER in excess of USD 40,000/QALY), but dominated strong opioids.
- No succinct evidence on cost-effectiveness was identified for other pharmacological interventions including muscle relaxants (other than as part of a multi-disciplinary intervention), opioids (other than as comparators for duloxetine), steroids, anti-depressants (other than duloxetine), benzodiazipines, anti-epileptics, glucosamine, herbal therapies or anti-TNF-Alpha therapy
- Only one study on antidepressants was identified. Evidence of cost-effectiveness of commonly used drugs for chronic low back pain is lacking.

3.3.2.2 Activity and physical treatments

Four reviews covered the areas of exercise therapy/physical therapy, back schools, spinal manipulation and acupuncture in chronic LBP. No cost-effectiveness studies were identified for yoga or traction/corsets/braces.

Indrakanti et al. observed that of 16 included studies comparing non-operative interventions, "*Nonoperative studies had substantial deficiencies in defining the pathology treated and the consistency of non-operative protocols*" and that "*five studies demonstrated considerable bias in baseline cohort selection*". Due to the heterogeneity of studies included, the authors concluded that "*direct comparison of CUA data across different studies is not feasible, and […] no definitive conclusions can be drawn regarding the superiority of one non-operative intervention over another".* Observing trends in the relative cost-effectiveness of different non-operative interventions, substantiated only by single studies, the authors suggested further substantiation before application to patient care or health care policy (Indrakanti et al., 2012). Treatments found to be more cost-effective than usual general practitioner

(GP) care by Lin et al, including Alexander technique, clinical rehabilitation and/or occupational intervention and acupuncture, were also substantiated by only one study, and these authors also highlight that "*the findings of this review are based on single studies as the heterogeneity of the included studies prevented the pooling of data*" (Lin et al., 2011b).

Lin et al. assessing the cost-effectiveness of general practitioner (GP) care for LBP noted that "*most studies evaluated 'usual GP care', i.e. they did not specify whether the treatments followed a protocol or guideline but provided care that included advice, exercises, rest and prescription of medications with or without referrals to other services. A number of studies did not describe details of the GP care, except that it was the normal or usual care provided by a GP"*. Of the 11 studies reviewed by Lin et al., only four were considered as having low risk of bias in the trial design according to the Cochrane Back Review Group. Quality of the 11 studies was assessed according to the Consensus on Health Economic Criteria (CHEC); five studies did not state the perspective (societal, payer etc.) adopted for the analysis, and only six conducted sensitivity analysis to address uncertainties in estimates of costs and effects. The authors were able to compare ICER's across only four studies that had adopted an identical outcome measure (QALY's) and identical cost perspective of the healthcare system (Lin et al., 2011b).

In a separate review of 27 studies, which included most of the 11 studies reviewed above, Lin et al. found largely the same pattern with seven studies not reporting the economic perspective adopted and only 13 studies having low risk of bias. The review revealed conflicting evidence for the cost-effectiveness of advice to patients (on prognosis, remaining active and on self-care options) and several methodological problems with the costing approach. In contrast, interdisciplinary rehabilitation, exercise and spinal manipulation were found to be relatively cost-effective in chronic LBP as evidenced by two or more studies (Lin et al., 2011a). The review by Michaleff et al, which included the same three studies addressing LBP as Lin et al, identified two clinical trials conducted from a UK health perspective which found SMT plus GP care to be cost-effective compared with GP care alone, with ICER's less than GBP 5,000/QALY. SMT plus GP care was also cost-effective compared with GP care plus exercise with an ICER of GBP 2,300/QALY. Two studies, one from a societal perspective and one of the studies mentioned above, compared SMT plus advice and exercise (A&E) with GP care. Data from one study suggested that, regarding pain and disability, SMT plus A&E was dominant over GP care , while in the second study SMT plus A&E was cost-effective over GP care alone with an ICER of GBP 3,800/QALY (Michaleff et al., 2012)

It was noted by Lin et al. that considering only direct costs to the health system resulted in lower costs for GP care alone than GP care in combination with other treatments such as physiotherapy. Studies including indirect costs such as loss of earnings and productivity found that total costs were lower when additional treatments were added to GP care (Lin et al., 2011b), highlighting the importance of costing methodologies and study perspective for cost-effectiveness conclusions.

One review cited a single cost-effectiveness study for massage, finding it was more expensive and less effective than GP care from the healthcare system perspective (Lin et al., 2011a).

Seven studies comparing non-operative with operative interventions were also reviewed by Indrakanti et al. Three of four studies reported that operative care was more cost-effective than non-operative in

lumbar disc herniation, while in non-specific lumbar degenerative disorders (such as failed back surgery syndrome) operative care was considered more cost-effective in only two studies (according to NICE threshold of US$45,000 per QALY). The authors note that "*operative versus nonoperative care studies were limited by high rates of patient crossover and poorly defined nonoperative protocols"* and that "*salient differences in the baseline characteristics between the surgical and nonoperative care groups were mentioned in two of the five studies*" (Indrakanti et al., 2012).

Of the treatments not covered by reviews, one study assessed the cost-effectiveness of yoga from a societal and health system perspective. From the health system perspective, adding yoga to usual care was more effective at higher cost, while from a societal perspective, adding yoga to usual care was a dominant intervention. This study was an RCT collecting quality of life and resource use data (Chuang et al., 2012).

One study reported the cost-effectiveness of lumbar support for home care workers, estimated alongside an RCT enrolling 360 participants, for prevention of recurrent LBP. Use of lumbar support resulted in direct cost savings, but indirect cost savings, changes in sick leave and quality of life improvements were not statistically significant, leading the authors to call for additional evidence (Roelofs et al., 2010).

Two studies describe the same RCT of 156 patients where LBP treatment is given according to a modified Delitto classification versus usual physiotherapy care. One of the three classification based treatments consisted of bracing exercises, however no significant differences were seen in costs or effects and the treatment was not considered cost-effective (Apeldoorn et al., 2012).

Main findings:

- Insufficient evidence exists to determine the relative cost-effectiveness of non-operative interventions (exercise therapy/physical therapy, back schools, spinal manipulation and acupuncture) where trends are primarily supported only by single studies.
- Spinal manipulation was found to be cost-effective in three studies which addressed various modalities and combinations: SMT plus GP vs GP alone (two studies), SMT plus GP compared with GP plus exercise (one study), SMT plus advice and exercise compared with GP care (two studies). No studies were identified which evaluated the cost-effectiveness of SMT alone compared to other treatments, further research is indicated in this area.
- The CUA literature for LBP exhibits poor inter-study reliability with no studies evaluating identical interventions or confirming each other's findings, limiting translational value (Indrakanti et al., 2012). In addition, costing perspectives and outcome measures are generally not comparable across studies, further limiting comparability (Lin et al., 2011b,a).
- Evidence for surgical versus non-surgical interventions appears to favor surgery for well-defined conditions (lumbar disc herniation) but not necessarily for non-specific conditions (such as failed back surgery syndrome), however these studies are limited by high cross-over rates and poorly defined non-operative treatment protocols.

- Considering treatment costs from a health care perspective results in GP care being less costly than when additional treatments are added, while inclusion of indirect costs such as loss of productivity and earnings cause GP care alone to become more costly (Lin et al., 2011b), highlighting the importance of costing perspective and inclusion of indirect costs.
- The quality of economic evidence for LBP is not optimal. Approximately half of studies reviewed by Lin et al. did not state the cost perspective and/or did not conduct sensitivity analysis, and only four of 11 studies could be directly compared by ICER (Lin et al., 2011b).
- A single study finds yoga added to usual care is dominant over usual care from a societal perspective
- One study suggest lumbar support is cost-effective for preventing LBP in home care workers but failed to achieve statistical significance in most outcomes

3.3.2.3 Psychological and multi-disciplinary interventions.

In one review, adding cognitive behavioral therapy (CBT) to other interventions was found to be cost-effective in several cases, but only single studies addressed each treatment. CBT was found to be cost-effective when added to inpatient rehabilitation (dominant intervention over inpatient rehabilitation alone); as a CBT pain management programme compared to exercise; and when given in combination with exercise prior to an operant conditioning programme , compared with no intervention ("waiting list") prior to the operant conditioning programme (Lin et al., 2011a). CBT with physiotherapy was also found to be cost-effective over patient advice (Indrakanti et al., 2012).

Main findings:

- Cognitive behavioral therapy is shown to be cost-effective compared with a range of interventions (inpatient rehabilitation alone, exercise, no intervention or patient advice) in a range of single studies addressing unique interventions.

3.3.2.4 Physical modalities

One review covered electrical nerve stimulation as reported in one study for the treatment of failed back surgery syndrome (FBSS), although the review noted "*this study was limited by its crossover randomized controlled trial study design as well as the small number of 40 patients enrolled. A more rigorous study design with a greater number of patients is thus required to confirm and validate the preliminary results obtained*". The study reported spinal cord stimulation (SCS) compared with reoperation was "*cost-effective with a probability of 59% and produced greater cost-utility with a probability of 72% at a willingness- to-pay threshold of $40,000/QALY*" (Indrakanti et al., 2012).

Additionally, two primary studies addressing FBSS were identified. One study, based on a Markov model, found spinal cord stimulation (SCS) dominated "non-surgical conventional medical management" over the lifetime of the patient, but was more costly over a 2-year horizon, discounting costs at 6% and health effects at 1.5%. The authors noted "*In the short-term, although SCS is potentially cost-effective, the model results are highly sensitive to the choice of input parameters. Further empirical data are required to improve the precision in the estimation of short-term cost-effectiveness"* (Taylor & Taylor, 2005). This study was funded by Medtronic, a manufacturer of SCS devices. In a second, more recent

study, 100 patients were randomized to receive "non-surgical conventional medical management" either with or without spinal cord stimulation, but despite evaluating quality of life and health care costs did not report a cost per QALY gained. The study reported that SCS was more effective but more costly than usual care (Manca et al., 2008).

Apart from electrical nerve stimulation, no evidence was identified for physical modalities including: interferential therapy, laser therapy, ultrasound, short-wave diatherapy or traction.

Main findings:

- Two relatively small randomized controlled trials have been carried out (40 and 100 patients) assessing the cost-effectiveness of electric nerve stimulation in failed back surgery syndrome, however the larger study does not report a cost/QALY or similar summary outcome, while the smaller study has methodological limitations. Both studies find SCS to be more effective but more costly than the comparator. Failed back surgery syndrome is estimated to have the same incidence and prevalence as rheumatoid arthritis, and is a specific lumbar pathology which follows unsuccessful surgical attempts to remedy low back pain (Thomson, 2013)
- A Markov model suggests spinal cord stimulation dominates non-surgical usual care over the lifetime horizon, however short-term cost-effectiveness estimates were highly sensitive to model parameters. This study was funded by a manufacturer of SCS devices.
- No evidence was identified for interferential therapy, laser therapy, ultrasound, short-wave diatherapy or traction.

3.3.2.5 Interventional diagnostic procedures

No reviews were identified. One primary study was identified for the cost-effectiveness of facet joint blocks as a diagnostic prior to radiofrequency denervation (Cohen et al., 2010), described in section 3.3.2.7.

3.3.2.6 Injections

No reviews or primary evidence was identified for the use of injections in chronic LBP.

3.3.2.7 Electrothermal and radiofrequency therapies

An RCT protocol with four minimal interventions for LBP was reported in 2012, which included radiofrequency denervation, Intradiscal Electrothermal Therapy (IDET), and combinations thereof. The protocol includes an economic evaluation "*from the societal perspective*" (Maas et al., 2012). The trial is reported to close in July 2015 (NTR, 2014) and no interim reporting was identified.

A trial of 151 patients randomized to three treatment arms studied the cost-effectiveness of diagnostic facet joint blocks prior to radiofrequency denervation (no blocks, single diagnostic block or comparative blocks with lidocaine bupivacaine), finding in favour of radiofrequency denervation without the use of diagnostic blocks. Cost-effectiveness was reported in the form of cost per successful treatment, with no reference to utility values (Cohen et al., 2010).

Main findings:

- A single study from the American perspective found facet joint block diagnostic procedures were not cost-effective in combination with radiofrequency denervation, however no utility data were reported
- One RCT studying cost-effectiveness of IDET and radiofrequency denervation is scheduled to conclude in 2015

3.3.2.8 Surgical treatment

If the specific pathology is known, such as disc herniation, surgery is a viable treatment option. Four studies reviewed by Indrakanti et al. compared operative treatments, all evaluating cost-utility of lumbar fusion. All observations by the review authors were supported by only a single study, and all studies compared different methods of lumbar fusion rather than lumbar fusion versus other surgical interventions (Indrakanti et al., 2012). Surgical interventions compared to non-operative treatments are dealt with in section 3.3.2.2.

Two studies were identified for lumbar disc replacement. One modelling study compared lumbar disc replacement with five methods of lumbar fusion, and found lumbar disc replacement to be less costly than three methods of fusion. The authors concluded "*AIDR is potentially a cost-saving treatment for lumbar disc degeneration, although longer-term follow-up data are required to substantiate this claim. The incremental cost-effectiveness depends on the outcome considered and the comparator, and further research is required before any firm conclusions can be drawn.*" (Parkinson, Goodall & Thavaneswaran, 2013).

An RCT of 152 patients also compared lumbar disc replacement with lumbar fusion, and considered both societal and healthsystem costs over two years. Differences in cost were not significant from a societal perspective, but from a healthsystem perspective were significantly lower for disc replacement. The study found no significant difference in QALY outcomes and therefore the authors did not estimate cost/QALY for the two interventions, noting "It was not possible to state whether TDR or FUS is more cost-effective after 2 years." (Fritzell et al., 2011).

Main findings:

- Studies reviewed by Indrakanti et al. comparing only surgical interventions are limited to four cost-utility analyses of lumbar fusion and do not include other surgical interventions as comparators.
- Two primary studies could not conclusively determine the cost-effectiveness of lumbar disc replacement compared with lumbar fusion

3.3.3 Prevention of lower back pain

Participatory ergonomics

For prevention of LBP, four studies were identified on ergonomic interventions. A discrete event simulation model was described as a tool to evaluate the "investment worthiness" of interventions to prevent LBP in the workplace from the employers perspective. The paper did not describe an economic

evaluation per se, except for a lifting intervention to prevent low back pain as an example of model usage (Hughes & Nelson, 2009).

An RCT of a participative ergonomics programme in the workplace enrolling 37 departments (3,047 workers) was reported (Driessen et al., 2008), and found that health care costs and lost productivity were higher in the intervention group after 12 months. Consequently the programme was not considered cost-effective from a societal perspective, and from the employer perspective the programme resulted in a loss (Driessen et al., 2012).

In contrast, a report of three case studies from the US described the net costs (cost of investment in equipment and labor, avoided costs of lost work time, medical care costs, and productivity improvements) of ergonomic interventions at the company level and found these interventions were cost-saving from a company perspective (Lahiri, Gold & Levenstein, 2005).

Other preventive studies

A retrospective survey study of 1,316 workers performing lifting activities found attending back training programmes was effective in avoiding back injuries, while wearing back belts appeared to be effective at borderline statistical significance. Cost of treatment was reported to be higher when employees were wearing back belts. No cost-utility or cost-effectiveness measures were reported (Mitchell et al., 1994).

A physical therapy programme implemented in the workplace was shown to produce significant benefits in one study, reducing absenteeism and representing a benefit to cost ratio of more than 9 to 1 from the perspective of the employer. The study did not appear to apply discounting over the 10 years examined, and estimated savings based on value of clinical services averted, travel to treatment averted, and savings related to accelerated recovery (Hochanadel & Conrad, 1993).

Main findings:

- Two studies reported conflicting findings on whether preventive ergonomics are cost-saving for companies, with an RCT finding an ergonomic intervention was not cost saving, and a report of three case studies using real-world data suggested the opposite.
- Economic evidence of other interventions did not report cost-effectiveness or applied methodology not consistent with current practices

3.4 Evidence gaps in cost-effectiveness of treatment of low back pain

Observations from published studies:

- The evidence for cost-effectiveness of pharmacological interventions (such as analgesics, muscle relaxants, opioids, steroids, other anti-depressants) for acute and chronic LBP is limited or lacking.
- Two clinical trials show that different forms of early intervention targeted at low back pain can be associated with significant economic benefits. Early intervention can be associated with reductions in both direct and indirect costs, reflecting decreased healthcare utilization and

accelerated return to work. The authors of one study suggest "*lack of a clear definition of the health system's role in the work disability process facilitates both the 'invisibility' of the problem in routine clinical practice and the provision of inadequate or delayed responses*" and that the success of the program was due to a "*simple but profound reengineering of the health care process*" with accelerated return to work as a central element (Abásolo, 2005).

- Evidence on cost-effectiveness of individual conservative treatments such as exercise/physical therapy, back schools, spinal manipulation and acupuncture in acute and chronic LBP is limited, with the majority of conclusions based on single studies.
- There is evidence to suggest that spinal manipulation is cost-effective when used in combination with other treatments e.g. SMT plus GP vs GP alone (two studies), SMT plus GP compared with GP plus exercise (one study), SMT plus advice and exercise compared with GP care (two studies). However, additional studies are required to improve the robustness of these conclusions.
- The inter-study comparability (definition of interventions, costing perspectives) is generally low for economic evaluations of LBP, limiting the generalizability of conclusions from individual studies.
- Evidence for cost-effectiveness of surgical versus non-surgical interventions appears to favor surgery for well-defined conditions (lumbar disc herniation) but not necessarily for non-specific lumbar degenerative disorders (such as failed back surgery syndrome), however these studies are limited by high cross-over rates and poorly defined non-operative treatment protocols.
- The methodological quality of cost-effectiveness studies on LBP tends to be poor, with approximately half of studies in one review not stating the cost perspective and/or conducting sensitivity analysis.
- Adding cognitive behavioral therapy to other interventions appears to be cost-effective, however only single studies support each conclusion.
- Because RCTs have evaluated the effectiveness of many interventions for LBP, publication bias among cost-effectiveness studies is very likely, i.e. the lack of published effectiveness- and cost-effectiveness studies suggests the interventions under evaluation are not effective and consequently no economic evaluations are reported.
- There is evidence that spinal cord stimulation is more effective but more costly than usual non-operative care, however this is based on a small number (40-100) patients enrolled in two studies.
- There is limited evidence on the relative cost-effectiveness of different surgical interventions such as lumbar fusion and lumbar disc replacement. Existing studies compare either different methods of lumbar fusion, or could not conclusively determine the relative cost-effectiveness between lumbar disc replacement and lumbar fusion.
- Evidence on the cost-effectiveness of interventions to prevent LBP (eg. ergonomics, physiotherapy in the workplace) was limited and inconsistent. Only one clinical trial was reported, with other studies using modelling or case study approaches.

Contributor	Comment
Dr. Maurits van Tulder Prof. Health Technology Assessment Director dept. Health Sciences VU University Amsterdam	Sufficient evidence is lacking on cost-effectiveness of treatments and there seems to be publication bias. Only few economic evaluations have been reported, they have methodological weaknesses, and they are often related to trials with a positive outcome. But we know that for most interventions the effects are not so positive. Trials that did not find a positive effect hardly ever report results of an economic evaluation. Even if they have measured cost data, the idea is that it does not make sense to conduct and publish a cost effectiveness study if the RCT did not show a difference in effect. Regarding acute low back pain, the study by Lloyd et al. on heat wrap therapy has a clear conflict of interest and does not seem to have used optimal methods. There is hardly any evidence on cost-effectiveness of pharmacological treatment for acute LBP. There are three or four RCTs on effectiveness of heat wrap therapy, but only one of them included an economic evaluation. The cost-effectiveness of heat wrap therapy can only be analysed if the results of effectiveness of the other three studies are also taken into account. For example, one of the studies shows a similar effect of heat wrap therapy as of exercise therapy for acute LBP. But exercise therapy is not recommended in most clinical guidelines for acute LBP. So there is a lack of robust cost-effectiveness analysis for the treatment of acute LBP which takes all known effectiveness studies into account. Importantly, there are no high quality economic evaluations on interventions for low back pain that are commonly used (exercise, pharmacology, physiotherapy, spinal manipulation, heat wrap), so we do not know at present what the most cost-effective intervention is.
Christine Lin Associate Professor Senior Research Fellow, Musculoskeletal Division The George Institute for Global Health Sydney Australia	It has been argued that the heterogeneous nature of LBP constitutes a limitation to cost-effectiveness studies of LBP, as studies often focus on LBP symptoms rather than a specific lumbar pathology (Indrakanti et al., 2012). However, in LBP research generally non-specific low back pain is considered one entity. Although there are debates about whether this is appropriate, attempts to further sub-group patients with non-specific LBP have not demonstrated a difference in treatment response due to sub-groups. This means that there are no consistent or agreed ways to sub-group people with non-specific LBP. There are specific pathologies that are excluded from the "non-specific" group, but they are serious pathology (e.g. LBP due to tumour, infection, cauda equina) or a few specific groups such as LBP due to pregnancy or patients post-spinal surgery. Otherwise there are no significant specific medical diagnoses to consider. The STarT Back RCT was published in 2011 and examined stratified care, ie. management of patients according to their prognosis (low, medium or high risk). The trial showed that a stratified approach, with matched

	treatment pathways, was more effective in terms of the Roland Morris Disability Questionnaire (RMDQ) and QALY's, and was also less costly than usual care (Hill et al., 2011). A similar trial was recently reported (Foster et al., 2014), showing that risk-stratified care implemented in 64 family physician practices improved RMDQ outcomes, particularly in high-risk patients, reduced time off work by 50% and sickness certifications by 30%. Stratified care was associated with cost savings of GBP 34 and QALY gains of 0.003 per patient. In terms of evidence gaps, I believe we should examine the cost-effectiveness of guideline-recommended treatments as a priority. These are the treatments that are already recommended for clinical use and we have some evidence of clinical effectiveness yet we need to know about their cost-effectiveness to complete the picture. Finally, we know that economic evaluation is sensitive to the underlying healthcare system and perspectives, and a treatment that is cost-effective in one setting may not be in another because of differences in reimbursement system etc. So even when cost-effectiveness evidence exists, it may not be applicable in all country contexts.
Dr Zoe Michaleff Honorary Research Fellow, Musculoskeletal Division The George Institute for Global Health Sydney Australia	Identifying the cost-effectiveness of guideline recommended treatments is arguably as important as effectiveness in order to optimize health care decisions and the allocation of scarce resources. In order to improve the strengths of recommendations there is a need for more high quality economic evaluations to be conducted alongside trials of effectiveness and for these to consider a variety of health care systems and perspectives. This evidence then needs to be incorporated into clinical practice guidelines as the most effective treatment or the least costly treatment may not always be the most cost-effective treatment.

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Health Economic Evidence Analysis: Treatment of Stroke

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4 Stroke

4.1 Bibliometrics

A total of 110 economic studies were mapped to the clinical model for stroke (Table 4.1 and Figure 4.1) with the majority[1] of studies published since 2006. Of the 20 reviews identified, seven were published between 2009 and 2014.

Table 4.1 Bibliometric data for stroke (ischemic and hemorrhagic)

PubMed/MEDLINE	
Search term	"Stroke"[MeSH Terms] ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	110
Included as "other"	69
Reviews	20
Excluded	262
Total	461
Additional studies suggested by reviewers	
Total	6

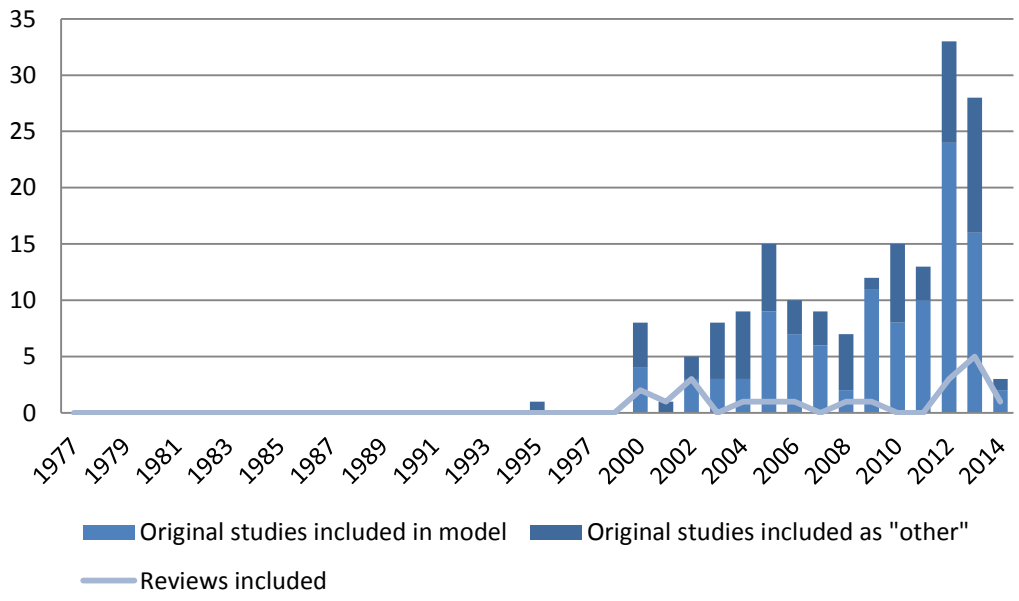

Figure 4.1 Bibliometric data for stroke by year

[1] 75% of studies or more

4.2 Review coverage

The clinical model for ischemic stroke consists of 52 treatment modalities. Of these, three treatments (6%) were addressed by one of the seven reviews published between 2009 and 2014 (Table 4.2). The remaining 49 treatments (94%) were not associated with any health economic reviews, though primary studies were available in several cases (described in sections 4.3.1 to 4.3.6).

Table 4.2 Table of reviews for stroke and associated treatments

Title and reference	Year	Treatments covered
"*Novel anticoagulants for stroke prevention in atrial fibrillation: a systematic review of cost-effectiveness models*" (Limone et al., 2013)	2013	Stroke prevention in atrial fibrillation patients
"*Stop the clots, but at what cost? Pharmacoeconomics of dabigatran etexilate for the prevention of stroke in subjects with atrial fibrillation: a systematic literature review*" (Marshall et al., 2013)	2013	Stroke prevention in atrial fibrillation patients
"*Cost effectiveness of treatments for stroke prevention in atrial fibrillation: focus on the novel oral anticoagulants*" (Kasmeridis et al., 2013)	2013	Stroke prevention in atrial fibrillation patients
"*Review of economics and cost-effectiveness analyses of anticoagulant therapy for stroke prevention in atrial fibrillation in the US*" (von Schéele et al., 2013)	2013	Stroke prevention in atrial fibrillation patients
"*Is dabigatran considered a cost-effective alternative to warfarin treatment: a review of current economic evaluations worldwide*" (Hesselbjerg et al., 2013)	2013	Stroke prevention in atrial fibrillation patients
"*Cost-effectiveness of endovascular therapy for acute ischemic stroke"* (Chen, 2012)	2012	Mechanical endovascular therapies for acute ischemic stroke
"*Cost-effectiveness of pharmacologic and invasive therapies for stroke prophylaxis in atrial fibrillation*" (Solomon et al., 2012)	2012	Stroke prevention in atrial fibrillation patients
"*Cost-effectiveness of stroke treatments and secondary preventions*" (Pan, Hernandez & Ward, 2012)	2012	Cost-effectiveness evaluations of medical treatments for acute stroke and long-term secondary prevention
"*Model-based cost-effectiveness analyses for the treatment of acute stroke events: a review and summary of challenges*" (Earnshaw et al., 2009b)	2009	Cost-effectiveness evaluations of medical treatments for acute stroke

4.3 Evidence analysis: ischemic stroke

The following sections present information gathered from recent (2009-2014) reviews when available, and from essential information on primary evidence where no reviews are available. Generally, the majority (six out of nine) of recent reviews considered only the use of pharmaceuticals for the prevention of stroke in atrial fibrillation patients (Table 4.2).

Table 4.3 Economic evidence for the management of acute stroke, post-acute care and prevention of recurrence

Acute and post-acute medical care	Studies	Reviews
Acute medical care		
Maintain blood oxygen levels - O2	0	0
Maintain intravascular volume (IV fluids)	0	0
Manage hyperglycemia	0	0
Blood pressure control if eligible for thrombolytic therapy target <185/110, if not eligible for thrombolytic only treat if >220/120. Agents: labetalol, nicardipine, nitroprusside	0	0
Maintain cerebral blood flow (keep head of bed flat for first 24 hours)	0	0
Maintain normal body temperature (acetaminophen)	0	0
DVT prevention: Intermittent pneumatic compression, aspirin, graduated compression stockings	1	0
Prevention of pneumonia: assessment of dysphagia, and adjust diet/position accordingly	1	0
Anti-platelet – Aspirin	0	0
IV thrombolytic therapy if meets eligibility and timing criteria: alteplase / tPA	14	3
Post-Acute Care / Prevention of Recurrence		
Hypertension: goal <140/90 more than 24H after symptom onset, non-pharmacological management (salt restriction, DASH diet, weight loss, exercise, decreased alcohol intake) or pharmacological (ACE-inhibitors, and/or Ca channel blockers)	4	0
Lifestyle Modifications: limited alcohol consumption, weight control, regular aerobic physical activity, salt restriction, and a diet that is rich in fruits, vegetables, and low-fat dairy products	0	0
Diabetes Mellitus: improved glycemic control through both pharmacological and non-pharmacological therapies	0	0
Smoking Cessation: behavioral counseling, pharmacology (bupropion, or varenicline), financial incentives	0	0
Dyslipidemia: Statins	1	0
Long-term antiplatelet therapy (aspirin, clopidogrel, dipyridamole, aspirin plus dipyridamole, Ticlopidine, Cilostazol, Triflusal, clopidogrel plus aspirin)	9	1

4.3.1 Acute medical care

The economic evidence for acute medical care was limited across most interventions, specifically for basic interventions during or shortly after the acute incident (maintaining blood oxygen, intravascular volume, managing blood pressure, body temperature and maintaining cerebral blood flow).

4.3.1.1 Prevention of deep vein thrombosis

A single primary study was identified for deep vein thrombosis (DVT) prevention, reporting a study protocol for a clinical trial of intermittent pneumatic compression (IPC) in immobile stroke patients. The study recruited 2,800 patients over 80 centres, and included quality of life (EQ-5D) as an outcome. Clinical results have been reported, showing intermittent pneumatic compression to be clinically effective in reducing the risk of DVT (Dennis et al., 2012, 2013). In a subsequent economic analysis, the direct costs of preventing a DVT and death were GBP 1,282 and GBP 2,756 respectively. Quality-adjusted survival with IPC was non-significantly higher than in the no-IPC group (CLOTS, 2014)

Main findings:

- A clinical trial has reported intermittent pneumatic compression to be effective in reducing the risk of DVT. An economic analysis is pending.

4.3.1.2 Prevention of pneumonia

One primary study addressed the management of dysphagia, which can be associated with aspiration pneumonia. This study modelled cost-effectiveness from a societal perspective of two screening strategies to identify dysphagia, finding videofluoroscopic examination more effective in terms of QALY's and less costly than a bedside swallowing evaluation or combination of the two (Wilson & Howe, 2012). In addition, two studies are discussed under prevention of pneumonia in the rehabilitation setting in section 4.3.6.1.

In addition, an ongoing pilot stepped wedge cluster RCT of enhanced oral health care in stroke care settings (SOCLE II) is in final stages of recruitment (current numbers of patient participants n=294) where primary outcome is pneumonia and health economic data is being collected as secondary outcome (NCT01954212, Brady et al, *personal communication*).

Main findings:

- A single modelling study found videofluroscopic examination to dominate a bedside swallowing evaluation in the assessment of dysphagia for prevention of pneumonia.
- A clinical trial is recruiting patients for a study of enhanced oral health care in stroke care for the prevention of pneumonia, which will collect health economic data.

4.3.1.3 Antiplatelets

No economic evidence was identified on the use of antiplatelets (aspirin) in acute stroke.

4.3.1.4 Thrombolytic therapy

Fourteen primary studies and three reviews covered the use of thrombolytic therapy in acute stroke. One review included MEDLINE indexed studies between 1990 and 2007 on the treatment of acute

stroke events, identifying 13 relevant studies, of which four were identified in the present search (Earnshaw et al., 2009b). The most recent review cited the same studies as Earnshaw et al, plus one additional study from 2010 which was not identified in the present search (Pan, Hernandez & Ward, 2012). The remaining 10 primary studies identified in the present search were published between 2007 and 2013 and are not covered by any reviews. The second review addressed costs and benefits of mechanical endovascular therapies, but only reviewed one cost-effectiveness model which was also identified in the present search (Chen, 2012). Consequently this review is not discussed further.

In the by Earnshaw et al., nine studies assessed the use of tPA against usual care, aspirin or placebo. tPA was the dominant intervention in seven studies, one study noted tPA was only dominant if a societal perspective was taken and otherwise cost EUR 2,733-2,841 per QALY when societal costs were excluded. One study noted the incremental cost was US$ 55,591/QALY over the first year, but that tPA was dominant over longer time horizons of 3-30 years (Earnshaw et al., 2009b). In the additional study reviewed by Pan et al. tPA was dominant, saving US$ 6,074 and adding 0.75 QALYs from the US societal perspective (Pan, Hernandez & Ward, 2012)

Of the additional ten recent primary studies identified in the present search, six assessed tPA in acute stroke. An Australian model of tPA within 4.5 hours of acute stroke cost AU$ 1,478/QALY gained (Tan Tanny et al., 2013). An American intervention to increase the number of acute stroke patients treated with thrombolysis resulted in an increased thrombolysis rate (44.3% vs 39.8% of patients) which increased lifetime QALY's and decreased lifetime costs (Dirks et al., 2012). The cost-effectiveness of tPA versus no treatment administered 3-4.5 hours after acute stroke was cost-saving for patients under 65 years, but cost US$ 35,813/QALY for patients aged 65+ based on a modelling study of lifetime costs from the payer perspective (Boudreau et al., 2013). Without considering subgroups by age, stroke severity etc. a similar study found tPA within 3-4.5 hours to be cost-effective at US$ 21,978/QALY (Tung, Win & Lansberg, 2011). Administered within 3 hours of acute stroke, alteplase was found to be cost-effective in the Brazilian setting at US$ 26,171-28,956/QALY considering both direct and indirect costs (Araújo et al., 2010). An economic appraisal for the UK NHS found alteplase (a recombinant tPA) was either cost-saving or cost less than GBP 10,000/QALY when administered within 4.5 hours of acute stroke (Chung et al., 2007; NICE, 2012)[2]

Four studies assessed non-tPA interventions. For stroke patients receiving treatment after 3 hours, mechanical thrombectomy was shown to cost US$ 12,120/QALY according to a modelling study including costs of care and rehospitalisations following the stroke event (Patil, Long & Lansberg, 2009). A similar study reported an ICER of US$ 9,386/QALY (Nguyen-Huynh & Johnston, 2011). Mechanical thrombectomy was also considered as an adjuvant to intravenous tPA. This modelling study from the US payer perspective estimated a lifetime ICER of US$ 16,001/QALY (Kim, Nguyen-Huynh & Johnston, 2011). Using penumbral-based MRI versus computerized tomography (CT) in selecting patients for intravenous tPA treatment was associated with marginally improved outcomes at US$ 1,840/QALY over a lifetime perspective (Earnshaw et al., 2009a).

[2] The study by Chung et al. referred to NICE Technical Appraisal 122, which was subsequently updated and replaced with TA 264. The latter (NICE, 2012) was therefore used for the present review.

Commenting on the economic evidence for acute stroke treatment, Pan et al. note "*Most of the published cost-effectiveness studies on acute stroke treatments are conducted for lifetime. Poststroke disease progressions, transitions of disability status and longterm mortality risks are the keys to the models. Some models assume patients achieve a stable health status at the end of short-term phase. Others allow patients to transit from one disability status to another, combining assumptions with some evidence from observed studies or expert panel. Lack of long-term outcome data and longterm resource use and cost data add tremendous uncertainty to the cost-effectiveness stories of the acute stroke treatments*" (Pan, Hernandez & Ward, 2012)

Main findings:

- Use of tPA in acute stroke was cost-saving in the majority of studies from 1990-2007 reviewed by Earnshaw et al. Evidence from more recent studies suggest patient subgroups can exhibit widely varying cost-effectiveness levels, but overall support conclusions from earlier work.
- Three studies suggest mechanical thrombectomy is cost-effective for patients receiving treatment 3 hours or more after the stroke event or as an adjuvant to intravenous tPA; and a single study that use of MRI over CT in selecting patients for intravenous tPA is cost-effective.
- The lack of long-term effectiveness and resource use data is a significant source of uncertainty in the present models

4.3.2 Post-acute care and prevention of recurrence

No economic evidence was identified for interventions consisting of lifestyle modifications or smoking cessation, and similarly no evidence was identified for stroke prevention in diabetics.

4.3.2.1 Hypertension management

No reviews were identified for hypertension management in prevention of recurrence in stroke patients. Four primary studies were identified, considering various pharmaceuticals for secondary prevention of stroke. In Australia, two strategies were analysed (ACE-inhibitors plus diuretic or any antihypertensive), which were both found to be cost-effective at AU$ 4,704 and AU$ 1,811 respectively, ranging from cost-saving to AU$ 8-10,000 in the 95% confidence interval (Cadilhac et al., 2012). Using perindopril was cost-effective at GBP 10,133 over a 20-year period compared to standard care in the UK (Tavakoli et al., 2009).

A model of eprosartan compared to nitrendipine across a range of European countries showed eprosartan was either cost-saving (Spain, Belgium) or cost-effective (Germany, UK, Norway, Sweden) in the range EUR 907 to 9,136 per QALY (Schwander et al., 2009). Eprosartan was also modelled in the South African context, and was found to be cost-saving compared with amlodipine and perindopril considering direct costs only (Wessels, 2007).

Main findings:

- Four studies evaluated different pharmaceuticals and comparators in secondary stroke prevention. Generally, secondary prevention was cost-saving or cost-effective, depending on the country of analysis and the comparators used.

4.3.2.2 Dyslipidemia

A single primary study was identified on the management of dyslipidemia in the prevention of recurrent stroke. The study was based on results from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial and was a discrete event simulation model examining atorvastatin against usual care. Increased pharmaceutical costs slightly outpaced reduced healthcare expenditures, resulting in an incremental cost of US$ 13,916 per QALY gained from the health system perspective (Kongnakorn et al., 2009).

Main findings:

- A single modelling study based on a clinical trial suggested atorvastatin was cost-effective from the healthsystem perspective in the prevention of recurrent stroke

4.3.2.3 Long-term antiplatelet therapy

One review addressed antiplatelet therapy in the prevention of stroke recurrence (Pan, Hernandez & Ward, 2012). Nine primary studies were identified, addressing largely different pharmaceuticals for secondary prevention of stroke. The review by Pan et al. included 14 studies, of which four were identified in the present search

One study specifically examined stroke prevention in atrial fibrillation patients with prior stroke or transient ischemic attack. Dabigatran was compared against warfarin and found to be cost-effective at US$ 25,000 per QALY gained, however the cost-effectiveness of dabigatran was worse when control of warfarin therapy was better (Kamel et al., 2012).

For secondary stroke prevention, five studies assessed aspirin, dipyridamole and/or clopidogrel. One modelling study compared aspirin, extended release dipyridamole/aspirin and clopidogrel against placebo. Aspirin was found to be cost-effective due to its low cost, while dipyridamole/aspirin was both more effective and more costly, while clopidogrel was dominated. The authors conclude that aspirin and dipyridamole/aspirin are both cost-effective while clopidogrel was rarely preferred in the sensitivity analysis (Matchar, Samsa & Liu, 2005). Similar results were previously reported in the UK, where aspirin was compared with dipyridamole/aspirin. Over five years the coformulation was more effective than aspirin but at higher cost, though the ICER of any treatment did not exceed GBP 11,000/QALY in the sensitivity analysis (Chambers, Hutton & Gladman, 1999). A third modelling study found dipyridamole/aspirin dominated aspirin alone, while clopidogrel was associated with an ICER of US$ 26,580/QALY over aspirin (Sarasin, Gaspoz & Bounameaux, 2000), and similar results were reported from France from the social security perspective, though the dipyridamole/aspirin combination was only cost-saving in the lower end of the 95% CI (Marissal & Selke, 2004). In the US from the payer perspective, dipyridamole/aspirin was cost-effective over aspirin at US$ 28,472 while clopidogrel incurred US$ 161,316 per stroke averted (Shah & Gondek, 2000). Aspirin alone (lysine acetylsalicylate) was assessed against placebo in a French modelling study from the social security perspective. In patients with prior ischemic stroke, lysine acetylsalicylate was a cost-saving intervention with net benefit of US$ 176-599 per avoided stroke (Marissal, Selke & Lebrun, 2000).

Two studies assessed other pharmaceuticals in secondary stroke prevention. One alternative antiplatelet, cilostazol, was found to be more effective and more costly than aspirin in Japan, incurring Yen 1,800,000 (approx. EUR 13,000) per QALY. In the Japanese setting, edaravone (a free radical scavenger) was compared to ozagrel sodium (an antiplatelet) for prevention of recurrent stroke. From a healthcare payer perspective, including nursing care, edaravone was found to dominate ozagrel sodium (Shinohara & Inoue, 2013).

The review by Pan et al. summarises the economic evidence as follows:

Aspirin vs no treatment: two studies find aspirin is dominant or incurs an ICER of US$ 1,725/QALY

Aspirin+extended release dipyridamole vs aspirin alone: combination treatment could be cost-effective or cost-saving in some scenarios (6 studies), ranging from dominance to US$ 28,472/QALY.

Clopidogrel: all economic evaluations at the time of writing used the on-patent price of clopidogrel. Following patent expiry, Pan et al. note that NICE in the UK updated its guidance to recommend clopidogrel as the first line therapy for secondary stroke prevention.

Main findings:

- In atrial fibrillation patients with previous stroke or TIA, dabigatran was considered cost-effective over warfarin at US$25,000/QALY but less so with better warfarin management
- Comparing aspirin, dipyridamole/aspirin and clopidogrel, five primary studies generally find the dipyridamole/aspirin to be cost-effective and in some cases cost-saving. Clopidogrel was generally not found to be cost-effective against aspirin in two out of three studies, however this situation is likely to have changed since the availability of generic clopidogrel
- For the use of alternative antiplatelets (eg. cilostazol) or drugs with other mechanisms of action (eg. edaravone) the present search revealed very limited economic evidence.

4.3.3 Prevention of recurrence and treatment of contributing vascular disease

The economic evidence identified for prevention of recurrence and treatment of contributing vascular disease, cardiac disease and blood disorders is given in Table 4.4. No economic evidence was identified for the management of cerebral/cervical artery dissection; carotid siphon, middle cerebral artery, vertebral artery, or basilar artery stenosis; small vessel disease (lacunar); or extracranial vertebral artery stenosis.

4.3.3.1 Carotid stenosis

No reviews were identified for the management of carotid stenosis in stroke patients, though 11 primary studies were identified, mostly on the cost-effectiveness of carotid stenting and/or endarterectomy.

In patients with symptomatic occlusion prior to stroke, an extracranial-to-intracranial (EC/IC) arterial bypass can be considered according to oxygen extraction fraction (OEF) results detected by PET scanning. A US modelling study assessed cost-effectiveness of PET scanning followed by EC/IC if indicated, and found that EC/IC bypass on 36 out of 45 patients yielded an additional 23.2 QALY's at US$

20,000 per QALY, compared with medical therapy alone. More restrictive diagnostic criteria, in which only half the patients were treated, yielded 22.6 QALY's at lower cost than medical therapy. PET followed by EC/IC in patients with increased OEF was therefore considered cost-effective (Derdeyn et al., 2000).

Eight studies assessed carotid endarterectomy (CEA) or carotid artery stenting (CAS). In an early US modelling study, CEA was compared against medical treatment (aspirin) over a lifetime horizon. CEA was found to increase survival by 0.13 QALYs at a lifetime cost of US$ 580, resulting in an ICER of US$ 4,462/QALY (Patel et al., 1999).

Subsequently CAS was considered against CEA. An economic evaluation from the perspective of the US healthcare system (hospital costs only) was performed alongside the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) trial, projecting 10-year costs and outcomes based on the first year of follow-up. The study found carotid endarterectomy (CEA) to be slightly less costly and yield slightly decreased rates of stroke over carotid artery stenting (CAS), however the relative cost-effectiveness did not differ greatly (Vilain et al., 2012). In patients with moderate to severe carotid stenosis, the ICER for CAS over CEA was US$ 229,429 based on the same trial results (Khan et al., 2012). In both studies, patients studied were at average surgical risk. In patients at increased surgical risk, also in the US setting, a separate clinical trial (SAPPHIRE) reported CAS hospital costs were only slightly higher than for CEA, and associated with an ICER of only US$ 6,555 per QALY gained (Mahoney et al., 2011). A model also based on the SAPPHIRE clinical trial, from the US perspective, found CAS to be associated with an ICER of US$ 67,891 over CEA (Maud et al., 2010).

One modelling study from the US perspective found CAS yielded fewer QALY's at higher cost than CEA (Young et al., 2010). A retrospective study of US hospital admissions also found treatment costs were significantly higher for CAS, but survival at 30-days or length of stay were not significantly different between the two treatments (Sternbergh et al., 2012).

A clinical trial in Argentina compared drug eluting stents (DES) with oral rapamycin plus bare metal stents (OR/BMS). The study found differences in the composite of death, myocardial infarction and stroke of 11% on OR/BMS vs 20% in DES, but the difference was not significant. Costs were significantly lower in the OR/BMS group, and the authors conclude DES was not more cost-effective than OR/BMS (Rodriguez et al., 2012).

The use of general or local anesthesia for CEA was modelled in the UK setting, with the outcome of cost per event-free day over 30 days. The study found local anesthesia cost less (GBP 178) than general anesthesia and resulted in slightly but insignificantly more event-free days. Local anesthesia was considered cost-effective when indicated (Gomes et al., 2010)

Following CEA, Doppler ultrasound (duplex) can be used to detect recurrent stenosis. A modelling study from the Dutch and US perspectives found routine screening did not yield improved outcomes. Symptom-guided screening was therefore considered to be the appropriate approach (Post et al., 2002).

- The majority of studies in this area consider hospital costs from the US perspective.

- PET scanning for cerebral oxygen extraction fraction, followed by potential EC/IC bypass, was cost-effective or cost-saving compared with medical treatment in patients with symptomatic occlusion prior to stroke, evidenced by a single study
- Overall, CAS appears to be more costly than CEA but can yield marginally improved outcomes, although in two studies CEA was found to dominate CAS. In patients with high surgical risk, CAS appears more cost-effective than in patients with average risk.
- A single study showed drug eluting stents are not more cost-effective than bare metal stents plus oral rapamycin
- Following CEA, a single study considered Doppler ultrasound (duplex) scanning to be cost-effective only when provided after symptoms appeared, and not as a routine screening.
- A single study reported local anesthesia to be more cost-effective than general anesthesia in the UK for CEA

Table 4.4 Prevention of stroke recurrence and treatment of contributing diseases

Prevention of Recurrence and Treatment of Contributing Disease	studies	reviews
Prevention of Recurrence and Treatment of Contributing Vascular Disease		
Carotid Stenosis	11	0
Cerebral or cervical artery dissection	0	0
Carotid siphon, middle cerebral artery, vertebral artery, or basilar artery stenosis	0	0
Small vessel disease (lacunar)	0	0
Extracranial vertebral artery stenosis	0	0
Prevention of Recurrence and Treatment of Contributing Cardiac Diseases Present		
Atrial fibrillation	39	6
MI and left ventricular thrombus	0	0
Heart failure due to left ventricular systolic dysfunction with sinus rhythm	4	0
Endocarditis	1	0
Rheumatic mitral valve disease	0	0
Mitral valve prolapse, mitral annular calcification, native aortic, or non-rheumatic mitral valve disease in patients who do not have atrial fibrillation	0	0
Aortic atheroma and thromboembolism	0	0
Patent foramen ovale, atrial septal aneurysm	0	0
Prevention of Recurrence and Treatment of Contributing Blood Disorders		
Antiphospholipid antibody syndrome	0	0
Sickle Cell Disease	1	0

4.3.4 Prevention of recurrence and treatment of contributing cardiac diseases

The economic evidence identified for the management of cardiac diseases associated with stroke is given in Table 4.4. No economic evidence was identified for myocardial infarction and left ventricular thrombus; rheumatic mitral valve disease; Mitral valve prolapse, mitral annular calcification, native aortic or non-rheumatic mitral valve disease in patients who do not have atrial fibrillation; aortic atheroma and thromboembolism; or patent foramen ovale and atrial septal aneurysm.

4.3.4.1 Atrial fibrillation

Atrial fibrillation was the most well studied aspect of stroke management, with six reviews and 39 primary studies identified. Reviews considered the cost-effectiveness of dabigatran, rivaroxaban and apixaban, which are considered the "Novel Oral Anticoagulants", usually against warfarin. The most recent review included studies published between 2004 and June 2013 (Kasmeridis et al., 2013).

Kasmeridis et. al. reviewed nine studies of dabigatran vs warfarin. In most cases the QALY gain over warfarin was relatively small (10.70 vs. 10.28, 8.54 vs 8.40, 6.82 vs 6.68 etc) and the cost of treatment was slightly higher in dabigatran. Despite warfarin being a generic drug, additional costs are associated with treatment monitoring to keep patients within a defined coagulation range. Consequently, the ICER's for dabigatran (150mg dose) against warfarin are in the range of US$ 25,000-86,000/QALY in the US, CA$ 9,041/QALY in Canada, and EUR 2,807 to approx. EUR 30,000/QALY in European countries. The ICER also depends on the quality of existing warfarin monitoring, with poor monitoring (worse health outcomes) associated with improved ICER's for dabigatran. The perspective differed across included studies (societal, Medicare, payer, NHS) and studies were based on varying population groups, including different risk characteristics ($CHADS_2$ score, age, prior stroke, etc) (Kasmeridis et al., 2013).

These authors also reviewed three studies of rivaroxaban or apixaban compared to warfarin. As with dabigatran, the QALY gains were relative modest (10.03 vs 9.81, 11.16 vs 10.69, 4.19 vs 3.91), and prices were slightly higher in two cases and in one case lower for apixaban than for warfarin. ICER's were in the range of US$11,400 to US$ 27,498 in two studies, while in the third study apixaban dominated warfarin. All three studies were in the American setting, two from Medicate and one from a societal perspective. As with dabigatran, the study populations differed by risk characteristics. All studies were Markov models (Kasmeridis et al., 2013).

The authors caution that "*only one major trial compared each new drug with warfarin and no trials have compared any of the new oral anticoagulants with each other*" and note that effectiveness data in modelling studies are based on clinical trials and not real world outcomes (Kasmeridis et al., 2013).

Conclusions from other reviews are largely similar. Limone et al. searched for studies published between January 2008 and October 2012 and included in total 18 studies, consisting of all studies reviewed by Kasmeridis et al. and an additional 6 studies. These authors conclude six of eight models found dabigatran 150mg to be cost-effective and three of seven found dabigatran 110mg to be cost-effective against warfarin. They note "*one of the challenges in attempting to evaluate the comparative cost-effectiveness of newer oral anticoagulants is the difficulty in making cross-model comparisons. This is likely true in the case of these newer SPAF models, even though a majority of them used the basic and*

common structures of Gage or Sorensen. This is because the models had some differences in health states included, made different assumptions and used varying inputs" and further that "*In some instances, similar models were performed from the perspective of varying countries, this was necessary in order to not only address differences in costs, discount rates and average life spans (life tables), but also to address the varying approved dosing schemes from country-to-country*" (Limone et al., 2013).

Limone et al. caution that studies using indirect comparison between newer anticoagulants, which are all studied clinically against warfarin, are likely to be misleading due to significant differences in the underlying trials: "*The ROCKET-AF trial enrolled patients at higher baseline ischemic stroke risk than the RE-LY or ARISTOTLE trials, with mean CHADS2 scores of 3.5, 2.1, and 2.1, respectively. In addition, the quality of warfarin dosing was not consistent across studies with patients spending less time within the therapeutic INR range in ROCKET-AF (55%) versus either RE-LY (64%) or ARISTOTLE (62%). In fact, methodological guidance documents would suggest this may be an inappropriate situation for indirect comparison due to the lack of comparability/heterogeneity of the trials to be pooled*" (Limone et al., 2013).

Marshall et al., reviewing six of the same references as above, note concerns around the use of the RE-LY trial as the sole source of efficacy data for these six studies. On the modeling side, the authors state that warfarin prescription is not universal or comprehensive in moderate-to-high risk cohorts, and that "*assuming that some subjects who are warfarin ineligible may be prescribed dabigatran, the authors would have preferred greater use of models that use a mixed comparator of warfarin/antiplatelet/no therapy*" (Marshall et al., 2013).

Ten primary studies identified in the present search assessed stroke prevention in atrial fibrilliation with interventions other than dabigatran, rivaroxaban or apixaban. Four studies assessed pharmacogenetic testing to guide therapy choice. Stratifying patients according to warfarin sensitivity was associated with an ICER of US$ 2,843/QALY from the US payer perspective (You, 2014), and in the UK an ICER of GBP 13,226/QALY was reported against usual warfarin therapy (Pink et al., 2014). An earlier study, assuming a genotyping cost of US$ 400-550, reported "*the cost-effectiveness of genetically-guided dosing was highly dependent on the assumed effectiveness of genotyping in increasing the amount of time patients spend appropriately anticoagulated. If genotyping increases the time spent in the target international normalized ratio range by <5 percentage points, its incremental cost-effectiveness ratio would be greater than $100,000 per quality-adjusted life year. The incremental cost-effectiveness ratio falls below $50,000 per quality-adjusted life year if genotyping increases the time spent in range by 9 percentage points*" (Patrick, Avorn & Choudhry, 2009). Genotyping was also found to be potentially cost-effective in elderly patients, due to reductions in bleeding-associated costs (Leey et al., 2009).

Five studies assessed other pharmaceuticals than the novel oral anticoagulants. Ximelagatran and warfarin were found to both cost more than US$50,000 per QALY over aspirin in patients with no additional risk factors (O'Brien & Gage, 2005), however ximelagatran was subsequently withdrawn from the market due to liver toxicity. Dronedarone was modelled against usual care in the setting of Canada, Italy, Sweden and Switzerland, resulting in ICER's of EUR 5,828 to EUR 14,970 per QALY (Åkerborg et al., 2012). Finally clopidogrel plus aspirin was assessed against aspirin alone from the US Medicare

perspective, yielding an ICER of US$ 26,928 per QALY (Coleman et al., 2012). Comparison of warfarin with aspirin over four years of follow-up found warfarin incurred lower total costs and marginally more QALY's gained, though the authors note "*the small differences in costs and effects indicate the importance of exploring patient preferences*" (Jowett et al., 2011). An American study modelled the impact of providing specific anticoagulation management services for elderly warfarin patients, which both improved QALY's gained and lowered costs (Sullivan et al., 2006).

Main findings:

- Dabigatran, rivaroxaban and apixaban are considered cost-effective across a range of studies with varying assumptions. Six of eight models found dabigatran 150mg to be cost-effective and three of seven found dabigatran 110mg to be cost-effective against warfarin
- Variations in the modelling approaches were observed across studies, and thus results should be interpreted and generalized with caution
- To date, there is no clinical evidence for the head to head efficacy of the newer anticoagulants, rather they are all compared individually with warfarin, in trials that are not amenable to indirect comparison
- Various strategies may improve the cost-effectiveness of warfarin treatment: Pharmacogenetic testing appears to be a cost-effective intervention, evidenced by four studies, however this finding is sensitive to the magnitude of clinical improvement in coagulation control and has only been tested against usual warfarin treatment, not aspirin or the novel oral anticoagulants. One study suggests coagulation control can also be improved with specialized services.

4.3.4.2 Heart failure due to left ventricular systolic dysfunction with sinus rhythm

Four primary studies were identified on the topic of left ventricular hypertrophy (LVH), all assessing the cost-effectiveness of losartan against atenolol for the reduction of hypertension in these patients and prevention of stroke. Using data from the Losartan Intervention For Endpoint reduction (LIFE) clinical trial, a Dutch model from the perspective of the healthcare system extrapolated trial data over the lifetime of LVH patients, and found a cost per life-year gained (LYG) of EUR 864 (Boersma et al., 2007). A similar model from the Canadian societal perspective, estimating an ICER of CA$ 1,337 (Anis et al., 2006). From the UK NHS perspective, it was GBP 2,130/QALY (McInnes, Burke & Carides, 2006) and from the Swedish national health system perspective EUR 4,188/QALY (Jönsson et al., 2005).

Main findings:

- Four modelling studies were based on the LIFE clinical trial, and all showed a favorable cost-effectiveness ratio of less than EUR 5,000/QALY gained

4.3.4.3 Endocarditis

A single primary study was identified on echocardiographic diagnosis of infective endocarditis. This US model compared surgery for high-risk patients determined either by echocardiography or usual clinical practice. The ICER for echocardiography was US$ 23,867/QALY, and varied with the risk of stroke. Between stroke risk of 3.65% to 14% the ICER remained under US$ 50,000/QALY (Liao et al., 2008).

- Echocardiography is cost-effective in identifying high-risk endocarditis patients for early surgery, as evidenced by a single study

4.3.5 Prevention of recurrence and treatment of contributing blood disorders

No economic evidence was identified for the management of antiphospholipid antibody syndrome.

4.3.5.1 Sickle cell disease

A single primary study was identified on the management of sickle cell disease (SCD). This study searched for economic evidence on the primary prevention of stroke in children with SCD, who were at high risk of stroke according to Transcranial Doppler (TCD) ultrasonography. The authors found no existing economic evidence, but developed a model for the cost-effectiveness of TCD ultrasound followed by blood transfusion when clinically appropriate. This was found to be cost-effective at GBP 24,075 per QALY gained. The authors note that "*the main limitations relate to the availability of published clinical data; no completed randomised controlled trials were identified which evaluated the efficacy of either bone marrow transplantation or hydroxycarbamide for primary stroke prevention*", which are two other clinical interventions in routine use in the UK for stroke prevention in SCD.

Main findings:

- The economic evidence for stroke prevention in children with sickle cell disease is severely limited. A single study indicated blood transfusion could be cost-effective in high risk children, but this was based on both limited clinical and cost data.

4.3.6 Rehabilitation

Table 4.5 summarises the economic evidence on stroke rehabilitation. No economic evidence was identified for the use of assistive devices; mobility aids; bathroom and self-care aids; environmental modifications; pharmaco- or psychotherapy for depression; dietary modifications for dysphagia; urinary tract infection associated with bladder catheter; prevention of falls and broken bones; or sexual dysfunction.

4.3.6.1 Prevention of pneumonia associated with dysphagia

A single primary study was identified on the prevention of pneumonia associated with dysphagia, which was also described in section 4.3.1.2 above. Briefly, the found videofluoroscopic examination was more effective in terms of QALY's and less costly than a bedside swallowing evaluation or combination of the two (Wilson & Howe, 2012).

In addition, two clinical trials are ongoing, both assessing the use of antibiotics to prevent pneumonia. One is addressing the clinical and cost-effectiveness of preventive antibiotics in stroke patients with difficulty swallowing, as opposed to treatment of incident infections , with incidence of infection, mortality, side effects and participation in rehabilitation as outcomes (Kalra, 2008). The second trial is assessing the effect of preventive antibiotics on functional outcomes measured by the modified Rankin Scale, as well as mortality, incidence if infection, length of stay, volume of post-stroke care and other outcomes. Swallowing difficulties were not part of the inclusion criteria for this study (Westendorp et al., 2014).

The clinical trial discussed in section 4.3.1.2 (SOCLE II), while not specific to people with dysphagia, applies to all stroke admissions, including people with dysphagia.

Main findings:

- A single modelling study found videofluroscopic examination to dominate a bedside swallowing evaluation in the assessment of dysphagia for prevention of pneumonia.
- Two ongoing clinical trials with cost-effectiveness components are assessing the clinical and economic benefits of antibiotics in the prevention of pneumonia in stroke patients.

Table 4.5 Economic evidence for rehabilitation

Rehabilitation	Studies	Reviews
Prevention of Pneumonia associated with dysphagia	1	0
Exercise	2	0
Assistive Devices (ie. a reacher)	0	0
Mobility aids (canes, crutches, walkers, wheelchairs)	0	0
Bathroom and self-care aids (raised toilet seats, grab bars)	0	0
Environmental Modifications	0	0
Therapy: physical therapy, occupational therapy, speech therapy	1	1
Depression treatment: pharmacotherapy and/or psychotherapy	0	0
Dietary modifications for dysphagia	0	0
DVT prevention: Intermittent pneumatic compression, heparin, aspirin, graduated compression stockings	2	0
UTI prevention: bladder catheter management	0	0
Fall prevention / broken bone prevention: assistive devices and environmental modification	0	0
Sexual dysfunction	0	0
Early supported discharge and home rehabilitation	4	1

4.3.6.2 Exercise

Two primary studies were identified for the use of exercise in stroke rehabilitation, reporting results and the protocol for two clinical trials, respectively.

A community-based, twice weekly exercise programme was implemented by volunteers and qualified instructors supported by a physiotherapist. The perspective of the economic analysis was the UK NHS plus social care and personal costs, relevant patient reported outcomes were included but QALY's were not calculated. Patients in the intervention arm were found to improve according to the outcome measures, and incurred additional costs GBP 296 per patient, excluding inpatient care (Harrington et al., 2010).

The second study reported a trial protocol for the FIT-Stroke trial, a structured, progressive task-oriented circuit class training (CCT) programme, compared to usual physiotherapeutic care during outpatient rehabilitation in a rehabilitation centre. Cost-effectiveness is assessed as a secondary outcome, including direct costs associated with the intervention, medications, service use, community support, individual spending, and adaptations in/around the house. Indirect costs will not be included (van de Port et al., 2009).

Main findings:

- Presently, limited economic evidence exists on the cost-effectiveness of exercise programmes in rehabilitation of stroke survivors. One study suggests a programme can be delivered at relatively low cost with beneficial outcomes, however no cost/QALY is reported. An economic evaluation of a structured, progressive task-oriented circuit class training programme is underway.

4.3.6.3 Deep vein thrombosis prevention

Two primary studies were associated with the prevention of deep vein thrombosis. One study was addressed in section 4.3.1.1, a clinical trial of intermittent pneumatic compression in immobile stroke patients (Dennis et al., 2012, 2013).

Screening for DVT by Doppler ultrasound at admission to stroke rehabilitation was compared with clinical surveillance followed by screening on signs of DVT. The model was based on a societal perspective in the US, and found an ICER of US$ 67,200 per QALY, due mainly to a very limited QALY gain of 0.0026 (23 hours) (Wilson & Murray, 2005).

- A clinical trial has reported intermittent pneumatic compression to be effective in reducing the risk of DVT. An economic analysis is pending.
- Screening of all patients for DVT on admission to stroke rehabilitation is not cost-effective from the US perspective, compared with screening and treatment prompted by clinical observation

4.3.6.4 Early supported discharge and home rehabilitation

The present search identified three primary studies evaluating home rehabilitation or early discharge in stroke patients. In addition, one review and three primary studies were suggested by reviewers.

A small clinical trial from Thailand randomized stroke patients (n=58) to hospital or home rehabilitation. The home-based care was found to improve outcomes with more patients avoiding disability, but at greater cost. No QALY's were reported, but the ICER was THB 24,364 (approx. EUR 600) per disability avoided (Sritipsukho et al., 2010).

In the UK, the DOMINO study (DOMiciliary rehabilitation In NOttingham) was a clinical trial comparing domiciliary with hospital based rehabilitation for stroke patients. No differences in outcomes were seen between the two approaches, but this study found hospital based rehabilitation to be overall 27% less costly. However, different results were observed when analyzing data according to the ward at hospital discharge. Geriatric ward patients were less likely to die or become institutionalized if allocated to hospital rehabilitation, which incurred 25% higher cost in this population. Patients from the Stroke Unit

receiving domiciliary rehabilitation had greater household and leisure abilities, but with 2.6 times higher cost than hospital rehabilitation. And patients from general medical wards had similar outcomes regardless of the rehabilitation setting, but incurred lower costs in the hospital setting. Consequently the clinically optimal and most cost-effective rehabilitation setting could differ according to the specific patient population (Gladman, Whynes & Lincoln, 1994). A second UK study found home-based physiotherapy to be more effective and less costly than hospital-based physiotherapy, based on the Bradford community stroke trial. The study found no differences in indirect costs between the two groups (Young & Forster, 1993).

A study from the Australian perspective reviewed efficacy data from seven clinical trials assessing interventions for early hospital discharge and home rehabilitation after stroke. There was no significant effect on mortality or other clinical outcomes, and the analysis showed early discharge and home rehabilitation to be associated with 15% lower costs (Anderson et al., 2002).

An economic evaluation of an Early Home-Supported Discharge (EHSD) programme incorporated evidence from 7 clinical trials of 1,108 patients over 3-12 months after discharge. The study found a significantly reduced risk of death or institutionalization with EHSD, as well as reduced length of hospital stay. The intervention cost USD 1,340 per EHSD, and was found to be dominant over usual care, however the authors noted that "*financial barriers between municipalities and health authorities have to be overcome*" for the economic benefits to materialize (Larsen, Olsen & Sorensen, 2006).

A recent Cochrane review of the costs and effects of early supported discharge (ESD) included outcome data from 14 clinical trials, which showed a significant reduction in the length of hospital stays and a significant benefit (OR = 0.80, 95% CI 0.67 to 0.97) in the outcome "death or dependency" at the end of follow-up without adverse effect on the mood or subjective health status of patients or carers. Cost data was reported in 7 trials, with a maximum follow-up of 1 year after randomization. Although underlying costs and assumptions were different for each analysis, all studies concluded the savings from reduction in length of stay were similar to or greater than the costs of the EHSD intervention. The authors note, however: "*Most of the evidence of ESD benefit appears to be for patients with moderate disability (initial Barthel index of > 9/20), although the balance of cost and benefit is not clear for this subgroup. For patients with more severe disability the substantial saving in bed-days may well be outweighed by a risk of poorer patient outcomes. We, therefore, cannot exclude the possibility that the clinical benefits enjoyed by the moderate disability subgroup required a net increase in rehabilitation input while the main cost savings (in terms of bed days) came from the severe subgroup.*"

The cost-effectiveness of a combination of Stroke Unit Care (SUC) followed by ESD in the UK, compared with either SUC or general medical ward treatment without ESD, was estimated in a modelling study. The ICERs against the two comparators, respectively, were GBP 17,721/QALY and GBP 10,661/QALY (Saka et al., 2009).

Main findings:

- One clinical trial and one modelling study found home rehabilitation to be more effective than hospital rehabilitation. Home rehabilitation may be cost-effective if hospital length of stay is reduced.
- A Cochrane review of 14 clinical trials, seven of which reported cost data, found early home discharge to be effective compared with usual care and found costs of the intervention were generally offset by savings related to shortened hospital stays. Additionally a separate study using evidence from seven clinical trials found early home-supported discharge to be both clinically effective and cost-saving, however financial barriers between municipalities and health authorities were considered a barrier in realizing the economic benefits. ESD combined with stroke unit treatment was not found to be cost-saving in a UK study which reported ICER's of GBP 10,661-17,721/QALY depending on the comparator.

4.3.6.5 Therapy: physical therapy, occupational therapy, speech therapy

The recent Cochrane review of Speech and Language Therapy (SLT) for aphasia after stroke sought evidence of economic effectiveness of interventions (SLT verses no SLT; SLT versus social support and SLT 1 versus SLT 2) (Brady et al., 2012). This data related only to participants with aphasia. Of 39 trials included only one (ACTNOW) reported health economic data (though others had described collecting it) and provided health utility and cost comparison data (Bowen et al., 2012). The study found an approximately 50% chance of SLT being cost-effective compared with attention control at a WTP of GBP 30,000 per unit of utility.

Since then the CACTUS trial of "Cost-utility of self-managed computer therapy for people with aphasia" has also reported cost effectiveness data (Latimer, Dixon & Palmer, 2013) with the follow-up BIG CACTUS trial now underway which also includes economic data (ISRCTN68798818). The CACTUS trial found self-managed computer therapy for people with long-standing aphasia post stroke in addition to usual stimulation was cost-effective against usual stimulation alone with an ICER of GBP 3,058/QALY.

Main findings:

- Two studies have reported cost-effectiveness of different speech therapy interventions. Compared with the significant volume of clinical evidence available (39 trials in the most recent Cochrane review), the cost-effectiveness of such interventions are widely understudied and/or under reported, given existing trials that intended to collect and analyse economic data but did not.

4.4 Evidence gaps in stroke

Observations from published studies:

- The use of technologies to assist or augment rehabilitation (e.g. robotics, virtual reality) is a developing area where little economic evidence has been published; studies investigating the cost-effectiveness of these interventions should consider the cost of equivalent dose conventional (therapist-led) interventions. The economic evidence on prevention of pneumonia in stroke patients with dysphagia is limited, except for two ongoing clinical trials.

- Use of tPA in acute stroke is shown to be cost-saving in a range of studies, however it is noted that long-term outcomes modelled in these studies is associated with significant uncertainty, and that long-term outcome data would improve estimates. There is also limited evidence on the cost-effectiveness of tPA given later than the 3-hour window.
- Relatively sparse evidence was identified for hypertension and lipid management in secondary prevention of stroke.
- Most pharmacological studies on clopidogrel were performed while the drug was on-patent. The cost-effectiveness profile is likely to have changed after patent expiry.
- Among contributing vascular, cardiac and blood disease, atrial fibrillation was the most intensively studied followed by carotid stenosis. Most contributing conditions were not associated with any economic evidence.
- Comparison between newer anticoagulants for stroke prevention in atrial fibrillation is hampered by the lack of head-to-head trials. Most newer agents are compared with warfarin, in trials that are not amenable to indirect comparison.
- The evidence on cost-effectiveness of exercise in stroke rehabilitation is very limited. One economic evaluation of a training programme is underway. In general, there is very limited evidence relating to the cost-effectiveness of stroke rehabilitation services and treatments. As current evidence suggests that dose of rehabilitation treatments (number, frequency and intensity of treatment sessions) is a key factor in clinical effectiveness, it is important that the impact of dose is carefully considered in any studies of cost-effectiveness.
- A Cochrane review suggests early supported discharge after stroke can reduce hospital length of stay and "death or dependency". The authors of this review state "*More research is required to define the important characteristics of effective ESD services and to define the balance of cost and benefit for different patient and service groups*" and "*The role of ESD services in poorer healthcare settings and in more dispersed rural communities has not really been adequately addressed*"(Fearon & Langhorne, 2012)

Contributor	Comment
Dr. Alex Pollock Nursing, Midwifery and Allied Health Professions Research Unit Glasgow Caledonian University	Different models of service delivery are associated with different costs. There is a reasonable body of evidence around the clinical effectiveness of different models (e.g. stroke units versus general wards, hospital versus home care) and Cochrane reviews covering a number of these topics, some of which include cost evidence. Reviews on services for reducing duration of hospital care for acute stroke patients (Fearon & Langhorne, 2012), and hospital at home early discharge (Shepperd et al., 2009) include cost-effectiveness results sporadically but much of the evidence presented is cost-consequence, ie. differences in total costs between two patient groups. Shepperd et al. also note that cost comparisons were not attempted in their review due to differences in costing methods. Consequently, from these reviews at least, the cost-effectiveness of these ways of delivering services is not well known. Importantly, there is a rapidly growing body of evidence relating to the use of telemedicine and telerehabilitation, including some evidence relating to

	costs of these different modes of service delivery. For example a virtual reality telerehabilitation programme for balance recovery was found to be as effective as clinical care and less costly (Lloréns et al., 2014), but the acquisition cost of equipment may have a bearing on the cost-effectiveness. For example, TeleStroke may not be cost-effective over a 3-month time horizon (more than USD 100,000/QALY) but may be cost-effective over a life-time horizon (USD 2,449/QALY) as suggested by one review (Hubert, Müller-Barna & Audebert, 2014). Finally, determining the cost-effectiveness of rehabilitation interventions is complex due to the fact that rehabilitation interventions generally seek to improve quality of life (rather than extend), and often small functional improvements will be perceived as very important to patients. These small functional improvements can be difficult to objectively measure and account for within cost-effectiveness models.
Anne Forster Professor of Stroke Rehabilitation Leeds Institute of Health Sciences University of Leeds UK	There is increasing interest in physical fitness following stroke (Saunders et al., 2013) it seems an important evidence gap that there has not been a review of the cost-effectiveness evidence for this intervention as it is now being widely promoted.
Gregory Lip Professor of Cardiovascular Medicine University of Birmingham UK	Screening for AF is a priority, especially since it is so common and coexists with other comorbidities. Screening for AF has been shown to be cost-effective in clinical trials of patients aged 65 and above (Hobbs et al., 2005) and in pharmacy screening in the same age group using a handheld device (Lowres et al., 2014). Unanswered questions: • Whether systematic screening for AF in high risk groups would enhance opportunities for primary prevention of stroke (Lowres et al., 2014) • Whether close monitoring of high risk patients would be cost effective in detection incident AF There are also open questions regarding interventions to improve the use of warfarin: • Whether using the SAMe-TT2R2 score can help stratify patients with AF who would be more suitable for a NOAC rather than warfarin, for primary prevention of stroke, and whether such an approach is cost-effective • Whether educational interventions would improve uptake of primary prevention measures for stroke prevention e.g. TREAT study (Clarkesmith et al., 2013)
Marian Brady Professor of Stroke Care and Rehabilitation Nursing, Midwifery and	Rehabilitation: The recent Cochrane review of Speech and Language Therapy (SLT) for aphasia after stroke (2012) sought evidence of economic effectiveness of SLT but of 39 trials included, only one (ACTNOW) reported health economic

Allied Health Professions Research Unit Glasgow Caledonian University	data (though others had described collecting it) and provided health utility and cost comparison data (ACTNOW). Since then the CACTUS trial of "Cost-utility of self-managed computer therapy for people with aphasia" has also reported cost effectiveness data (Latimer, Dixon & Palmer, 2013) with the follow-up BIG CACTUS trial now underway which also includes economic data as an outcome (ISRCTN68798818), however, given the volume of clinical evidence available the cost-effectiveness of SLT interventions is significantly under-studied. Some specific challenges are raised in the evaluation of health economic data specifically in relation to aphasia after stroke as standard measures contributing to such evaluations (such as the EQ-5D for example) are language based measurement tools and thus exclude or limit the participation of people with language impairments (difficulty reading, writing, speaking and understanding speech) such as aphasia. Similar challenges exist for people with other stroke related impairments such as cognitive or visual problems for example. Very often those that may be experiencing significant impacts on QoL (and in turn benefits of any therapeutic intervention) are often those least able to directly report these impacts or benefits themselves.
David Meads **Leeds Institute of Health Sciences** **University of Leeds** **UK**	As in many other therapeutic areas, the economic modelling conducted in stroke has often been limited to cohort models with little consideration of issues such as real time resource use, queuing and the downstream health-system impact of upstream interventions. While decision modelling must strike a balance between reflecting reality and complexity, it is possible important aspects are being missed with the simplified approach. An exploration of the value of thrombolysis, for example, needs to take into account the time to arrival in hospital, the speed at which the patient can be scanned/treated, the available staff at any one time (and consequently the number of other patients needing care). This approach combines traditional economic evaluation with more operational research and useable platforms to achieve this would be beneficial (Meads et al., 2010). Another under-explored issue from a different economic perspective is the efficiency of stroke units. Little research has been done to identify the optimal configuration of units in terms of staffing levels and grades.

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Health Economic Evidence Analysis: Management of major depressive disorder

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5 Depression

5.1 Bibliometrics

A total of 61 economic studies were mapped to the clinical model for major depressive disorder (Table 5.1 and Figure 5.1) with the majority[1] of studies published since 2007. Of the 3 reviews identified, all were published between 2009 and 2014.

Table 5.1 Bibliometric data for major depressive disorder

PubMed/MEDLINE	
Search term	(“Depressive Disorder, Major”[MeSH Terms] OR “Depressive Disorder, Treatment-Resistant”[MeSH Terms]) ("cost-benefit analysis"[MeSH Terms] OR “Economics, Pharmaceutical”[MeSH Terms] OR “Technology Assessment, Biomedical”[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR “English Abstract”[pt] OR Letter[pt])
Number of studies	
Included in model	61
Included as “other”	41
Reviews	3
Excluded	46
Total	151

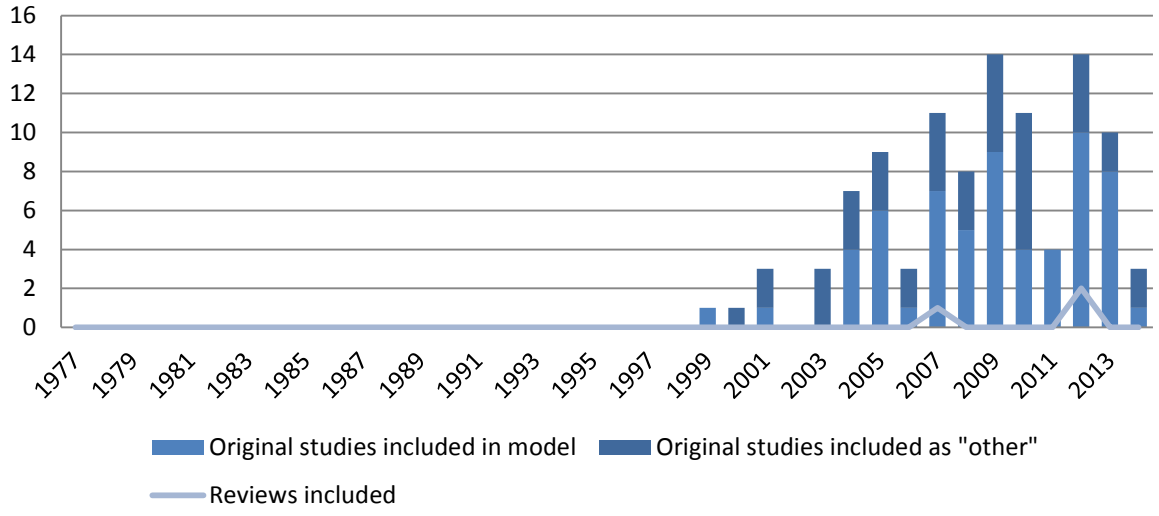

Figure 5.1 Bibliometric data for major depressive disorder by year

[1] 75% of studies or more

5.2 Review coverage

The clinical model for major depressive disorder (MDD) consists of 14 treatment modalities. Of these, two treatments (14%) were addressed by one of the two reviews published between 2009 and 2014 (Table 5.2). The remaining 12 treatments (86%) were not associated with any health economic reviews, though primary studies were available in several cases (Table 5.3, Table 5.4 and described in sections 5.3.1 to 5.3.4).

Table 5.2 Table of reviews for major depressive disorder and associated treatments

Title and reference	Year	Treatments covered
"*The role of transcranial magnetic stimulation in treatment-resistant depression: a review*" (Lee et al., 2012)	2012	Transcranial Magnetic Stimulation in treatment of refractory major depressive disorder
"*Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how?*" (Rabheru, 2012)	2012	Electroconvulsive therapy as maintenance treatment in major depressive disorder

5.3 Evidence analysis

The following sections present information gathered from recent (2009-2014) reviews when available, and from essential information on primary evidence where no reviews are available. Table 5.3 summarises the volume of health economic studies and reviews identified according to each treatment modality.

Table 5.3 Primary health economic evidence and reviews for the treatment of major depressive disorder

Major Depressive Disorder	Studies	Reviews
Mild to Moderate		
Exercise	0	0
Self-Guided Self-Help Therapy (internet based and other)	2	0
Therapy: Cognitive-Behavioral Therapy, Interpersonal Therapy, Family and Couples Therapy, Psychodynamic Therapy, Life Review Therapy, or Supportive Therapy	18	0
Pharmacology Monotherapy: SSRIs: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Fluvoxamine CR, Paroxetine, Paroxetine CR, Sertraline. SNRIs: Desvenlafaxine, Duloxetine, Milnacipran, Venlafaxine, Venlafaxine XR. Tricyclics and tetracyclines: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine. MAOIs: Isocarboxazid, Phenelzine, Selegiline transdermal, Tranylcypromine. Serotonin Modulators: Nefazodone, Trazodone, Trazodone ER, Vilazodone. Atypical Anti-Depressants: Agomelatine, Bupropion, Bupropion SR 12 hour, Bupropion XL 24 hour, Bupropion hydrobromide 24 hour, Mirtazapine.	35	0

Therapy + Pharmacology	6	0
Severe		
Therapy + Pharmacology	0	0
Electroconvulsive Therapy	2	0
Refractory		
Electroconvulsive Therapy	1	0
Transcranial Magnetic Stimulation	3	1
Ablative Neurosurgery	0	0
Augmented pharmacology	5	0
Surgical Implant Devices - Deep Brain Stimulation, Vagus Nerve Stimulation, or Direct Cortical Stimulation	1	0
Recurrence		
Discontinue Therapy Once Depression Has Resolved, and Monitor for Recurrence of Symptoms	0	0
Maintenance Therapy	3	1

5.3.1 Mild to moderate major depressive disorder

5.3.1.1 Exercise and self-guided self-help therapy

In the present review, no economic evidence was identified on the use of exercise as a treatment for mild to moderate MDD. Two studies were identified for self-guided self-help therapy, both reporting the protocols for new clinical trials. One Spanish trial is comparing the use of "self-guided internet-delivered psychotherapy" with "Low intensity Internet-delivered psychotherapy" and thus incorporates a remote treatment element. A cost-utility analysis from the societal perspective is planned, but no results have been reported at time of writing (López-del-Hoyo et al., 2013). The second trial assesses nurse-led preventive cognitive therapy (PCT) for prevention of MDD recurrence, in which the PCT intervention is structured as a self-help programme. Cost-utility analysis is planned from the societal perspective, but not yet reported (Biesheuvel-Leliefeld et al., 2012)

Main findings:

- Two ongoing clinical trials are assessing the efficacy and cost-effectiveness of self-help based treatments with limited intervention by health professionals (through internet or contact with nurses).

5.3.1.2 Therapy

Various forms of therapy were extensively studied in the economic literature with 18 primary studies, however no reviews were identified.

Seven primary studies compared therapy with pharmacotherapy. Comparing cognitive behavioral therapy (CBT) with fluoxetine (a selective serotonin reuptake inhibitor [SSRI]), or a combination of both in American adolescents, after 12 weeks of treatment fluoxetine alone was more cost-effective than

fluoxetine combined with CBT (Domino et al., 2008). However data from the same clinical study resulted in opposite conclusions at 36 weeks follow-up, where the combination of fluoxetine and CBT was found to be more cost-effective than fluoxetine alone (Domino et al., 2009). Conclusions from Australia and Thailand point towards the latter, with CBT being more cost-effective than SSRI's (Haby et al., 2004; Prukkanone et al., 2012). In Romania, no difference in effectiveness was observed between cognitive therapy, rational emotional behavioral therapy (REBT) and fluoxetine, and due to price differentials fluoxetine was considered least cost-effective (Sava et al., 2009). One study did not distinguish between an SSRI (paroxetine) and an atypical antidepressant (bupropion) in the pharmacotherapy group, but found pharmacotherapy to be slightly more cost-effective than CBT measured in cost per depression-free day(Revicki et al., 2005).

Two studies considered the cost-effectiveness of interventions targeting work as an outcome. A relatively small clinical trial (n=62) found adding occupational therapy to usual care did not improve depression outcome, but did result in a reduction of lost work days over 18 months with a 76% chance of being cost-effective over usual care (Schene et al., 2007). A more recent trial of a similar intervention showed that while overall work participation (hours of absenteeism and duration until return to work) did not improve in the occupational therapy group, the intervention did increase long-term depression recovery and long term return to work (Hees et al., 2010, 2013).

Three studies addressed the prevention of relapse or recurrence in MDD patients. In a Japanese study from the perspective of the national health insurance, provision of family psychoeducation resulted in significantly more relapse-free days in patients undergoing maintenance treatment, and was considered cost-effective at a willingness to pay (WTP) of US$ 30 per depression-free day, however no cost-utility results were reported (Shimodera et al., 2012). In the Netherlands, an ongoing clinical trial is assessing the societal cost-effectiveness of self-management plus online cognitive therapy and SMS based tele-monitoring of depressive symptoms in MDD patients in remission. No results have been reported to date (Bockting et al., 2011). A psychoeducational prevention program (PEP) was also studied in the Netherlands, in which PEP was offered in combination with psychiatric or CBT treatment. Study limitations prevented accurate assessment of QALY gains, and the authors concluded that the most efficient combination PEP+CBT would only be efficient at high WTP, and consequently that PEP should not be considered generally cost-effective (Stant et al., 2009).

Management of MDD in specific patient populations was assessed by two studies. For elderly patients (55+) identified by screening in primary care, interpersonal psychotherapy did not result in significant clinical improvement over 12 months but did incur higher total costs. Significant uncertainty around the cost-effectiveness estimate led the authors to include the intervention was not cost-effective (Bosmans et al., 2007). An ongoing clinical trial is assessing the cost-effectiveness of CBT for MDD in type II diabetics. Economic analysis will be performed from the societal perspective and include QALY's as outcome. No results have been reported at time of writing (Chernyak et al., 2009).

Finally, four studies assess the cost-effectiveness of various forms of therapy in MDD. One Spanish clinical trial is comparing the use of "self-guided internet-delivered psychotherapy" with "Low intensity Internet-delivered psychotherapy". A cost-utility analysis from the societal perspective is planned, but

no results have been reported at time of writing (López-del-Hoyo et al., 2013). Two types of short-term psychological therapy were compared in the Finnish context, short-term psychodynamic treatment and solution-focused therapy, though no significant differences in cost or effects were observed, though SPP trended towards lower costs and greater improvements. No cost/QALY was reported (Maljanen et al., 2012). An ongoing clinical trial is comparing Cognitive Therapy (CT) with Interpersonal Therapy (IPT) and a "rudimentary analysis of the cost-effectiveness" is planned. Several psychological outcome measures are used but no QALY scores. To date no results are reported (Lemmens et al., 2011). A clinical trial has compared Short Psychodynamic Supportive Psychotherapy with CBT over one year (Driessen et al., 2007), but found no significant differences in outcome (Driessen et al., 2013). An economic evaluation has not been reported on this trial.

Main findings:

- Reports from the same study comparing fluoxetine and CBT+fluoxetine at different follow-up points have given opposite conclusions, underlining the importance of study design and time to follow-up when summarizing evidence. In the longer term, CBT+fluoxetine was found to be more cost-effective.
- Four studies find CBT alone or in combination with fluoxetine to be more cost-effective than pharmacotherapy with SSRI's alone (incl. fluoxetine).
- Two clinical trials concur that occupational therapy is likely to be cost-effective in improving return-to-work in the long term
- There is limited comparability between three studies assessing various psychological therapies to prevent recurrence of MDD. One of these studies is an ongoing clinical trial.
- There is limited evidence on the cost-effectiveness of psychological therapy in specific patient groups such as elderly or diabetics. One ongoing clinical trial of CBT in type II diabetics with depression has yet to report results.
- Economic evaluations are expected from 2-3 clinical trials of different psychological treatments, while effectiveness and cost-effectiveness evidence from two trials suggest there is limited difference in effectiveness between psychological therapies.

5.3.1.3 Pharmacotherapy

No reviews were identified for pharmacotherapy. Primary studies are summarized by topic (study drug and comparators) in Table 5.4. Notably the Selective Serotonin Re-uptake Inhibitor (SSRI) class of drugs is the most well studied, followed by Serotonin-Norepinephrine Reuptake Inihibitors (SNRI). Very few studies addressed the older Tricyclic Antidepressants (TCA).

In addition, three primary studies addressed the use of genetic testing in guiding treatment decisions. One study modelled the potential effect of stratifying patients according to polymorphisms in the serotonin 2A receptor (*HTR2A*) gene, which has been associated with citalopram (an SSRI) response. The study found testing prior to treatment choice was more expensive but yielded additional benefit at US$93,520/QALY (Perlis et al., 2009). Testing for another genetic polymorphism, the 5-HTTLPR (serotonin-transporter-linked polymorphic region) which affects the serotonin transporter, also results in higher costs for increased benefit (Olgiati et al., 2012; Serretti et al., 2011).

Table 5.4 Economic evidence for pharmacotherapy in mild/moderate major depressive disorder

	SSRI						TCA		SNRI		
	Citalopram	Escitalopram	Sertraline	Fluoxetine	Paroxetine	Fluvoxamine	Amitriptyline	Imipranine	Milnacipran	Venlafaxine	Duloxetine
(Mencacci et al., 2013)	?	?	?	?	?	?			?	?	?
(Parker et al., 2013)											
(Ostad Haji et al., 2013)	x										
(Maniadakis et al., 2013)		x	x	x						x	
(Solomon, Adams & Graves, 2013)											
(Leelahanaj, 2012)			x							x	
(Nuijten et al., 2012)		x									
(Nordström et al.)		x								x	
(Prukkanone et al., 2012)				x							
(Domino et al., 2009)				x							
(Sado et al., 2009)					x						
(Lenox-Smith et al., 2009)				x			x			x	
(Sava et al., 2009)				x							
(Wade et al., 2008)		x									x
(Kongsakon & Bunchapattanasakda, 2008)		x		x						x	
(Domino et al., 2008)				x							
(Bosmans et al., 2008)					x						
(Byford et al., 2007)				x							
(Sørensen et al., 2007)	x	x								x	
(Fantino et al., 2007)	x	x									
(van Baardewijk, Vis & Einarson, 2005)										x	x
(Revicki et al., 2005)					x						
(Vos et al., 2005)	?	?	?	?	?	?	?	?			
(Wade, Toumi & Hemels, 2005)	x	x									
(Demyttenaere et al., 2005)	x	x								x	
(Trivedi et al., 2004)				x	x	x				x	
(Haby et al., 2004)	x		x	x	x	x					
(Hemels et al., 2004)	x	x									
(Doyle et al., 2001)	?	?	?	?	?	?	?	?		x	
(Dardennes et al., 1999)				x		x		x	x		
(Olgiati et al., 2013)*	x		x							x	
(Malone, 2007)*	x	x	x	x	x					x	
	9	11	5	12	6	3	1	1	1	12	2

*Indicates treatments studied as second line therapies. "?" indicates the class but not specific drug was reported.

Main findings:

- Genetic testing to improve pharmacotherapy treatment choice results in added clinical benefit but at additional cost, as reported by three studies.

5.3.1.4 Therapy and pharmacology

Of six primary studies addressing this combination, two were discussed in section 5.3.1.2. Briefly, adding CBT to fluoxetine therapy in American adolescents was cost-effective at 36 weeks followup, but not at 12 weeks (Domino et al., 2008, 2009). One study is an ongoing clinical trial assessing CBT as an adjunct to pharmacotherapy. An economic evaluation using quality of life as outcome will be performed from the societal, health system and patient/carer perspectives, but no results are reported to date (Thomas et al., 2012). In young people with SSRI-resistant depression, CBT was considered as an add-on to medication switch. Adding CBT was associated with higher costs but also gains in depression-free days. Costs included "*intervention, nonprotocol services, and families*" but not productivity losses (Lynch et al., 2011). In Japan, the economic evaluation of CBT added to pharmacotherapy depended strongly on the perspective, with a health system perspective resulting in increased cost and benefit, but a societal perspective resulting in a dominant intervention due to significant reduction of productivity loss (Sado et al., 2009). In UK adolescents, adding CBT to SSRI therapy did not result in significantly different outcomes or costs at 12 or 28 weeks follow-up(Byford et al., 2007).

Key points:

- There is mixed evidence for the cost-effectiveness of CBT as an add-on to pharmacotherapy, though it appears cost-effective in three studies, conclusions are likely to be affected by follow-up period and economic perspective taken.

5.3.2 Severe Major Depressive Disorder

5.3.2.1 Therapy and pharmacology

The present search did not identify any reviews or primary evidence on the combined use of psychological therapy and pharmacotherapy.

5.3.2.2 Electroconvulsive therapy

No reviews were identified on the use of electroconvulsive therapy. One American primary study compared electroconvulsive therapy (ECT) with repetitive transcranial magnetic stimulation (rTMS). The authors concluded rTMS was significantly more cost-effective than ECT, and that offering patients a sequence of rTMS followed by ECT for non-responders was more effective and less costly than ECT alone (Kozel, George & Simpson, 2004). Conversely, a study in the UK setting found ECT to be more cost-effective than rTMS. This study found ECT to be more clinically effective, and total costs for rTMS (including costs of informal care) to be higher (Knapp et al., 2008).

Main findings:

- Two primary studies evaluated ECT versus rTMS with opposite conclusions. Inclusion of different types of costs (eg. for informal care in one study), follow-up period and other methodological differences are likely to be a contributing factor.

5.3.3 Refractory Major Depressive Disorder

5.3.3.1 Electroconvulsive therapy

One primary study was identified for electroconvulsive therapy in refractory MDD, already addressed in section 5.3.2.2 (Kozel, George & Simpson, 2004).

5.3.3.2 Transcranial magnetic stimulation

One review and three primary studies were identified on the topic of transcranial magnetic stimulation. Of the three primary studies, two were addressed in section 5.3.2.2 and offered opposite conclusions on cost-effectiveness versus ECT (Kozel, George & Simpson, 2004; Knapp et al., 2008). In the third study in an American setting, TMS was compared with no treatment, resulting in an ICER of US$34,999 or US$6,667 if productivity gains from early recovery were included. Additionally, comparison with usual care resulted in TMS being a dominant treatment (Simpson et al., 2009).

The review (Lee et al., 2012) did not specify search strategy or cut-off dates, but did include the three studies reviewed in the present search along with one additional study (McLoughlin et al., 2007). Lee et al. noted that the study finding rTMS to be less cost-effective than ECT (Knapp et al., 2008) "*had a number of significant limitations including a small sample size (less than one hundred), failure to take into account lost employment and productivity associated with ECT (including lost work days and the necessity for accompaniment to and from the ECT suite), and use of a now outdated fixed-dose paradigm (110% above motor threshold) of rTMS as a comparator*".

Lee et al. also summarise the findings of McLoughlin et al., who in their study randomized 46 individuals to ECT or rTMS. An attrition rate of 25% (6 of 24) was observed for rTMS versus 0% for ECT, and differences in outcomes between the groups differed according to outcome, with no differences observed for cognition of QALY's, but ECT found to be favoured according to remission rate and Hamilton Rating Scale for Depression. Lee et al. noted "*The table delineating caregiver input by treatment group reveals an apparent baseline difference in child-care hours with the ECT group receiving none, and the rTMS group receiving 32 hours per week*" which was found to be of major importance for the results. This study was also found to use a sub-optimal rTMS course (Lee et al., 2012)

Main findings:

- TMS is addressed by three studies in the present review and one additional study reviewed by Lee et al. Two studies in American settings find TMS cost-effective or dominant compared with ECT or usual care, while two studies from UK find TMS less cost-effective than ECT. However, both UK studies were found to use inappropriate treatment protocols for rTMS, and both were based on small sample sizes.

5.3.3.3 Ablative neurosurgery

No economic evidence was identified for the use of ablative neurosurgery in refractory MDD.

5.3.3.4 Augmented pharmacology

The use of augmented pharmacology in refractory MDD was assessed in five primary studies. One study, discussed in section 5.3.1.4, assessed the addition of CBT along with medication switching in youths with SSRI-resistant depression. Adding CBT was associated with higher costs but also gains in depression-free days. Costs included "*intervention, nonprotocol services, and families*" but not productivity losses (Lynch et al., 2011).

Four studies addressed atypical antipsychotics/antidepressants or lithium. One study assessed aripiprazole, quetiapine, and olanzapine/fluoxetine in combination with usual antidepressants. Against usual antidepressants alone, these combinations were more effective at higher cost, resulting in US$ 3,447 to US$ 8,725 per additional respondent (Taneja et al., 2012). In Thailand, augmenting usual treatment with aripiprazole against placebo resulted in an increased cost of 2,561 Baht (approx. 62 Euro) per remission (Leelahanaj, 2010a). Also in Thailand, switching SSRI non-responders to bupropion was more cost-effective than bupropion plus continued SSRI treatment at 22,937 Baht (approx. 560 Euro)/remission against 29,346 Baht (approx. 715 euro)/remission (Leelahanaj, 2010b). Comparison of lithium with atypical antipsychotics (AAP), based on pooled effectiveness of clinical trials with SSRI's and AAP's, indicates augmentation of SSRI treatment with lithium dominates augmentation with an AAP in the UK setting. However the authors note a "*lack of direct evidence comparing the clinical effectiveness of augmenting an SSRI with an AAP compared with augmenting with lithium*" (Edwards et al., 2013).

Main findings:

- Addition of CBT to pharmacotherapy in SSRI treatment resistant youths appears to be cost-effective according to a single study, and may be more cost-effective if a societal perspective is adopted
- Four studies assessed the addition of an atypical antipsychotic or lithium to usual pharmacotherapy. All studies reported cost per additional remission as outcome, and overall augmentation of usual pharmacotherapy resulted in better outcomes at additional cost. Lithium appears to be more cost-effective (dominant over atypical antipsychotics), evidenced by a single study.

5.3.3.5 Surgical implant devices

One primary study was identified on vagus nerve stimulation. The study followed nine patients over one year, and found that vagus nerve stimulation improved symptoms, reduced duration and frequency of hospital stays and reduced consumption of pharmaceuticals compared to nine controls. The economic consequences of reduction in service utilization was not reported (Sperling, Reulbach & Kornhuber, 2009).

5.3.4 Recurrent Major Depressive Disorder

5.3.4.1 Discontinuation of therapy

The present search identified no economic evidence on the discontinuation of therapy followed by monitoring for recurrence.

5.3.4.2 Maintenance therapy

Three primary studies and one review were identified for maintenance therapy of patients in remittance. In elderly American patients initially responding to electroconvulsive therapy (ECT), maintenance treatment with ECT was cheaper and more effective than pharmacotherapy (Aziz et al., 2005). A clinical trial is ongoing in the UK, comparing Mindfulness-based CBT with pharmacotherapy in the prevention of depressive recurrence. An economic evaluation is planned and "*will take a broad perspective, covering use of all hospital, community health and social services, including complementary therapies, plus productivity losses resulting from time off work or reduced productivity at work due to illness*". No results have been reported to date (Kuyken et al., 2010). In Australia, maintenance treatment with SSRI's was found to be more expensive at AU$ 17-20,000 per DALY than treatment of depression episodes with bibliotherapy, group/individual CBT or TCA's at less than AU$ 10,000 (Vos et al., 2005).

- The diverse treatments examined as maintenance therapy in the three studies identified precludes general comments. Single studies indicate maintenance ECT is more cost-effective than pharmacotherapy, and that SSRI's are less cost-effective in prevention remission than other treatments are in treatment.

5.4 Evidence gaps in Major Depressive Disorder

Observations from published studies:

- Little is known about the economics of exercise as a moderate lifestyle intervention for the treatment of mild to moderate MDD and/or prevention of progression to more severe disease
- Ongoing trials are assessing the cost-effectiveness of self-help programmes delivered through the internet or healthcare workers other than qualified psychotherapists. Similar trials are ongoing in this area, which do not look at MDD specifically but eg. internet delivered treatment of depressive symptoms (Warmerdam et al., 2010), which may provide a cost-effective approach to limiting disease progression with early intervention.
- The evidence suggests in some cases CBT is more cost-effective than pharmacological management, however the distinction is not clear-cut. CBT appears to be more cost-effective over longer time horizons.
- Limited evidence was found for the treatment of MDD as a co-morbidity, with one ongoing study assessing CBT in type-II diabetes patients. Depression is a co-morbid condition in particularly chronic conditions, eg. COPD (van den Bemt et al., 2009), heart disease (Musselman, Evans & Nemeroff, 1998) and stroke (Aben, 2003).
- Pharmacogenetic testing to stratify patients by expected treatment outcome appears to provide clinical benefit but at a cost not usually considered cost-effective. However, such studies mostly

assume significant cost of the genetic test which can swamp the marginal clinical benefit achieved - in one study the ICER ranged from US$ 19,152 to US$ 186,029 when the cost of testing was varied from US$ 100 to US$ 1,000 (Perlis et al., 2009). If whole genome sequencing is applied in the clinic, the cost of genetic testing may be spread over several potential applications.

- There is limited evidence on the relative cost-effectiveness of electroconvulsive therapy and transcranial magnetic stimulation in severe and refractory MDD. Two studies reviewed here give opposite conclusions.
- No economic evidence was identified for ablative neurosurgery, and only a single study for surgical implant devices (vagus nerve stimulation)

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Health Economic Evidence Analysis: Management of lung cancer

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6 Non Small Cell Lung Cancer

6.1 Bibliometrics

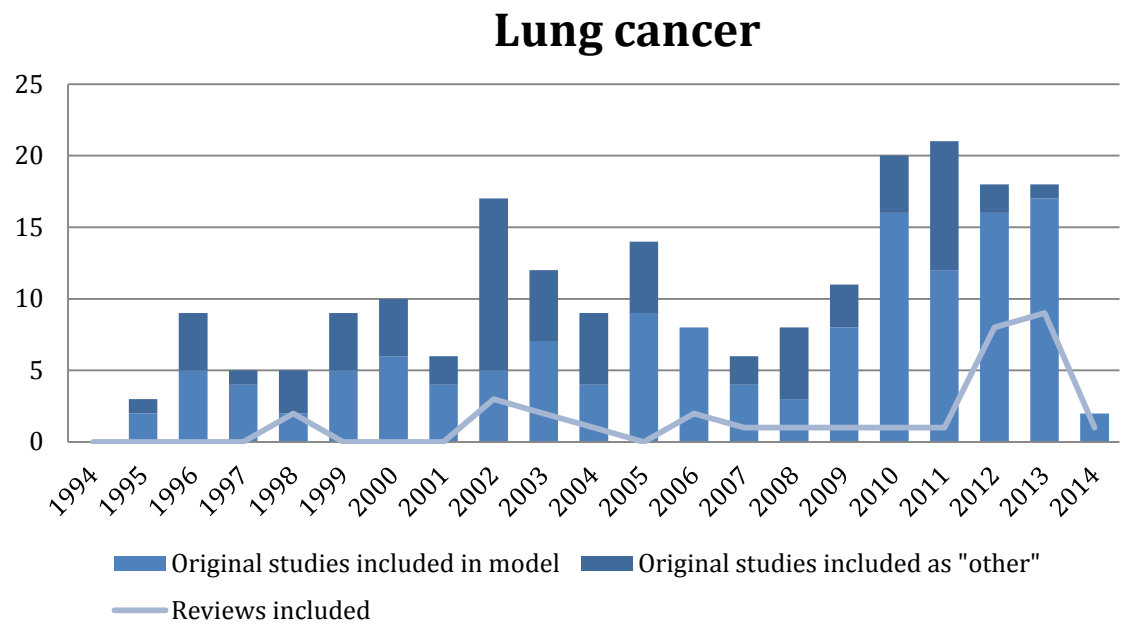
Lung cancer and the management of lung cancer is complex. In the first instance lung cancer can be categorized as small cell lung cancer (SCLC - approximately 15% of cases) or non-small cell lung cancer (NSCLC - approximately 85% of cases) (Zeng et al., 2013). In the second instance, health technologies can be divided into non-definitive (NDTx - screening, diagnosis, staging, management), and definitive (DTx - surgery, chemo- and radio-radiotherapy, etc.). This report focuses on DTx of NSCLC because these are the core clinical treatments for the most commonly diagnosed form of lung cancer.

As illustrated in Table 6.1 and Figure 6.1 below, 139 articles were included in the lung cancer model in total, 49 of these were relevant to DTx of NSCLC, and the majority (76%) of studies were published between 2003 and 2014.

Table 6.1 Bibliometric data for lung cancer (definitive treatment of non-small cell lung cancer)

PubMed/MEDLINE	
Search terms	lung neoplasms[MeSH Terms] AND ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	139 (49 for DTx of NSCLC)
Included as "other"	95
Reviews	31 (6 for DTx of NSCLC since 2009)
Excluded	421
Total	686

Figure 6.1: Bibliometric data for lung cancer by year



6.2 Review coverage

The clinical model is illustrated in Figure 6.2, which shows that NSCLC can be divided into 3 stages:

- Stage I, II, & IIIa
- Stage III & IV, No Driver Mutation Identified
- Stage III & IV, Driver Mutation Identified

These stages then branch-off into 25 different treatment pathways for DTx of NSCLC, 9 of which were addressed by the 6 reviews tabulated below (Table 6.2). The branches addressed by these reviews are: [1], [2], [4], [5], [6], [10], [11], [14] and [20]. No health economic reviews were identified for branches [3], [7], [8], [9], [12], [13], [14], [18], [19], [21], [24] and [25], though treatments in these pathways may have been studied in other braches of the model, and; primary studies were available in several cases, as outlined in Table 6.3 and Figure 6.3 to Figure 6.5 and described in section 6.3.

Figure 6.2 Definitive treatment options for non-small cell lung cancer

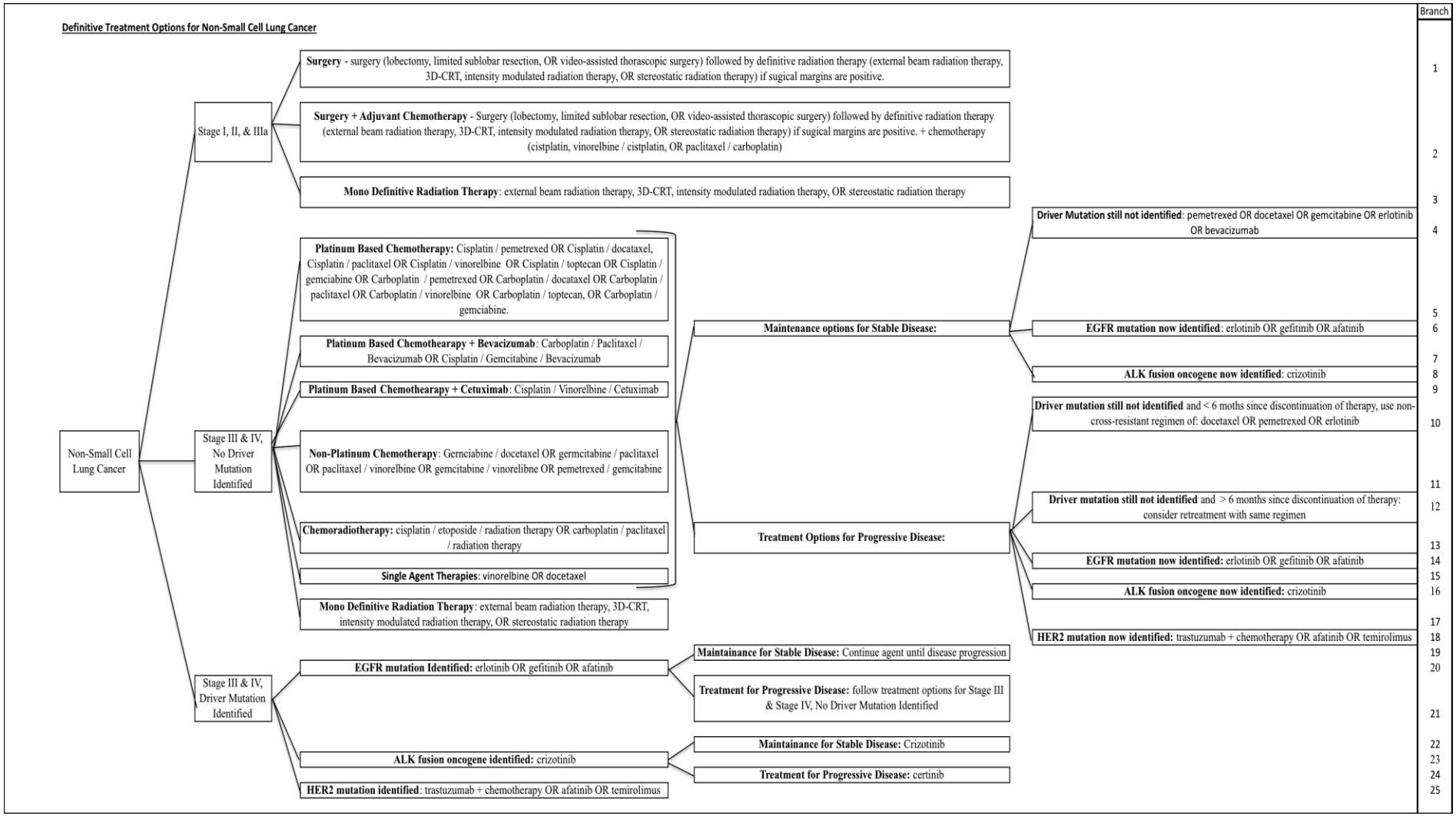


Table 6.2 Table of reviews for non-small cell lung cancer and associated definitive treatment options, published between 2009 and 2014

Review Title and reference	Year	Treatments covered
***"Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation"*, (Brown et al., 2013)**	2013	Pemetrexed Platinum-based chemotherapy Gemcitabine Paclitaxel Docetaxel Gefitinib Vinorelbine
***"Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours"*, (Ford et al., 2013)**	2013	Denosumab Zoledronic acid
"Reducing the burden of bone metastases: current concepts and treatment options", (Moos et al.,2013)	2013	Denosumab Zoledronic acid
***"A systematic review of economic evaluations in second and later lines of therapy for the treatment of non-small cell lung cancer"*, (Jäkel et al., 2013)**	2013	Docetaxel, Pemetrexed Erlotinib Best standard care
***Cost effectiveness of treatment with new agents in advanced non-small-cell lung cancer: a systematic review, (Bongers et al.,* 2012)**	2012	Gemcitabine+cisplatin Paclitaxel, docetaxel and vinorelbine Pemetrexed+cisplatin Gemcitabine+cisplatin Erlotinib
***"Economics of treatments for non-small cell lung cancer"*, (Chouaid et al. 2009)**	2009	"Particular emphasis on more recently approved agents" Chemotherapy, surgery and/or radiotherapy Docetaxel Pemetrexed Erlotinib

6.3 Evidence analysis – definitive treatment of non-small cell lung cancer

The following sections present information gathered from recent (2009-2014) reviews when available, and then from essential information on primary evidence where no reviews are available. The evidence identified for the DTx of NSCLC is presented in Table 6.3, along with the respective number of primary studies and reviews.

Table 6.3 Primary evidence and reviews identified for definitive treatment of non-small cell lung cancer

Definitive Treatment Options for NSCLC	Primary studies	Number of reviews
Stage I, II, & IIIa		
1) Surgery - Surgery (lobectomy, limited sublobar resection, OR video-assisted thorascopic surgery) followed by definitive radiation therapy (external beam radiation therapy, 3D-CRT, intensity modulated radiation therapy, OR stereostatic radiation therapy) if surgical margins are positive.	3	1
2) Surgery + Adjuvant Chemotherapy - Surgery (lobectomy, limited sublobar resection, OR video-assisted thorascopic surgery) followed by definitive radiation therapy (external beam radiation therapy, 3D-CRT, intensity modulated radiation therapy, OR stereostatic radiation therapy) if surgical margins are positive. + chemotherapy (cistplatin, vinorelbine / cistplatin, OR paclitaxel / carboplatin)	6	1
3) Mono Definitive Radiation Therapy: External beam radiation therapy, 3D-CRT, intensity modulated radiation therapy, OR stereostatic radiation therapy	1	-
Stage III & IV, No Driver Mutation Identified • **Initial treatment**		
5) Platinum Based Chemotherapy: cisplatin / pemetrexed OR cisplatin / docataxel, cisplatin / paclitaxel OR cisplatin / vinorelbine OR cisplatin / topotecan OR cisplatin / gemcitabine OR Carboplatin / pemetrexed OR carboplatin / docataxel OR Carboplatin / paclitaxel OR Carboplatin / vinorelbine OR carboplatin / topotecan, OR carboplatin / gemcitabine.	13	3
7) Platinum Based Chemotherapy + Bevacizumab: carboplatin / paclitaxel / bevacizumab OR cisplatin / gemcitabine / bevacizumab	3	-
9) Platinum Based Chemothearapy + Cetuximab: Cisplatin / Vinorelbine / Cetuximab	2	-
11) Non-Platinum Chemotherapy: Gemcitabine / docetaxel OR gemcitabine/paclitaxel OR paclitaxel / vinorelbine OR gemcitabine / vinorelibne OR pemetrexed / gemcitabine	9	3
13) **Chemoradiotherapy:** cisplatin / etoposide / radiation therapy OR carboplatin / paclitaxel / radiation therapy	2	-
Stage III & IV, No Driver Mutation Identified • **Maintenance options for Stable Disease:**		

4) Platinum based chemotherapy ➔ Maintenance ➔ Driver Mutation still not identified: pemetrexed OR docetaxel OR gemcitabine OR erlotinib OR bevacizumab	2	1
6) Platinum based chemotherapy ➔ Maintenance ➔ EGFR mutation now identified: erlotinib OR gefitinib OR afatinib	1	1
8) Platinum based chemotherapy ➔ Maintenance ➔ ALK fusion oncogene now identified: crizotinib	1	-
Stage III & IV, Driver Mutation Identified • **Treatment Options for Progressive Disease:**		
10) Driver mutation still not identified and < 6 moths since discontinuation of therapy, use non-cross-resistant regimen of: docetaxel OR pemetrexed OR erlotinib	1	3
12) Driver mutation still not identified and > 6 months since discontinuation of therapy: consider retreatment with same regimen	-	-
14) **EGFR mutation now identified:** erlotinib OR gefitinib OR afatinib	-	1
16) **ALK fusion oncogene now identified:** crizotinib	1	-
18) **HER2 mutation now identified:** trastuzumab + chemotherapy OR afatinib OR temirolimus	-	-
Stage III & IV, Driver Mutation Identified • **Maintenance options for stable disease:**		
20) EGFR mutation Identified: erlotinib OR gefitinib OR afatinib:	14	1
19) ➔ **Maintainance for Stable Disease:** Continue agent until disease progression	- -	- -
21) ➔**Treatment for Progressive Disease:** follow treatment options for Stage III & Stage IV, No Driver Mutation Identified		
24) **ALK fusion oncogene identified:** crizotinib	1	-
23) ➔ **Maintainance for Stable Disease:** crizotinib	1	-
25) ➔ **Treatment for Progressive Disease:** certinib	-	-

6.3.1 Stage I, II, & IIIa: Surgery; Surgery + Adjuvant Chemotherapy, and; Mono Definitive Radiation Therapy

6.3.1.1 Reviews

Only 1 of the 6 reviews evaluated surgery – the preferable treatment for early-stage diagnosis, and categorized herein as Stage I, II & IIIa. The review by Chouaid et al., (2009) found that high quality economic analyses are lacking, though for patients with localized disease, adjuvant chemotherapy appears to have greater cost effectiveness than observation; and in locally advanced disease, combined modalities (chemotherapy, surgery and/or radiotherapy) are probably cost effective.

There were no reviews examining mono definitive radiation therapy, including external beam radiation therapy, 3D-CRT, intensity modulated radiation therapy and stereostatic radiation therapy.

6.3.1.2 Primary studies

One primary study by Kent et al., (2005) found that postoperative computed tomography (CT) may be a cost-effective intervention to detect the incidence of second primary lung cancer (SPLC) in selected patients with previously resected stage IA NSCLC. In the initial (base case) analysis, the cost of surveillance CT was $US 47,676 per QALY gained, implying cost effectiveness. However, many factors rendered surveillance CT cost ineffective, including:

(1) being over age 65 age at entry into the surveillance program

(2) cost of CT greater than $700

(3) incidence of SPLC of less than 1.6% per patient per year of follow-up, and

(4) a false positive rate of surveillance CT greater than 14%.

6.3.2 Stage III & IV, No Driver Mutation Identified', and 'Stage III & IV, Driver Mutation Identified'

It is difficult to disaggregate reviews and studies into the two categories of Stage III and IV NSCLC, because many of the primary studies and reviews state that the population studied had 'advanced disease', but do not always state whether the treatment is being assessed in patients with/without driver mutation having been identified. For this reason, reviews and primary studies are discussed in relation to the treatments used, as opposed to the diagnosis or treatment pathway. In Table 6.2, stage III and IV NSCLC are further divided into initial treatment; maintenance options for stable disease, and; treatment options for progressive disease. The numbering (e.g. **1) Surgery**), refers to the treatment branch number, meaning that Surgery is treatment branch number 1.

6.3.2.1 Reviews

Cisplatin/platinum-based chemotherapy and/or various combinations of gemcitabine, paclitaxel, docitaxel, gefitinib, vinorelbine, pemetrexed and erlotinib

The 5 remaining reviews focused on treatments for advanced stages of disease, especially cisplatin/platinum-based chemotherapy and/or various combinations of gemcitabine, paclitaxel, docitaxel, gefitinib, and vinorelbine. This is perhaps not surprising, given that approximately 51% of patients present with advanced disease at diagnosis (Ferlay et al., 2010).

A review by Jäkel et al., (2013) included 29 studies evaluating second-line or later-line regimens for NSCLC. Most studies included in the review were either cost-effectiveness or cost-utility evaluations. Jäkel et al. found that docetaxel, pemetrexed and erlotinib are for the most part cost-effective/cost-saving second-line therapies compared with best supportive care (BSC). Within this review, Jäkel et al. identified 6 erlotinib HTAs, across England's National Institute for Health and Care and Excellence (NICE), the Scottish Medicines Consortium (SMC), and Australia's Pharmaceutical Benefits Advisory Committee

(PBAC), and four for pemetrexed - one by NICE and three by SMC - and found that erlotinib and pemetrexed were considered to be cost effective versus docetaxel by NICE, and the SMC in the final submissions. PBAC considered erlotinib to be cost effective versus BSC following a price reduction in 2008.

Brown et al., (2013) identified twenty-three trials involving >11,000 patients in total. They found that poor trial quality and a lack of evidence for all drug comparisons complicated and limited the data analysis, and outcomes and adverse effects were not consistently combined across the trials, which reduces generalizability. Few trials reported quality-of-life data despite their relevance to patients and clinicians. In the case of patients with squamous disease, there were no statistically significant differences in overall survival between treatment regimes. The mixed-treatment comparison demonstrated that, in patients with non-squamous disease, pemetrexed + platinum increases overall survival statistically significantly compared with gemcitabine + platinum [hazard ratio (HR) = 0.85; 95% confidence interval (CI) 0.74 to 0.98]; and that docetaxel + platinum increases overall survival statistically significantly compared with paclitaxel + platinum (HR = 0.79, 95% CI 0.66 to 0.93). None of the comparisons found any statistically significant differences in overall survival among patients with EGFR M+ status. Direct meta-analysis showed a statistically significant improvement in progression free survival with gefitinib compared with docetaxel + platinum and paclitaxel + platinum (HR = 0.49; 95% CI 0.33 to 0.73; and HR = 0.38; 95% CI 0.24 to 0.60, respectively). However, none of the studies reviewed were deemed relevant to decision-making in the NHS because they were not UK focused and/or they do not estimate incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY gained.

Finally, Bongers et al., (2012) conducted a systematic review to assess published cost-effectiveness studies comparing docetaxel, paclitaxel, vinorelbine, gemcitabine and pemetrexed, and the targeted therapies erlotinib and gefitinib with one another. The review identified 222 potential studies; 11 studies and six reviews were included. Bongers et al., (2012) found gemcitabine+cisplatin was cost effective compared with other platinum-based regimens (paclitaxel, docetaxel and vinorelbine). In one study, pemetrexed+cisplatin was cost effective compared with gemcitabine+cisplatin in patients with non-squamous-cell carcinoma. In second-line treatment, docetaxel was cost effective compared with best supportive care; erlotinib was cost effective compared with placebo; and docetaxel and pemetrexed were dominated by erlotinib. The review found that gemcitabine+cisplatin displayed superior cost-effectiveness in a first-line setting, as did erlotinib in a second-line setting. The Bongers et al., (2012) review found the methodological quality of economic evaluations included in their review to be 'fairly good', although transparency in costs and resource use, details on statistical tests and sensitivity analysis were points for improvement.

Zoledronic acid and denosumab

Ford et al., (2013) conducted a systematic review on randomised controlled trials assessing denosumab, bisphosphonates (BPs) or BSC in patients with bone metastases. The review found denosumab is effective in delaying skeletal-related events compared with zoledronic acid and placebo, but is similar with regard to quality of life and pain. Cost-effectiveness showed that without a patient access scheme denosumab was not estimated to be cost-effective relative to either zoledronic acid or BSC. With the

patient access scheme, denosumab was estimated to be cost-effective relative to zoledronic acid but not BSC.

von Moos, et al., (2013) also found that zoledronic acid reduces the incidence of skeletal-related events compared with placebo, and that recent phase III trials have shown that therapy with the RANK ligand inhibitor denosumab is dominant over zoledronic acid for preventing or delaying skeletal-related events in patients with bone metastases from solid tumours. von Moos, et al., (2013) also found denosumab to have a comparable safety profile to bisphosphonates, with reduced risk of renal toxicity and acute phase reactions. European data suggests denosumab is cost-effective for the prevention of skeletal-related events compared to zoledronic acid.

Main findings:

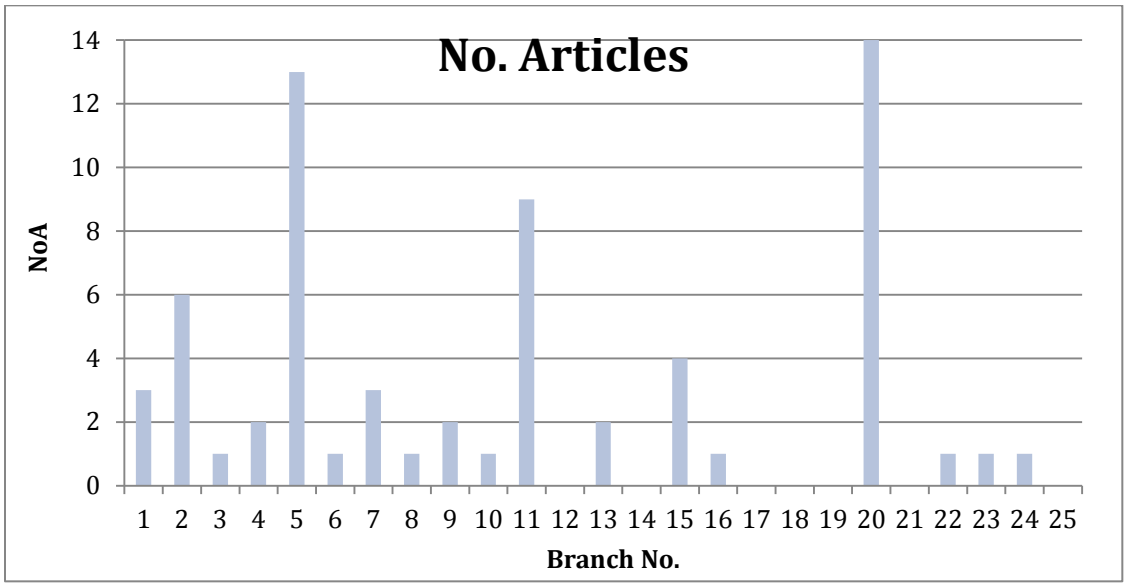
- Third-generation chemotherapies used in the first-line setting generally have acceptable incremental cost effectiveness, and docetaxel, pemetrexed and erlotinib have acceptable cost effectiveness in the second-line setting.
- Each review commented on the lack of robust economic evaluation literature, and/or commented on the poor quality of existing literature.

There were no health economic evaluation reviews for afatanib, trastuzumab, temirolimus, crizotinib or certinib.

6.3.2.2 Primary Evidence

Despite there being no health economic evaluation reviews for afatanib, trastuzumab, temirolimus, crizotinib or certinib, the following section highlights that a number of these treatments had one or more primary HEEs assessing cost effectiveness.

Figure 6.3: Articles per branch.



As illustrated in Figure 6.3, eight treatment branches had zero corresponding health economic evaluation (HEE) correlating with their use.

Figure 6.4: Branches [8] [16}

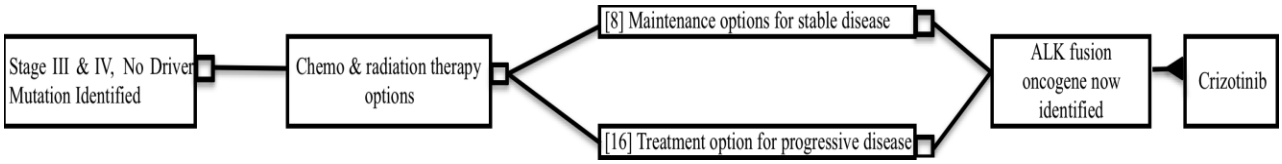
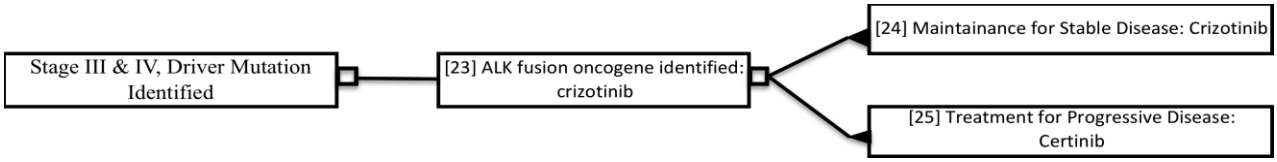


Figure 6.5 Branches [23] [24] [25]



Crizotinib is the terminal node in branches [8], [16] and [24], and an intermediate node in [23] (see Figure 6.4 and Figure 6.5). However there is only one HEE article relating to its use (Atherly and Camidge, 2012), and it does not specify which pathway, or at which stage of NSCLC it is assessed in. This means that crizotinib is being used in treatment pathways though the clinical and cost-effectiveness evidence is not necessarily relevant to its use in that context. This has considerable implications, because clinical assumptions relating the use of crizotinib in branch [8] (for example), may not hold true for the use of crizotinib in branch [16] or [24]. This could impact on both the clinical and cost-effectiveness of the treatment.

The single HEE article relating to crizotonib examined the impact of different predictive biomarker screening techniques and population enrichment criteria on the cost-effectiveness of targeted drugs in lung cancer, using ALK and crizotinib to build the initial model (Atherly and Camidge, 2012). This study found that the cost of screening dominates (compared to ALK screening of all advanced NSCLC patients) at low frequencies, and strategies to improve cost-effectiveness based on the assay cost, drug cost and the group screened should be considered

There were no articles correlating with Certinib [25].

Figure 6.6: Branch [6] [14]

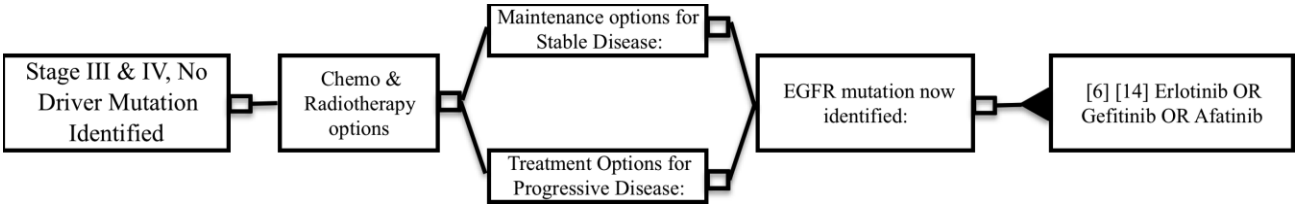


Figure 6.6 above shows branches [6] and [8]. Erlotinib and gefitinib have both been evaluated in different stages of other pathways, though there were no HEEs on afatibin. Branch [6] had one study, by Dickson et al. (2011), examining erlotinib monotherapy after previous platinum-containing chemotherapy. Dickson et al, (2011) found ICERs for the stable disease squamous population of £44,812 per QALY gained, in the stable disease non-squamous population of £68,120 per QALY gained, and, when erlotinib was compared with pemetrexed, the result was £84,029 per QALY gained. All values were above NICE's perceived willingness-to-pay threshold, and as such the use of erlotinib was not recommended in this patient population.

6.3.2.3 Generalisability

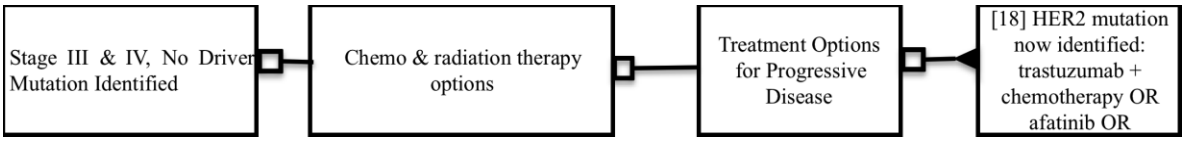
As reported in the 6 reviews, there is a paucity of robust HEE literature pertaining to NSCLC. This is exacerbated by significant variation, heterogeneity and sub-optimal reporting which further reduces the generalizability and usability of studies by decision makers. Such issues were apparent amongst the 49 primary studies evaluated for DTx of NSCLC. Improving the quality, uniformity and transparency of HEEs will increase their value to decision makers. The following facets of HEE reports represent areas where the heterogeneity made the generalizability of outcomes from the 49 primary studies included in this report impossible:

- Transparent and appropriate use of costs, especially in relation to perspective taken, which also need to be clearly categorized into one of the four main perspectives (societal, health service, hospital or patient). Despite this, there were 13 different 'perspectives' reported in the 49 articles. Of greater concern still, only 3 articles reported using a societal perspective. 4 articles did not report a perspective.
- Discounting: Although a discount rate of 3% was the most common rate applied, 5 different rates were reported, one of which applied 3% in Korea and 5% in Taiwan within the one HEE study.

- Duration of time horizons: 28 articles did not explicitly state the time horizon, and there were 10 different time horizons used, highlighting significant heterogeneity amongst those reported.
- Methods for informing preference-based outcomes: 24 of the 49 articles used QALYs as their unit of measurement. However, only 20 of these articles explicitly communicated how utility weights had been informed.
- Testing for uncertainty within HEE studies was sub optimal, especially with regards to appropriate use of probabilistic sensitivity analysis (PSA). 30% of primary studies did not report any sensitivity analysis, and only 33% of those that did conducted a PSA.
- Although QALYs and LYG represented the most commonly used measures among the primary studies, health outcomes should be limited exclusively to those relevant to decision makers. 10 of the 49 articles expressed health outcomes in terms other than QALY or LYG.

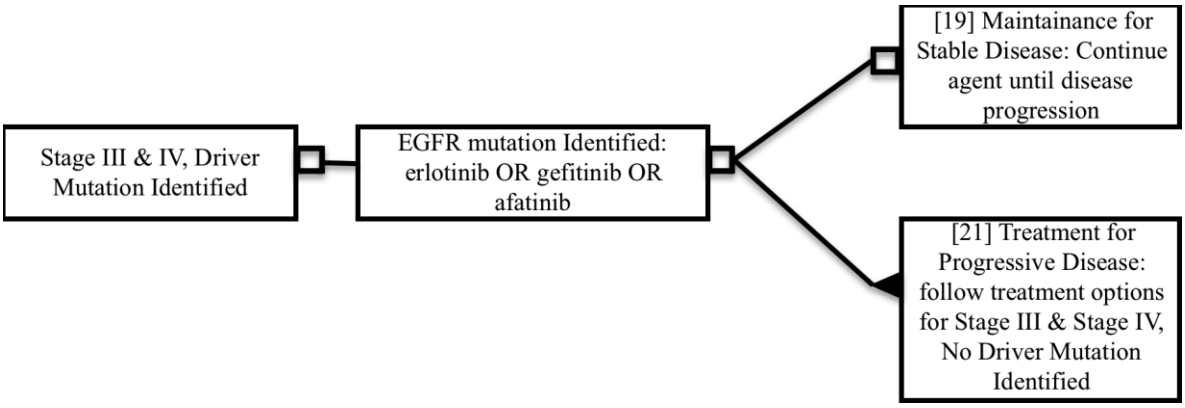
6.4 Evidence gaps in DTx for NSCLC

Figure 6.7: Branch [18]



None of the treatments (trastuzumab + chemotherapy OR afatinib) included in the terminal node in branch [18] had any HEE literature pertaining to its use.

Figure 6.8: Branch [19], [21]



There was no HEE literature exploring Branch [19] or [21]. Note that [21] is a guideline, not a treatment. There was zero literature evaluating this guideline, although the treatments recommended in the guideline may have been evaluated elsewhere.

The following pathways for NSCLC do not have any HEE literature examining cost-effectiveness: [14] afatanib, [18] trastuzumab + chemotherapy OR afatinib OR temirolimus, [24] certinib, or [25] trastuzumab + chemotherapy OR afatinib OR temirolimus.

Branches [3],[4],[6],[8],[10],[13],[16],[22] and [23] only have 1 or 2 primary studies examining their cost-effectiveness.

6.5 References

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Von Moos R et al. (2013). Reducing the burden of bone metastases: current concepts and treatment options. *Support Care Cancer*, 21(6):1773–83.

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Health Economic Evidence Analysis: Prevention and management of falls and fall risks

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7 Falls

7.1 Bibliometrics

A total of 36 economic studies were mapped to the clinical model for fall prevention in elderly populations (Table 7.1 and Figure 7.1) with the majority[1] of studies published since 2005. Of the three reviews identified, two were published between 2009 and 2014.

Table 7.1 Bibliometric data for fall prevention

PubMed/MEDLINE	
Search term	(“Accidental falls”[MeSH Terms] OR “Accident Prevention”[MeSH Terms:noexp]) ("cost-benefit analysis"[MeSH Terms] OR “Economics, Pharmaceutical”[MeSH Terms] OR “Technology Assessment, Biomedical”[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR “English Abstract”[pt] OR Letter[pt])
Number of studies	
Included in model	39
Included as “other”	13
Reviews	3
Excluded	125
Total	180
Additional references from reviewers	
Total	3

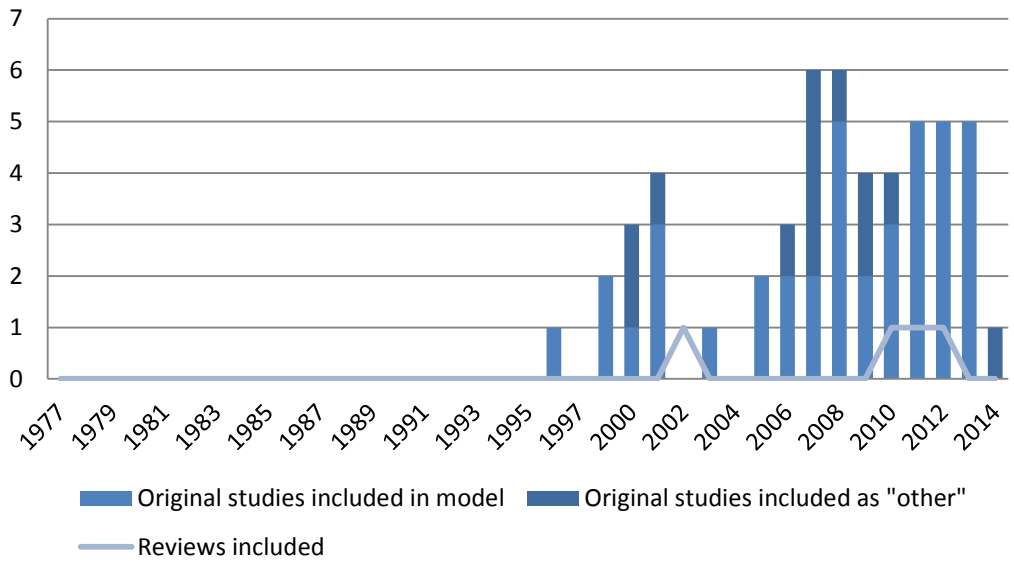

Figure 7.1 Bibliometric data for fall prevention

[1] 75% of studies or more

7.2 Review coverage

The clinical model for falls consists of 14 interventions. Of these, three (21%) were addressed by one of the two reviews published between 2009 and 2014 (Table 7.2). The remaining 11 interventions (79%) were not associated with any health economic reviews, though primary studies were available in several cases (Table 7.3 and described in sections 7.3.1 to 7.3.3).

The reviews identified for fall prevention did not address specific categories of interventions, but described studies across the range of interventions such as exercise, multifactorial interventions and home modifications (Corrieri et al., 2011). Consequently only 1-3 studies per intervention type was addressed in each review.

Table 7.2 Table of reviews for falls and associated interventions

Title and reference	Year	Interventions covered
"*Cost-effectiveness of fall prevention programs based on home visits for seniors aged over 65 years: a systematic review*" (Corrieri et al., 2011)	2011	Fall prevention based on home visits in elderly 65+ covering exercise, multifactorial interventions and home modifications
"*Does a home-based strength and balance programme in people aged > or =80 years provide the best value for money to prevent falls? A systematic review of economic evaluations of falls prevention interventions*" (Davis et al., 2010)	2010	Home based strength and balance programmes in elderly 80+

7.3 Evidence analysis

The following sections present information gathered from recent (2009-2014) reviews when available, and from essential information on primary evidence where no reviews are available. Table 7.3 summarises the volume of health economic studies and reviews identified according to each intervention.

Table 7.3 Primary health economic evidence and reviews for interventions related to fall prevention

Prevention of falls in elderly adults		
Treatment of contributory medical problems	Studies	Reviews
Vision Correction (if indicated) - with glasses or cataract surgery	3	0
Carotid Sinus Hypersensitivity Treatment - Pacemaker	1	0
Malnutrition Treatment (in individuals at risk / recently hospitalised) - Oral Nutritional Supplementation	1	0
Postural Hypotension Treatment - medication reduction, fluid optimisation, elastic stockings, or medications such as fludrocortisone or midodrine.	0	0
Foot Pain - podiatry care, orthotics, footwear subsidy, foot and ankle exercises	0	0
Osteoporosis Prevention - Calcium and vitamin D supplementation, weight bearing activities	4	0
Treatment of Delirium and Dementia - including behavioral modifications, orientation protocols, environmental modification, non-pharmacological sleep aids (eg. warm milk or herbal tea offered at bedtime, relaxing music, soft lighting, massage); use of visual and hearing aids, adequate pain treatment, and reduction in polypharmacy	0	0
Patient interventions		
Exercise - gait and balance training, strength training, flexibility, movement, general physical activity, endurance	16	2
Medication Modification - neuroleptics, benzodiazepines, antidepressants, and other sedatives	6	0
Patient Education	3	0
Multifactoral Prevention Programme - individualised	11	1
Environmental interventions and surveillance		
Environmental Assistive Technology - home safety assessments, Non-slip devices worn on shoes in winter weather conditions. Environmental Modification - do not overcrowd rooms with furniture, modify toilet seat height and / or bed height, carpeting	9	1
Call Alarm Systems	1	0
Caregiver / Provider Surveillance	0	0

7.3.1 Treatment of contributory medical problems

7.3.1.1 Vision correction

No reviews were identified for the correction of vision with glasses or cataract surgery in fall prevention. Three primary studies were identified.

One study compared a range of interventions for the general population (exercise and multi-factorial interventions) and specific populations, where expedited cataract surgery was included (Church et al., 2011). A clinical trial examined expedited first eye cataract surgery (4 weeks wait vs 12 months wait) in women over 70 years with minimal visual impairment, which averted 0.456 falls over one year and marginally increased quality of life. Economic analysis resulted in costs of GBP 4,390 per fall avoided, and GBP 35,704 per QALY gained from the health service and personal social service perspective over the first year, which was not considered cost-effective by UK standards. However the authors noted the intervention was cost-effective if a life-time perspective was taken, at GPB 13,172/QALY gained. Additionally the study sample consisted of women with minimal visual impairment, implying the cost-effectiveness could be more favorable in patients with moderate to severe visual impairment (Sach et al., 2007). A modelling study from Australia also addressed expedited cataract surgery, reporting significantly better cost-effectiveness at AU$ 2,211/QALY gained and an incremental cost of AU$ 153 per fall avoided, assuming costs were incurred in the first year and benefits accrued over 10 years. However the authors noted "*the effectiveness of these interventions is less certain due to small numbers of trials and participants*" (Church et al., 2012).

Main findings:

- Expedited cataract surgery can avert some falls in elderly over 70-75 years, but only appear cost-effective over a life-time perspective (10+ years).

7.3.1.2 Carotid sinus hypersensitivity treatment

One primary study assessed cardiac pacing against no intervention, finding 2.987 falls avoided per patient at an incremental cost of AU$ 56,111. This ICER was higher than for psychotropic medication withdrawal and expedited cataract surgery, both compared with no intervention, but was considered cost-effective by the authors. They note"*benefits associated with both [cataract surgery and cardiac pacing] are generally large and occur for a number of years […] however, this result is based on limited effectiveness data and should be interpreted with caution* " (Church et al., 2012).

Main findings:

- Cardiac pacing is associated with a higher ICER than medication withdrawal and expedited cataract surgery, but may still be considered cost-effective.

7.3.1.3 Malnutrition, postural hypotension, foot pain, delirium and dementia

No economic evidence was identified on interventions to prevent falls related to postural hypotension, foot pain, delirium or dementia. A single study was identified addressing multidisciplinary nutritional support for undernourished elderly people in nursing homes and home care. Nutrition coordinators are

active in the control and intervention groups, and the intervention group in addition receive the multidisciplinary nutrition support for 11 weeks, focusing on treating modifiable nutritional risk factors. Quality of life is collected via EQ-5D, together with physical performance, nutritional status, fall incidence and other outcomes. The economic evaluation is planned as a cost-effectiveness and cost-utility analysis including direct costs and cost of training of relevant staff for the intervention (Beck et al., 2014).

Main findings:

- A clinical trial is assessing the effect of a nutritional intervention for undernourished elderly care home residents. A cost-effectiveness analysis is planned but not yet reported.

7.3.1.4 Osteoporosis prevention

No reviews were identified on the prevention of osteoporosis in relation to falls, however four primary studies were identified. One American study assessed cost-effectiveness of universal vitamin D supplementation versus vitamin D deficiency screening, but included only direct costs of supplements and treatment following falls. The authors concluded population screening was slightly more cost-effective than universal supplementation among ages 65-80 (Lee, Weber & Colón-Emeric, 2013). In a clinical trial in New Zealand, participants aged 75+ with impaired vision received either a home safety and modification programme or an exercise programme plus vitamin D supplementation. The exercise and vitamin D supplementation programme did not reduce fall incidence although within the group stricter adherence was associated with fewer falls. The authors concluded the home safety and modification programme was more cost-effective (Campbell et al., 2005).

An Australian study estimated the cost-effectiveness of vitamin D supplementation, finding an incremental cost per fall avoided at AU$6, per hospitalization avoided of AU$80, and per QALY gained of AU$106 which was considered cost-effective (Church et al., 2011). In America, seven interventions to prevent falls were compared including vitamin D supplementation, which was found to be the most cost-effective together with home modification. Home modification was associated with an ICER of US$ 14,794 over vitamin D supplementation. Four interventions (two multifactorial interventions, medication management, muscle/balance training) were dominated by vitamin D supplementation, home modification, or both. As the study addressed multiple interventions with the same goal, the authors noted "f*uture studies can focus on whether there are other opportunities for synergistic effects of multiple interventions that can be combined. Such analyses were not conducted in the current study, because there is little evidence to suggest that the costs or effects are anything other than simply additive*" (Frick et al., 2010).

Main findings:

- Study and intervention designs of the four studies were too dissimilar to draw general conclusions. It is unclear whether home modification or vitamin D supplementation is more cost-effective, however these interventions appear to be among the more cost-effective compared to multifactorial interventions, psychotropic medication management and muscle/balance training.

7.3.2 Patient interventions

7.3.2.1 Exercise

Exercise was used as an intervention to prevent falls in various populations and risk groups. Two reviews addressed the topic, one of which identified nine primary studies covering exercise and other interventions. Only one of these reported a cost-utility analysis, with the remaining studies reporting cost-effectiveness (seven) or cost-benefit analysis (one). The most common economic outcome was cost per fall prevented (Davis et al., 2010). All studies covered by the review were also identified in the present search, where 15 studies were identified. In the second review, one intervention on exercise was analysed along with interventions of other types (Corrieri et al., 2011)

Three studies addressed interventions in elderly people with Parkinson's Disease (PD). A clinical trial evaluated an exercise program in 130 PD patients over 20 weeks but was not sufficiently powered to identify significant differences. The authors report a tendency towards lower health and social care costs and increased QALY's in the intervention group and estimate an 80% probability of the intervention being cost-effective according to UK standards. The authors also call for larger trials over a longer time horizon (Fletcher et al., 2012). Two Australian clinical trials are assessing the cost-effectiveness of exercise and physical therapy in fall prevention among PD patients. The exercise program targets "*three potentially remediable risk factors for falls (reduced balance, reduced leg muscle strength and freezing of gait)*", will enroll 230 patients and will establish cost-effectiveness from the health provider's perspective. No results are reported to date (Canning et al., 2009). Two physical therapy interventions are being compared in the second study: strategies to prevent falls, enhance balance and improve mobility; compared with progressive resistance strength training. Cost-effectiveness will be estimated from the health system perspective (Watts et al., 2008).

Falls in elderly with cognitive impairment is being addressed by a clinical trial where a combined exercise and home modification intervention is compared with usual care. An economic analysis is planned from the perspective of the health and community service provider, including cost-effectiveness (falls prevented, emergency department presentations avoided, hospitalisations avoided) and cost-utility (based on EQ-5D) analyses (Close et al., 2014).

Among elderly people (75+) with impaired vision, a clinical trial with 391 participants in New Zealand compared a home modification programme, an exercise programme plus vitamin D supplementation, a combination of both, versus social visits alone. As described in section 7.3.1.4, the home modification programme was most effective in reducing incidence of falls, and was the most cost-effective intervention (Campbell et al., 2005).

A nurse delivered home exercise programme was studied in two clinical trials in New Zealand, enrolling 240 people aged 75+ at a community health service clinic and 450 people aged 80+ from 32 general practices. In the first trial, the cost per avoided fall was NZ$ 1,803 or NZ$ 155 if averted hospital costs were considered (Robertson et al., 2001a). In the second study, cost per avoided fall was NZ$ 1,519 but no differences in hospital costs were observed in exercise vs control centres (Robertson et al., 2001b). Both studies conclude that nurse led exercise interventions are effective in reducing falls.

Nine studies addressed cost-effectiveness of exercise interventions in the home and community, of which three focused on elderly women. A modelling study considered the cost-effectiveness of a strength and balance exercise programme in Norwegian women aged 80+, and concluded that cost savings for averted fall treatments were 1.85 times higher than the cost of implementing the programme (Hektoen, Aas & Lurås, 2009). A similar programme of muscle strength and balance improvement in women age 80+ was evaluated in New Zealand, but despite a decrease in falls, the authors concluded there was no significant reduction in healthcare costs (Robertson et al., 2001c). A third study compared of resistance training with balance and toning exercises in women aged 65 to 75 over 1 year, and found resistance training dominated balance/toning exercises (Davis et al., 2011a).

The remaining five studies addressed the general elderly population. A clinical trial in elderly people (65+) compared class-based and home-based exercise with usual care (Iliffe et al., 2010). Class-based exercise was associated with fewer falls during 12 months after the intervention phase, and both exercise interventions showed improvement in balance confidence, however there was no difference in QALY's compared with usual care and consequently no cost/QALY ICER was calculated (Iliffe et al., 2014). In Australia, an economic analysis was performed for a community-based falls prevention programme, specifically comparing the cost of programme versus hospital costs averted. The study compared the intervention region with two control regions (region with similar demographics or state-wide), and concluded significant hospital costs were averted per intervention dollar at the ratio 20.6:1 (Beard et al., 2006). Also in Australia, the most cost-effective intervention in fall prevention was Tai Chi, in comparison with 12 other interventions including exercise, expedited cataract surgery, psychotropic medication withdrawal, various multifactorial programmes and vitamin D supplementation (Church et al., 2011). Similar results were reported separately by the same author (Church et al., 2012).

Group thai chi was one of the most cost-effective options for preventing falls in elderly adults compared with vitamin D supplementation, home modifications, muscle balance training, multifactorial interventions and usual care, although the authors note it was only supported by one clinical trial (Frick et al., 2010).

Commenting on methodological issues in their review, Davis et al. note "*we have not found quality-of-life measures to be sensitive to change in our falls prevention studies despite the beneficial outcomes of the trials*", potentially explaining why cost per fall averted tends to be the outcome of choice in fall prevention economic evaluations. The authors also note "*One major problem with comparing the economic evaluations in our systematic review was that some incremental cost-effectiveness ratios incorporated intervention costs only, some included fall-related costs, and some included total healthcare costs*" (Davis et al., 2010), which is likely to be a general issue across conditions and interventions, and is one example of how study heterogeneity can limit practical conclusions from the literature.

Main findings:

- Out of three clinical trials, two are ongoing/unreported and only one has reported on cost-effectiveness of fall prevention in Parkinson's disease patients. This study was inconclusive, but suggested a tendency for exercise to be cost-effective in avoiding falls.
- In people with impaired vision, home modification may be more cost-effective than exercise plus vitamin D supplementation, as evidenced by a single study.
- A nurse-led exercise intervention appears effective in preventing falls but at higher cost even when averted hospitalization costs are taken into account.
- Studies from Norway, New Zealand and Australia report conflicting conclusions on the economic consequences of exercise programmes, ranging from no significant effect on health care costs (New Zealand), over somewhat beneficial (Norway) to very beneficial (Australia).
- Various forms of exercise can be beneficial and cost-effective in reducing falls, however subtle differences in the interventions offered (home-based, class-based, Tai Chi, strength, balance, etc.) appear to have a significant impact on the cost-effectiveness.

7.3.2.2 Medication modification

No reviews were identified for the modification of medications in fall prevention. Five primary studies were identified in the present search.

A clinical trial in the Netherlands is assessing the cost-effectiveness of withdrawing fall-risk increasing drugs in people aged 65+ having presented at an emergency department after a fall. Costs and quality of life are recorded, and an economic evaluation will be performed according to Dutch guidelines. No results have been reported at time of writing (Hartholt et al., 2011). A modelling study from the Netherlands estimated drug withdrawal, when appropriate, reduced the risk of falls and resulted in net cost savings of EUR 491 per fall averted (van der Velde et al., 2008). In Australia, psychotropic medication withdrawal was associated with a cost of AU$ 1,123 per fall averted and AU$ 16,584 per QALY gained, which was more cost-effective than a range of other interventions (by QALY) including exercise and multifactorial interventions (Church et al., 2011).

Two studies were set in America. One addressed a pharmaceutical intervention in elderly patients in rehabilitation centres and estimated cost savings of US$ 7.74 per patient per day in the intervention group (Haumschild et al., 2003). The other, a modelling study of seven interventions, found psychotropic medication withdrawal was the most cost-effective intervention compared with multifactorial interventions, home modification, vitamin D supplementation and exercise (Frick et al., 2010).

An as yet unpublished cluster randomized trial of 30 care homes assessed the clinical and cost-effectiveness of a multi-professional team approach to medication reviews in care homes, using number of falls and potentially inappropriate prescribing as primary outcomes. An economic evaluation from the NHS and personal social services perspective was undertaken as part of this (Desborough et al., 2011).

Main findings:

- Four separate studies have found psychotropic medication withdrawal to be either cost-saving or more cost-effective than other interventions to prevent falls. Economic analyses from two clinical trials are anticipated.

7.3.2.3 Patient education

No reviews were identified on the topic of patient education in fall prevention. Three primary studies were identified. One study reported an economic evaluation from a clinical trial assessing a fall prevention intervention in a hospital setting. A cost-effectiveness study was undertaken from the health system perspective, showing the intervention cost AU$ 294 per fall averted. The study found the intervention would be dominant over usual care if the proportion of patients falling under usual care conditions was 4% or greater (Haines et al., 2013).

Two studies addressed specifically the fear of falling in the elderly. One clinical trial is assessing the effect of using the Nintendo WiiActive video game in improving fall efficacy (a measure of fear of falling in performing daily activities) and in reducing self-reported falls vs. standard gym-based rehabilitation in the elderly. Quality of life (assessed with EQ-5D) and fall history is recorded, cost-effectiveness (cost per fall averted) and cost-utility analysis will be carried out (Kwok et al., 2011).

Finally, a multicomponent cognitive behavioral group intervention was compared with usual care in terms effect on fear of falling and activity avoidance. The economic evaluation was based on a clinical trial of 540 community-living adults aged 70+ who reported fear of falling and fear-induced activity avoidance. Total costs were comparable between the intervention group and usual care, but the intervention group resulted in statistically significantly reduced fear of falling and activity avoidance. The cost per additional patient who was no longer afraid of falling was EUR 1,070, and the cost per additional patient no longer avoiding activity due to fear of falling was EUR 683. Regarding fear of falling, the authors estimated a 44% chance that the intervention is more cost-effective than usual care, and a 54% chance that the intervention is more effective but at a higher cost (van Haastregt et al., 2013)

Main findings:

- A single study indicated a patient education programme in hospitals could be dominant over usual care if the incidence of falls in usual care was 4% or more.
- A clinical trial is assessing the cost-effectiveness of using the Nintendo WiiActive video game in improving fall efficacy (fear of falling) and preventing falls. An economic evaluation is not yet published.
- An economic evaluation of a clinical study of a multicomponent cognitive behavioral group intervention compared with usual care found the cost per additional patient who was no longer afraid of falling was EUR 1,070, and the cost per additional patient no longer avoiding activity due to fear of falling was EUR 683. The authors estimated a 44% chance that the intervention is more effective and less costly in reducing fear of falling than usual care.

7.3.2.4 Multifactorial prevention programme

Eleven primary studies addressed various multifactorial fall prevention programmes in different settings. One review analysed two multifactorial interventions along with other types of interventions (Corrieri et al., 2011).

Two studies specifically addressed a multifactorial fall prevention program in elderly people living in nursing homes or residential care. Of these, one study using time free of femoral fractures as the economic outcome reported a mean total direct cost of EUR 29 per resident for the intervention, and an ICER of EUR 7,481 per year free of femoral fracture in residents aged 65+ (Heinrich et al., 2013). The second study was a UK clinical trial enrolling elderly people aged 60+ living at home or in residential care who had experienced a fall and contacted emergency services. A fall prevention programme was reported to incur savings of GBP 1,551 per patient over 1 year from the health and social services perspective, resulting in 5.34 fewer falls and improved quality of life. The intervention was considered dominant over usual care (Sach et al., 2012).

In contrast, in Australia multifactorial interventions were found to be among the least cost-effective interventions compared with Thai Chi and other types of exercise (Church et al., 2012) and similar results were reported in Canada (Jenkyn, Hoch & Speechley, 2012). In the Netherlands, a clinical trial assessed a multifactorial intervention consisting of assessment and treatment of fall risk factors over one year. The intervention group did not exhibit significantly improved clinical outcomes (proportion of fallers and utility) and was more costly than usual care, leading the authors to conclude the intervention was not cost-effective (Peeters et al., 2011). Virtually identical results were reported for an earlier clinical trial in the Netherlands, which also showed no effect of the intervention and therefore was not considered cost-effective (Hendriks et al., 2005, 2008). In their review, Corrieri et al. identified several limitations of this study: "*one year of follow-up may be too short to detect differences in health care consumption. Secondly, no baseline correction concerning health care utilization was conducted, so that data before the first fall remain unknown. [..] Thirdly, the calculated costs contained all health care, family and patient costs, so that results cannot be related to falls only.*" (Corrieri et al., 2011)

A modelling study showed multifactorial interventions were among the least cost-effective interventions, to which the authors note: "*Any multifactorial intervention will be more expensive than an intervention involving only one facet. The key from an economic standpoint is whether observed incremental and possibly synergistic gains in clinical outcomes outweigh the inherent incremental costs of multifactorial interventions over more efficiently mounted and applied interventions (e.g., medication management and supplementation)*" (Frick et al., 2010). Finally, a clinical trial was setup to treat risk factors in elderly people aged 65+ with a high risk of falling. An economic evaluation was planned from the societal perspective, including cost-effectiveness and –utility (Peeters et al., 2007) but the intervention was eventually shown to be ineffective (de Vries et al., 2010) and consequently no economic evaluation has been published.

Two studies suggest multifactorial fall prevention could be cost-effective. An economic evaluation was performed alongside a clinical trial of a multifactorial intervention in people aged 70+ with high risk of falling. Over one year, the rate of falls was marginally lower in the intervention arm, resulting in an ICER

of GBP 3,320 per fall averted (Irvine et al., 2010). In America, a clinical trial of people aged 70+ enrolled in a Health Maintenance Organisation (HMO) showed a multifactorial intervention was associated with cost-savings and fewer falls (dominant), particularly so for participants at high risk of falls (Rizzo et al., 1996).

Main findings:

- In nursing home residents, femoral fractures could be averted at an incremental cost of EUR 7,481 per fracture as evidenced by a single study.
- Multifactorial fall prevention programmes were dominant over usual care in two studies, potentially cost-effective in two, but least or not cost-effective in five largely due to lack of clinical effectiveness of the intervention.

7.3.3 Environmental interventions and surveillance

7.3.3.1 Environmental assistive technology

Various forms of environmental and home modifications to prevent falls or reduce consequences were evaluated in seven primary studies, no reviews were identified on the topic.

Five studies reported home or other environmental modification could be a dominant strategy. A clinical trial assessed home modifications by an occupational therapist for participants aged 65+ recruited during hospital stays. The intervention was estimated to cost US$ 4,986 per fall averted. When high cost outliers were removed, the ICER was US$ 1,921 for all subjects but dominant for subjects who had fallen in the 12 months prior to the study (Salkeld et al., 2000). Investment in energy absorbing flooring was estimated to be recouped over 10.5 years if only direct costs avoided were considered, or 11 months if indirect costs were also included. The intervention was considered dominant in terms of cost per hip fracture prevented and life year saved (Zacker & Shea, 1998). A model designed for the Australian setting showed an additional cost of US$ 1,721 per fall prevented over one year, or US$ 17,208 per injury averted. Over a 10-year period, the intervention was dominant and saved US$ 92 per person (Smith & Widiatmoko, 1998). Home modifications were also considered to be cost-saving in Hawaii according to a model using construction costs and published costs and effectiveness (Ling et al., 2008). In hospital wards for older people in the UK, the cost-effectiveness of shock-absorbing flooring was estimated from a clinical trial. Though the intervention saved costs, the authors observed a higher fall rate in the intervention arm, and noted the intervention could be dominant if the flooring itself does not result in a higher rate of falls (Latimer et al., 2013).

In elderly people 75+ with severe visual impairment in New Zealand, a home modification programme was found to reduce falls while an exercise programme did not. Neither of the interventions were effective in reducing injuries from falls. The home modification intervention cost NZ$ 650 per fall averted (Campbell et al., 2005). In an American modeling study from the health system perspective, home modification was associated with an ICER of US$ 14,794/QALY over vitamin D supplementation. Home modification dominated multifactorial interventions, muscle/balance training and standard care (Frick et al., 2010).

The "6-PACK programe", a combination of environmental modifications and nurse interventions ('falls alert' sign, supervision of patients in the bathroom, ensuring walking aids are within reach, establishment of a toileting regime, use of a low-low bed, use of bed/chair alarm), aims at reducing falls in acute care hospital wards. An economic evaluation is being carried out alongside the clinical trial, which will report costs per fall averted and cost per fall related injury averted (Morello et al., 2012). An ongoing trial of combined environmental and home modification programme was discussed in section 7.3.2.1.

Main findings:

- ICER's for home modifications are reported as costs per fall averted. Few studies report cost per injury prevented, which may be much higher and potentially a more relevant outcome.
- One study shows home modification is cost saving over 10 years but not over 1 year. Generally, studies report only cost-effectiveness over a 1-year horizon.
- Five studies suggest home modification is or can be a dominant strategy under certain conditions, ie. targeting high risk individuals or considering costs over a longer (10 year) time horizon. Under other conditions, the intervention could be more effective at additional cost.
- Two studies found home modification was associated with reduced incidence of falls or increased QALY's but at additional cost
- Two clinical trials have yet to report economic analyses, one assessing a nurse-led intervention including environmental modifications in the acute hospital setting; the other assessing environmental modifications in combination with exercise in elderly with cognitive impairment

7.3.3.2 Call alarm systems

One study assessed the cost-effectiveness of bed and bedside chair pressure sensors linked to radio-pagers in hospital care for the reduction of fall incidence. A randomized trial of 1,839 participants showed there was a slight but insignificant difference in the incidence of falls between the intervention and control group, and no significant difference in QALY's. The authors conclude the intervention was not effective or cost-effective in reducing in-patient bedside falls or time to first fall (Sahota et al., 2014).

Main findings:

- Bed and bed-side chair pressure sensors linked to radio-pagers were not found to be effective or cost-effective in preventing falls in the acute in-patient setting in the UK (one study)

7.3.3.3 Caregiver/provider surveillance

No economic evidence was identified on caregiver/provider surveillance in the management of falls.

7.4 Evidence gaps in interventions to prevent falls

Observations from published studies:

- Though some studies assess a variety of interventions such as home modification, exercise, medication withdrawal and cardiac pacing (Church et al., 2012) there is no evidence on the interaction between interventions, ie. whether costs and effects may be additive, synergistic or

even counter-effective, except for the cases of "multifactorial interventions". The evidence for multifactorial interventions is mixed between dominant, cost-effective and non-cost-effective.

- Falls may be a relevant outcome in economic evaluation of a range of treatments, such as eye surgery, but are not always included. Health effects may be captured to some extent in HRQoL measures such as EQ-5D and SF-36, although it is debated how well sensory perceptions such as hearing and vision are captured (Sach et al., 2010), and falls may only be registered if leading to significant injury.
- Studies tend to present cost per fall averted. This is not necessarily informative, as falls do not always result in (treatment requiring) injury. Further, cost per fall averted is not a policy relevant measure. An open question is how to best undertake economic evaluations if generic tools are inadequate and fall-specific outcomes are too narrow
- Economic research requires a common meaningful definition of what a fall is and how this is recorded/monitored accurately.
- Falls are not an independent issue – they are linked with a number of other issues including vision, lack of independence and pharmacy.
- Follow-up tends to be over a one year period in most studies. Coerrieri et al. note this as a limitation in all the studies of their review (Corrieri et al., 2011) and the cost-effectiveness may change significantly if considered over a life-time horizon, eg. GBP 35,704 per QALY over the first year compared with GPB 13,172/QALY over a lifetime horizon (Sach et al., 2007)
- Recommendations have been made for conducting and reporting economic evaluations of fall prevention strategies (Davis et al., 2011b) based on the general checklist by Drummond et al (Drummond et al., 2005), however adherence to this checklist in studies subsequently published is not known.

7.5 References

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Health Economic Evidence Analysis: Management of Chronic Obstructive Pulmonary Disorder

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8 Chronic obstructive pulmonary disorder

8.1 Bibliometrics

A total of 68 economic studies were mapped to the clinical model for chronic obstructive pulmonary disorder (COPD) (Table 8.1 and Figure 8.1) with the majority[1] of studies published since 2004. Of the 11 reviews identified, four were published between 2009 and 2014.

Table 8.1 Bibliometric data for chronic obstructive pulmonary disorder

PubMed/MEDLINE	
Search term	"Pulmonary Disease, Chronic Obstructive"[MeSH Terms] ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	68
Included as "other"	63
Reviews	11
Excluded	125
Total	267

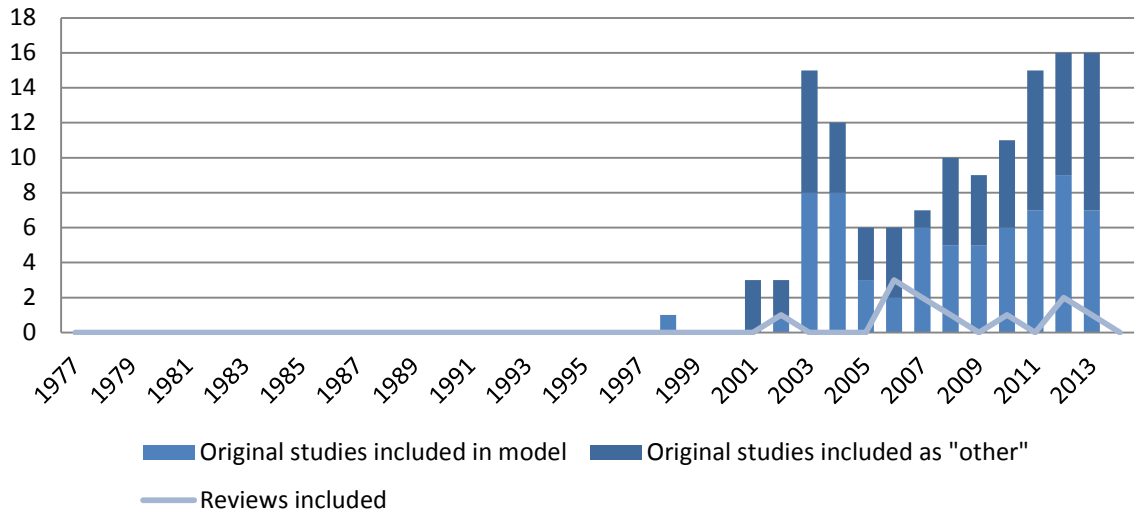

Figure 8.1 Bibliometric data for chronic obstructive pulmonary disorder by year

8.2 Review coverage

The clinical model for chronic obstructive pulmonary disorder (COPD) consists of 58 treatment modalities. Of these, 10 treatments (17%) were addressed by at least one of the four reviews published

[1] 75% of studies or more

between 2009 and 2014 (Table 8.2). The remaining 48 treatments (83%) were not associated with any health economic reviews, though primary studies were available in several cases (Table 8.3 and described in sections 8.3.1 to 8.3.7).

Of the four reviews, three addressed pharmaceuticals for the treatment of COPD. The fourth review covered multidisciplinary disease management programmes (DMP's), in which the authors note "*essential determinants in improving health outcomes of COPD patients are behavioural changes in physical activity, diet and smoking. Thus, assessment and treatment of the airways alone is evidently insufficient in the care of COPD*" and "*COPD requires an integrated, tailor-made approach. Such integrated approach mostly asks for a transformation in the healthcare organization from acute and reactive to proactive and planned healthcare*". Some elements which are commonly part of DMP's include self-management and multidisciplinary care, as well as integration of healthcare delivery with the community. Such elements are addressed in a few sections of this report (ie. 8.3.3.2 and 8.3.6.1) but DMP's are not systematically addressed in this report. Briefly, the authors of the DMP review note that these programmes tend to decrease healthcare costs if programme costs are excluded, but that "*the results need to be interpreted with caution as the inclusion of all relevant costs could result in much lower cost savings, or even a total cost increase*". Overall, DMP's tend to be associated with small but positive changes in biomedical/physiological health outcomes and quality of life (Boland et al., 2013).

The most recent review on pharmacological treatment of COPD included studies published until November 2011 and considered all main types of pharmacotherapy (Rutten-van Mölken & Goossens, 2012).

Table 8.2 Table of reviews for chronic obstructive pulmonary disorders and associated treatments

Title and reference	Year	Treatments covered
"*The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis*" (Boland et al., 2013)	2013	Multidisciplinary disease management programmes for COPD
"*Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues*" (Rutten-van Mölken & Goossens, 2012)	2012	Pharmacological maintenance of COPD
"*Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease*" (Chong, Karner & Poole, 2012)	2012	Comparison of relative clinical effects of tiotropium alone versus long-acting beta$_2$-agonists (LABA) alone
"*Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence*" (Mauskopf et al., 2010)	2010	Cost-effectiveness of tiotropium compared with other current COPD therapies

8.3 Evidence analysis

The following sections present information gathered from recent (2009-2014) reviews when available, and from essential information on primary evidence where no reviews are available. Table 8.3 lists the volume of evidence identified per intervention.

Table 8.3 Identified economic evidence on chronic obstructive pulmonary disorder

Stable COPD	Studies	Reviews
Lifestyle Modifications		
Smoking Cessation / Avoid Smoke Exposure	11	0
Regular Physical Activity	1	0
Nutrition Counseling: Sufficient Protein Intake	0	0
Vaccination		
Pneumococcal Vaccine	0	0
Annual Influenza Vaccine	2	0
Respiratory Therapy		
Long-Term Oxygen Therapy	4	0
Pulmonary Rehab	4	0
Non-invasive positive pressure ventilation	1	0
Secretion Clearance: postural drainage, positive expiratory pressure therapy, forced expiratory technique, and flutter valve therapy	0	0
Pharmacology		
Short-acting bronchodilators (SAMA, SABA, combinations)	1	1
Long-acting bronchodilators (LAMA, LABA)	20	3
Combination of LAMA plus LABA plus ICS	3	1
Long-acting bronchodilator plus ICS	10	1
Phosphodiesterase-4 (PDE4) inhibitors	4	1
Surgical Treatment		
Lung Volume Reduction Surgery	6	0
Transplantation	1	0
Patient Education		
Proper medication administration, recognizing symptoms, and making end-of-life decisions	8	0
Palliative Care		
Options: morphine, hydromorphone, oxycodone, fentanyl, benzodiazipines, tri-cyclic antidepressants, major tranquilizers, oxygen, hospice	1	0

8.3.1 Lifestyle modifications

Lifestyle modifications include smoking cessation, regular physical activity and nutrition counselling. No economic evidence was identified for nutrition counselling.

8.3.1.1 Smoking cessation

A clinical trial assessed the cost-effectiveness of a high- vs. medium-intensity smoking cessation programme in COPD patients over 12 months. The high-intensity programme resulted in lower overall

health care costs than the medium-intensity programme, including the cost of the intervention, as well as fewer exacerbations, fewer hospital days and more tobacco quitters. The high-intensity programme was consequently considered dominant over the medium-intensity programme (Christenhusz et al., 2012). Prenger et al. subsequently argued that the effect of behavioral interventions may be understated if future behaviors beyond the study period are not taken into account. They re-analysed the clinical trial of Christenhusz et al., using the Transtheorical Model,[2] and found that the proportion of simulations in which the high-intensity smoking cessation was dominant rose from 58% to 79%. They concluded *"this study showed that modeling of future behavioral change in CEA of a behavioral intervention further strengthened the results of the standard CEA. Ultimately, modeling future behavioral change could have important consequences for health policy development in general and the adoption of behavioral interventions in particular*" (Prenger et al., 2013).

An additional clinical trial with 255 participants assessed the use of two different antidepressants against placebo in smoking cessation over a 12-week intervention and 1-year followup. Both antidepressants, bupropion and nortriptylene, resulted in higher but statistically insignificant prolonged abstinence rates than placebo. The cost per quitter compared with placebo was EUR 2,097 for bupropion or EUR 10,640 for nortriptylene. Costs of the intervention, medications and indirect costs (absenteeism) were included, but not costs of any exacerbations (Van Schayck et al., 2009).

Four modeling studies also addressed cost-effectiveness of smoking cessation in COPD patients. One study evaluated varenicline, a nicotine receptor partial agonist, against placebo from the perspective of the health care systems of Spain, UK, France, Germany, Greece and Italy, and reported ICER's of EUR 4,519 to EUR 10,167 per QALY gained (Lock et al., 2011).

Two studies evaluated cost-effectiveness of smoking cessation without considering specific interventions or using categories of interventions. For a modelled UK cohort of COPD patients, smoking cessation would yield an additional 0.68 QALY's to remaining life and incur savings of GBP 1,824 per patient. Interventions were considered to be cost-effective "*even when hypothesizing expensive smoking cessation intervention programmes associated with low success rates*" (Atsou, Chouaid & Hejblum, 2011). A second model, based on nine clinical trials, assessed several categories of intervention: usual care, minimal counseling, intensive counseling and intensive counseling plus pharmacotherapy, with continuous abstinence rates of 1.4%, 2.6%, 6.0% and 12.3% respectively. The model assumed 1-year implementation, and modelled outcomes over 25 years. Compared with usual care, ICER's for minimal, intensive and intensive counseling plus pharmacotherapy were EUR 16,900, EUR 8,200 and EUR 2,400 respectively (Hoogendoorn et al., 2010).

[2] The Transtheoretical model is "a stage-oriented model that describes readiness to change […] A number of qualitatively different, discrete states, the 'stages-of-change', are key constructs of the Transtheoretical model. It provides an algorithm that distinguishes 6 stages; the focus of this study is on the first three 'pre-action' stages: (1) precontemplation (e.g., no intention to quit smoking within the next 6 months); (2) contemplation (e.g., intending to quit smoking within the next 6 months); and (3) preparation (e.g., intending to quit smoking within the next 30 days) [..] These pre-action stages provide probabilities for the actual transition to the fourth stage, the 'action stage', in which full behavioral change is achieved" (Prenger et al., 2013)

Finally a model of interventions for COPD in Ontario, Canada, included intensive counselling, nicotine replacement therapy, nicotine replacement plus intensive counselling, and bupropion against usual care. The model included all direct costs including hospitalisations, but not indirect costs since the base case starting age was 65. All smoking cessation interventions dominated usual care (Chandra et al., 2012).

Main findings:

- High-intensity behavioral interventions can be dominant over medium-intensity interventions (one clinical trial study). Additionally, future intentions not captured by follow-up data can have a significant impact on the cost-effectiveness of the intervention.
- Anti-depressants appear to be cost-effective in smoking cessation (one clinical trial study), however the clinical effects reported were not statistically significant
- Four modelling studies gave mixed conclusions, with some reporting counseling and/or nicotine replacement therapy to be cost-saving and others only cost-effective. All base case ICER's however were reportedly below EUR 16,900.

8.3.1.2 Regular physical activity

A single study evaluated physical activity in COPD patients, reporting results of a small clinical trial of 38 moderate to severe COPD patients randomized to 8 sessions of supervised exercise in a hospital-based management programme, or usual care. The intervention resulted in improvements across various quality of life tools and a decrease in COPD medication costs, however no differences were observed in hospital length of stay or costs and the costs of the program were not specified. No ICER was reported (Ninot et al., 2011).

Main findings:

- Supervised exercise may be effective in improving quality of life in COPD patients and reduce medication costs (one study), however the overall cost-effectiveness of the programme is unknown.

8.3.2 Vaccination

Pneumococcal and influenza vaccines are used for patients with COPD. No economic evidence was identified for pneumococcal vaccination.

8.3.2.1 Annual influenza vaccine

Two primary studies were identified for annual influenza vaccine in COPD patients. One modelling study comparing cost-effectiveness of various interventions in sub-Saharan Africa and south-east Asia found the most cost-effective intervention was low dose inhaled corticosteroids, followed in south-east Asia by influenza vaccination, whereas in sub-Saharan Africa, vaccination was not in the top-3 most cost-effective interventions. The preferential cost-effectiveness in south-east Asia was considered to be "*because of the higher underlying burden of COPD in that region*" and because "*flu vaccine is expected to have no impact on COPD associated disability, whereas use of long term anticholinergic bronchodilator is expected to reduce COPD associated disability by up to 97%*" (Stanciole et al., 2012).

A clinical trial of 125 mild to severe COPD patients in Thailand compared costs of acute respiratory illness (ARI) between vaccinated and unvaccinated patients. Cost-savings accrued from fewer outpatient consultations, hospitalisations and mechanical ventilations required and the study estimated cost savings of Thai Baht 125,629; 538,184; and 680,647 (approx. EUR 3,060; 13,100; and 16,560) per 100 mild; moderate and severe patients, respectively (Wongsurakiat et al., 2003).

Main findings:

- The cost-effectiveness of influenza vaccination relative to other COPD interventions may depend on contextual factors such as overall burden of disease in the country, with higher burden associated with more favorable cost-effectiveness.
- In- and outpatient costs associated with acute respiratory illness averted by influenza vaccination may outweigh the cost of providing vaccination, particularly in severe COPD patients (one study)

8.3.3 Respiratory therapy

On the topic of respiratory theory, no evidence was identified on secretion clearance, including drainage, positive expiratory pressure, forced expiratory technique or flutter valve therapy

8.3.3.1 Long-term oxygen therapy

Four studies addressed the cost-effectiveness of long-term oxygen therapy. A modelling study from the US using Medicare costs found continuous oxygen therapy to be cost-effective at an ICER of USD16,124, which the authors note is more favorable than ICER's for commonly used medical and surgical therapies for COPD (Oba, 2009). It has been noted that oxygen concentrators incur additional patients costs through high electricity consumption in the order of USD11-50 per month for a 400 W device (Reisfield & Wilson, 2004).

In Ontario, Canada, long-term oxygen therapy was reported to cost on average CAD 2,261 per patient, and in the base case cost CAD 38,993 per QALY over usual care. Compared with other interventions, long-term oxygen therapy was less cost-effective than smoking cessation, multidisciplinary care teams, pulmonary rehabilitation and ventilation strategies (Chandra et al., 2012).

In sub-Saharan Africa and south-east Asia, oxygen therapy plus drugs was the least cost-effective of all strategies, at several times the cost/DALY averted as the next most cost-inefficient intervention. ICER's were reported as USD 39,307 per DALY in SSA and USD 50,651 per DALY in SE Asia, compared with eg. USD 13,261 and USD 4,010 for influenza vaccination, respectively (Stanciole et al., 2012).

Main findings:

- In the US context (one study), long-term oxygen therapy is reportedly more cost-effective than in the Canadian context (one study), where it is among the least cost-effective interventions compared with smoking cessation, multidisciplinary care teams, pulmonary rehabilitation and ventilation strategies. Oxygen therapy was also the least cost-effective intervention in the sub-Saharan African and south-east Asian context.

8.3.3.2 Pulmonary rehabilitation

Four primary studies assessed pulmonary rehabilitation in COPD patients, of which one focused on manual chest physiotherapy (MCP) techniques. This was a clinical trial of 526 participants in the UK setting, where the intervention arm received MCP in addition to active cycle of breathing techniques (ACBT) which was used in both arms. The study found no significant benefits of the MCP intervention according to the St George's Respiratory Questionnaire (SGRQ) at 6 months, and a slight decrease in EQ-5D rated quality of life. As the MCP intervention was also associated with lower costs, the authors tentatively suggested it was cost-effective, but highlighted significant uncertainty around the finding (Cross et al., 2010).

Three studies were identified on cost-effectiveness of pulmonary rehabilitation delivered in various settings. An ongoing clinical trial of 166 patients is assessing the cost-effectiveness of a home-based exercise intervention, including direct healthcare and patient-related costs. At time of writing no results have been reported from the trial (Holland et al., 2013).

A Canadian community-based pulmonary rehabilitation program was studied over two years, with healthcare costs assessed over 1 year before and after the intervention. As a control, a non-intervention group was assessed over the same time. Health status improved in the intervention arm and health service utilization and costs decreased by approx. CAD 344 per person per year (Golmohammadi, Jacobs & Sin, 2004). In Ontario, Canada, pulmonary rehabilitation was associated with an ICER of CAD 17,938 over usual care. The authors note the cost of a programme could vary depending on the setting, and reported a range of CAD 665 to CAD 2,388 for outpatient programmes. With the exception of long-term oxygen therapy, pulmonary rehabilitation was the least cost-effective of the interventions studied, including smoking cessation, multidisciplinary care teams and ventilation strategies (Chandra et al., 2012).

Main findings:

- Manual chest physiotherapy was not conclusively shown to be cost-effective, and was associated with marginally worse quality of life outcomes (one study)
- A clinical trial assessing cost-effectiveness of home-based interventions is underway
- Community-based rehabilitation appears to provide improved outcomes and is associated with lower healthcare costs following the intervention (one study), although rehabilitation in the outpatient setting was associated with an ICER of CAD 17,938.

8.3.3.3 Non-invasive positive pressure ventilation

One study from the perspective of the Ontario health system assessed cost-effectiveness of non-invasive positive pressure ventilation (NPPV) in acute COPD episodes. NPPV was compared with usual in-patient care, and additionally weaning with NPPV was compared with weaning with invasive mechanical ventilation (IMV). In both cases, NPPV dominated the comparator (Chandra et al., 2012).

Main findings:

- According to one Canadian study, non-invasive positive pressure ventilation dominates usual in-patient care in in-patient care of acute COPD episodes. Weaning with non-invasive positive pressure ventilation also dominates weaning with invasive mechanical ventilation.

8.3.4 Pharmacology

Various strategies and combinations are available for the maintenance of COPD patients using bronchodilators and inhaled corticosteroids (ICS), as described in sections 8.3.4.1 to 8.3.4.5.

As a cross-cutting observation, one study modelled the relative cost-effectiveness of treatments available in the UK setting, showing that "*for ICS-tolerant patients the cost-effectiveness frontier suggested LAMA as initial treatment. Where patients continue to exacerbate and additional therapy is required, LAMA + LABA/ICS can be a cost-effective option, followed by LAMA + LABA/ICS + roflumilast [..] The ICER in ICS-intolerant patients, comparing LAMA + LABA + roflumilast versus LAMA + LABA, was £13,764/QALY gained*" (Hertel et al., 2012).

In the present search, 10 identified studies were published after the review cutoff date of the most recent review by Rutten-van Molken and Goossens (November 1st, 2011). These are described briefly in the relevant sections.

8.3.4.1 Short-acting bronchodilators

Short-acting bronchodilator therapy includes treatment with the short acting beta agonists (SABA) albuterol or levoalbuterol; the short acting anticholinergics also known as short acting muscarinic antagonists (SAMA) ipratropium; or combinations of SABA/SAMA usually ipratropium + albuterol.

Since these drugs have been on the market for more than four decades, limited economic evaluations have been performed. Two studies have compared ipratropium with either placebo or salbutamol. Rutten-van Molken and Goossens note in their review "*the placebo controlled, trial-based cost-effectiveness study found ipratropium to be dominant*" and "*the direct comparison between ipratropium and salbutamol was an inconclusive modelling study that showed ipratropium to improve lung function but worsen SGRQ score at slightly higher cost than salbutamol*". The authors also note "*there is high-level evidence from clinical studies for the treatment guidelines to report that both of these drugs are central to the symptomatic treatment of COPD when given on an as needed or regular basis*" (Rutten-van Mölken & Goossens, 2012).

Rutten-van Molken and Goossens identified three studies on the combination of a SABA with ipratropium (SAMA). These studies concluded, respectively, that short-acting bronchodilator combination therapy was associated with a lower rate of exacerbations and net cost savings compared with either salbutamol or ipratropium monotherapy; that combination therapy significantly reduced COPD-related healthcare costs, although it did not significantly reduce all-cause and COPD related events (i.e. hospital admissions and ED visits); and that the fixed combination of salbutamol and apratropium in the same device vs. in two separate devices did not significantly alter the use of COPD related medication, although overall costs of inhaled bronchodilator use was lower in patients using the fixed combination (Rutten-van Mölken & Goossens, 2012).

Main findings:

- The SABA and SAMA drugs, having been available for over four decades, are not well studied in the economic literature, but are considered to be central to the symptomatic treatment of COPD
- Combinations of SABA+SAMA are associated with lower treatment costs vs monotherapy and lower rates of exacerbations (two studies)

8.3.4.2 Long acting bronchodilators

Long acting bronchodilators include the long acting beta agonists (LABA) salmeterol, formoterol, arformoterol, indacaterol, and vilantero, as well as the long acting anticholinergics, also known as long acting muscarinic antagonists, (LAMA): tiotropium, aclidinium, umedlidinium, and glycopyrronium. Apart from the review by Rutten-van Molken and Goossens, the LAMA tiotropium was reviewed by two recent reviews (Mauskopf et al., 2010; Chong, Karner & Poole, 2012). Chong et al. reviewed 6 studies, all of which were also reviewed by Rutten-van Molken and Goossens. Mauskopf et al. review 17 studies, the majority of which were also reviewed by Rutten-van Molken and Goossens.

Rutten-van Molken and Goossens identified 11 studies addressing salmeterol vs placebo, standard therapy, no maintenance therapy or ipratropium. According to the authors, "*all except three studies concluded that salmeterol improved health outcomes at the expense of a cost increase. Two of the three exceptions found that salmeterol was not only more effective but also less costly in the Netherlands and in Italy. The third exception found that salmeterol significantly reduced COPD-related but not total healthcare costs, nor events defined as hospital admissions and ED visits*". Only two of the 11 studies were performed alongside a clinical trial, of which only one reported a cost/QALY which was up to USD 197,000/QALY when using placebo as comparator. Modelling studies generally reported lower ICER's at USD 21,000 to USD 56,000 per QALY, with the lower ICER associated with a study extrapolating 3-year trial results to a lifetime horizon. Only one study addressed formoterol, a modelling study reporting improvements in lung function and health status at a small cost increase over ipratropium (Rutten-van Mölken & Goossens, 2012)

The same authors identified 11 primary studies on tiotropium against placebo, ipratropium or salmeterol. Total COPD related costs including drug costs were lower for tiotropium in many comparisons, and ICER's were all below USD 26,000 per QALY. Three trial-based studies over 6-12 months concurred that increased cost of maintenance treatment with tiotropium was largely or fully offset by savings in other healthcare costs, chiefly hospital admissions, compared with placebo or ipratropium. Modelling studies reported lower ICER's for tiotropium vs. ipratropium, ranging from dominant (Netherlands, Switzerland, UK) over EUR 78/QALY in Canada and EUR 8,287/QALY in Spain. For tiotropium vs. salmeterol, ICER's ranged from dominant (Netherlands, Greece, Switzerland, UK) over EUR 144/QALY in Canada to EUR 4,118 in Spain. According to the review authors, Spanish results were less favorable due to relatively short length of hospital stay for severe COPD exacerbations and relatively low cost of ipratropium (Rutten-van Mölken & Goossens, 2012).

Following the cut-off date of the review of Rutten-van Molken and Goossens, a Markov model from the NHS perspective was used to evaluate indacaterol against tiotropium or salmeterol in moderate-severe COPD patients. Indacaterol was found to dominate salmeterol with an increase in 0.008 QALY's at a cost saving of GBP 110 per patient over 3 years. Compared with tiotropium, indacaterol produced the same QALY gain but saved GBP 248 per patient. Patients in each COPD stage and mortality rate associated with very severe COPD were the most sensitive parameters of the model (Price et al., 2013). Indacaterol was was also studied from the German health service perspective against tiotropium or salmeterol. According to this study, indacaterol at 150 microgram dose was dominant against both comparators, while the maximum 300 microgram dose against tiotropium incurred EUR 28,300 per QALY gained (Price et al., 2011).

Additionally a trial-based cost-effectiveness analysis of tiotropium versus salmeterol found tiotropium was more expensive by EUR126 (health insurance perspective) or EUR 170 (societal perspective) per patient, and the ICER was EUR 1,961 or EUR 2,647 per exacerbation avoided, respectively, over 1 year. Tiotropium thus reduced exacerbations but at a higher cost (Hoogendoorn et al., 2013). Compared with usual care in the UK and Belgium for moderate to very severe COPD, tiotropium incurred EUR 18,617 in Belgium and GBP 15,567-15,890 per QALY over four years (Hettle et al., 2012). In Italy, tiotropium was modelled over a lifetime horizon against usual care from a national health service perspective and incurred EUR 7,916 per QALY gained (Zaniolo et al., 2012). Finally in the Netherlands, tiotropium was compared with salmeterol from the healthcare perspective, and was associated with an ICER of EUR 1,015 per QALY after 1 year, while tiotropium became dominant when modelled over 5 years. From a societal perspective, tiotropium was dominant after both 1 and 5 years (Hoogendoorn et al., 2012).

In the review of Mauskopf et al, 13 of the 17 studies assessing tiotropium were funded by industry (Boehringer-Ingelheim, Pfizer, PhRMA or GSK), 3 did not disclose funding, and one study disclosed "independent research funding". The review was also funded by Boehringer-Ingelheim and Pfizer, and prepared by industry authors. The authors conclude "*use of tiotropium monotherapy is associated with lower hospital and other non-drug costs and better health outcomes and is either cost saving or cost effective compared with other maintenance monotherapies*" (Mauskopf et al., 2010).

Main findings:

- Two out of 11 studies suggest salmeterol is a dominant intervention, while 8 studies demonstrate improved health outcomes at additional cost. Modelling studies suggest ICER's of USD 21,000-56,000/QALY.
- Only a single study was identified on formoterol vs ipratropium, finding formoterol to be cost-effective
- Tiotropium is cost-effective against placebo, ipratropium and salmeterol according to 11 studies, with ICER's under USD 26,000/QALY. In several modelling studies tiotropium was dominant or very cost-effective over ipratropium, depending on the cost of hospital admissions avoided. Similar results were seen for tiotropium vs. salmeterol. In both cases ICER's were EUR 8,287/QALY or less.
- Indacaterol appears to be dominant over usual care except at high doses (two studies)

- Tiotropium added to usual care is cost-effective at less than EUR 20,000/QALY (one study) or EUR 2,647 per exacerbation avoided.

8.3.4.3 Long acting bronchodilators plus inhaled corticosteroids

Combinations of long-acting bronchodilator and inhaled glucocorticoids in clinical practice include salmeterol-fluticasone, budesonide-formoterol, mometasone-formoterol, umeclidinium-vilanterol and indacterol-glyopyrronium.

Of 12 studies on inhaled bronchodilators plus inhaled corticosteroids (ICS) reviewed by Rutten-van Molken and Goossens, three reported cost-savings relative to bronchodilator monotherapy or placebo, with the remaining nine studies reporting additional benefits at higher cost. Three studies were based on clinical trials: one studied formoterol/budesonide against placebo, formoterol or budesonide and found the combination dominated all comparators. The second study, enrolling 4,237 patients from 21 countries, compared salmeterol/fluticasone individually or as a fixed dose combination against placebo. This study reported ICER's of USD 77,100/QALY in the US, and USD 24,200/QALY in Europe for the combination therapy against placebo, due to higher unit costs in the US. The third trial reported salmeterol/fluticasone dominated salmeterol monotherapy (Rutten-van Mölken & Goossens, 2012).

Five of the studies reviewed by Rutten-van Molken and Goossens were modelling studies extrapolating trial results to wider patient populations or longer time horizons, generally reporting lower ICER's than the clinical studies. One study reported cost-effectiveness was significantly better in patients with severe to very severe COPD, at CAD 21,000-26,000 per QALY, compared with moderate COPD at CAD 247,000 per QALY. Four studies were based on managed care claims data, of which one reported the ICER to reduce from USD 91,400 per life year (LY) gained to USD 27,600 per LY gained when extrapolating from 3 years to a lifetime horizon (Rutten-van Mölken & Goossens, 2012).

After the review cut-off date of Rutten-van Molken and Goossens, budesonide/formoterol plus tiotropium was compared against placebo plus tiotropium in a model covering Nordic countries. From the societal perspective the ICER was found to be EUR 174 per severe exacerbation avoided in Finland, but the intervention was dominant in Denmark, Norway and Sweden. From the healthcare perspective, the intervention was dominant in Norway but cost EUR 165-307 per exacerbation avoided in the other countries (Nielsen et al., 2013).

Main findings:

- Formoterol/budesonide dominates placebo and both components as monotherapy (one trial study).
- Salmeterol/fluticasone cost USD24,200-77,100 per QALY gained over placebo depending on country context. Salmeterol/fluticasone was however dominant over salmeterol monotherapy (two trial studies)
- Cost-effectiveness in one modelling study is shown to be improved in severe-very severe COPD over moderate COPD patients
- One medical claims data analysis showed ICER reduced from USD91,400/LY to USD27,600/LY when effects were extrapolated from 3 years to lifetime.

8.3.4.4 Combination long-acting bronchodilators, anticholinergics and inhaled glucocorticoid

Rutten-van Molken and Goossens identified two studies addressing these combinations. One study assessed tiotropium plus salmeterol (LAMA/LABA) and triple therapy with tiotropium plus fixed dosed combination of salmeterol plus fluticasone (LAMA/LABA/glucocorticoid) against tiotropium monotherapy, concluding that neither combination was economically attractive due to high additional costs with limited health gains. In contrast, a shorter clinical trial (12 weeks) concluded triple therapy with tiotropium plus budesonide/formoterol, also a LAMA/LABA/glucocorticoid combination, was cost-saving in Austrlia and Canada, and cost-effective in Sweden compared to tiotropium monotherapy.

Main findings:

- Two studies comparing triple therapy of LAMA/LABA/glucocorticoid against tiotropium monotherapy yielded opposite results, being reported as non-cost-effective (tiotropium+salmeterol+fluticasone in Canada) or dominant (tiotropium+budesonide+formoterol in Australia, Canada).

8.3.4.5 Phosphodiesterase-4 (PDE-4) inhibitiors

Rutten-van Molken and Goossens identify a single study on the PDE-4 inhibitor roflumilast. They note the cost-effectiveness analysis performed alongside the initial randomized placebo-controlled trial of roflumilast found it was not cost-effective over the whole sample due to lack of benefit. Cost-effectiveness was much better in patients with severe COPD, a subgroup with higher rates of exacerbations and higher health-care utilization prior to the trial. A new clinical trial was established for roflumilast in this patient population, finding lung function was significantly improved and rates of moderate/severe exacerbation were decreased (Rutten-van Mölken & Goossens, 2012).

Since the cutoff date for the review by Rutten-van Molken and Goossens (November 1st, 2011), two studies have been published on roflumilast. One compared roflumilast/tiotropium against tiotropium (LAMA) monotherapy in severe to very severe COPD patients using a Markov model over a 5-year horizon. This study reported an ICER of USD 15,815 per QALY (Sun et al., 2011). Roflumilast was considered as an add-on to usual COPD regimens (LAMA, LABA/ICS, LAMA/LABA/ICS) in Switzerland using a Markov model from the payer perspective over a lifetime horizon. The ICER's were CHF 12,313 (EUR 10,200), CHF 11,456 (EUR 9,500) and CHF 13,671 (EUR 11,300) for roflumilast added to LAMA, LABA/ICS or LAMA/LABA/ICS respectively (Samyshkin et al., 2013).

Main findings:

- Roflumilast was initially considered non-cost-effective for COPD patients of all severity classes (one study). Subsequently roflumilast was shown to be cost-effective in severe-very severe COPD patients when added to LAMA, LABA/ICS or LAMA/LABA/ICS at ICER's less than EUR 15,000/QALY (two studies)

8.3.5 Surgical treatment

8.3.5.1 Lung volume reduction surgery

Six primary studies were identified for lung volume reduction surgery (LVRS). An early study compared video-assisted thoracoscopy with sternotomy for LVRS through medical records of 42 emphysema patients. Postoperatively, sternotomy was associated with higher healthcare utilization and longer hospital stays. Both groups reported higher quality of life and improved oxygen dependence. Direct costs associated with the video-assisted thoracoscopy intervention were lower than for sternotomy, suggesting video-assisted thoracoscopy may be the more cost-effective intervention (Ko & Waters, 1998).

The National Emphysema Treatment Trial enrolled 1,218 patients and compared lung-volume reduction surgery with medical therapy for emphysema. Costs included medical care, medication, transport and time spent receiving treatment and were based on US Medicare records. Cost-effectiveness was calculated over the trial duration and estimated for 10 years follow-up. The ICER was estimated at USD 190,000 per QALY at 3 years, and USD 53,000 per QALY at 10 years. Subgroup analysis found surgery in patients with predominantly upper-lobe emphysema and low exercise capacity after pulmonary rehabilitation was more cost-effective at USD 98,000/QALY and USD 21,000/QALY at 3 and 10 years respectively (Ramsey et al., 2003; Ramsey, Sullivan & Kaplan, 2008). An update to these results found ICER's of USD 140,000/QALY at 5 years, projected to USD 54,000 at 10 years across all patients. In the subgroup described above, figures were USD 77,000/QALY at 5 years and USD 48,000/QALY at 10 years showing worse cost-effectiveness in the longer term that initially expected for this subgroup (Ramsey et al., 2007).

A comparison of LVRS between patients who were awake and under general anaesthesia found awake patients trended towards greater clinical improvements and survival, however the differences were not significant. Awake patients did however incur significantly lower costs (Pompeo & Mineo, 2007).

A Canadian clinical trial enrolling 62 patients, 0.21 QALY's were gained in the LVRS arm over best medical care, at an additional cost of CAD 133,900/QALY over a two-year follow-up. Surgery improved various clinical indicators such as forced expiratory volume, six minute walk test and Health Utility Index 3 (Miller et al., 2006).

Main findings:

- A single study compared video-assisted thoracoscopy with sternotomy for lung volume reduction surgery, and suggested the former was more cost-effective.
- Lung volume reduction surgery is a high-cost intervention (USD 98,000-190,000 or CAD 133,900 per QALY, three studies) but may show improved cost-effectiveness compared with medical care over time if observed benefits are sustained
- Surgery in awake patients appears to be more cost-effective than patients in general anesthesia (one study)

8.3.5.2 Transplantation

A single primary study was identified for lung transplantation, comparing the cost-effectiveness ratios of lung transplantation between patients with COPD, alfa-1 antitrypsin deficiency, bronchiectasis, cystic fibrosis, primary pulmonary hypertension, secondary pulmonary hypertension and pulmonary fibrosis. The model was implemented from a Dutch societal perspective, including direct medical and non-medical costs (such as travel costs, home help) and indirect costs in the form of productivity losses. The analysis found lung transplantation to be less cost-effective in COPD than in all other studied conditions at USD 87,400/QALY gained against USD 74,200 to USD 85,500/QALY at 3% discount rate, using a do-nothing comparator (Groen et al., 2004).

Main findings:

- According to one study, COPD is the condition in which lung transplantation is least cost-effective vs. doing nothing, when compared with alfa-1 antitrypsin deficiency, bronchiectasis, cystic fibrosis, primary pulmonary hypertension, secondary pulmonary hypertension and pulmonary fibrosis. The difference in ICER however was relatively modest.

8.3.6 Patient education

8.3.6.1 Proper medication administration, symptom recognition and end-of-life decisions

Seven primary studies addressed self-management of COPD and exacerbations. Five of these described selv-management under different conditions. A clinical trial with 116 participants assessed a layperson-led self-management support programme in moderate-severe COPD patients delivered as group sessions over 7 weeks. The course addressed five self-management skills: defining the problem, decision making, finding and using resources, forming partnerships with healthcare providers, and taking action. The intervention vs usual care trended towards higher quality of life (not statistically significant), and incurred higher total costs including healthcare and intervention costs. Indirect costs were not included. The ICER was GBP 11,700 per QALY gained. The authors note that few differences were observed between groups at 2 months, but the intervention arm showed greater improvement at 6 months follow-up (Taylor et al., 2012). A similar self-management programme was implemented in a managed care medical group in the US, which found reduced costs in the intervention group but increased primary care use. A non-significant trend towards fewer hospital admissions, bed days and emergency department visits was observed in the intervention group (Chuang, Levine & Rich, 2011).

In Norway, 62 patients with mild-moderate COPD were studied over 12 months following a patient education program employing 4 hours of schooling and consultations with a nurse and physiotherapist, emphasizing step-wise self-management. Total costs from a societal perspective in the intervention group were almost half of the control group, and clinical outcomes (reduced rescue medication and GP use) were better. The authors concluded the intervention provided improved outcomes at lower costs (Gallefoss & Bakke, 2002; Gallefoss, 2004).

An earlier self-management clinical trial with 248 COPD patients also included self-treatment guidelines for exacerbations and an exercise component. The study took a societal perspective and included costs related to healthcare use and productivity losses associated with exacerbations over one year. The

intervention and usual care arms were equally effective and costs were higher in the intervention group. The authors concluded the intervention was not cost-effective (Monninkhof et al., 2004). Similarly, a more recent clinical trial of 142 patients addressed the self-management of COPD exacerbations, randomizing patients to self-management with or without training in self-management of exacerbations. Total costs from the healthcare provider perspective, including programme costs, were lower in the intervention group, there was a non-significant trend towards lower probability for hospital admission, and a significant reduction in health care contacts. The authors conclude that self-treatment of exacerbations within a self-management programme leads to fewer exacerbations at lower cost (Effing et al., 2009).

Telephone coaching was considered as a method to decrease inpatient care among COPD patients. Trial participants were followed over median 25.5 months, and received approximately one call per month from a healthcare worker as well as a personal healthcare plan. The trial found emergency admissions and outpatient attendances were higher in the intervention group, as were secondary care costs (Steventon et al., 2013).

Main findings:

- Two clinical trials reported on self-management programmes. A layperson-delivered self-management programme was cost-effective, while a professional delivered education programme was cost-saving.
- Two clinical trials assessed self-management of exacerbations in addition to self-management of COPD. Self-management including self-management of exacerbations was non-cost-effective compared to usual care in one trial, while adding self-treatment of exacerbations to COPD self-management was dominant in another trial.
- Telephone coaching does not appear to be effective in reducing healthcare utilization of COPD patients

8.3.7 Palliative care

8.3.7.1 Pharmaceuticals, oxygen and hospice

A Breathlessness Support Service was implemented as a multiprofessional outpatient service at a London university hospital for the palliation of breathlessness from advanced disease of malignant and non-malignant origin. The service is being studied in a clinical trial vs usual care, including an economic evaluation from the societal perspective to include direct costs, costs of informal care and lost employment. No results have been reported at time of writing (Bausewein et al., 2012).

Main findings:

- An economic evaluation will be reported based on an ongoing clinical trial of a Breathlessness Support Service from the societal perspective.

8.4 Evidence gaps in treatment of chronic obstructive pulmonary disorder

Observations from published studies

- Intensive interventions to promote smoking cessation are found to be cost-effective or cost-saving. In behavioral interventions, additionally, future behavioral changes not captured during study follow-up may further improve cost-effectiveness of these interventions.
- The cost-effectiveness of exercise in improving quality of life in COPD patients is unknown
- Cost-effectiveness of influenza vaccine is not well studied, and may be sensitive to the prevalence of influenza and the severity of COPD.
- Long-term oxygen therapy appears to be the least cost-effective intervention compared with smoking cessation, multidisciplinary care teams, pulmonary rehabilitation and ventilation strategies.
- Manual Chest Physiotherapy may be cost-effective due to lower costs, but appears to offer similar or worse health outcomes than Active Cycle of Breathing Techniques. These results were associated with significant uncertainty.
- Pulmonary rehabilitation appears to be more cost-effective when delivered in a community setting than in an outpatient setting, according to two single studies.
- Having been used clinically for several decades, the SAMA and SABA drugs are not well studied in the economic literature despite being central in clinical management of COPD.
- Tiotropium and salmeterol are the most well-studied of the LABA drugs (11 studies each). Little economic evidence is available for other LABA's.
- Combinations of LABA and inhaled corticosteroids are analysed in 1-2 studies per combination, ranging from dominant over placebo and monotherapy to incurring ICER's of up to USD 77,100 per QALY. Cost-effectiveness appears to improve in more severe patients, and over longer time horizons. Conflicting evidence is available for LABA+anticholinergics+inhaled glucocorticoid therapy.
- Phosphodiesterase-4 (PDE-4) inhibitors are non-cost-effective across all COPD patients but are found to be cost-effective added to LAMA, LABA/ICS or LAMA/LABA/ICS in severe to very severe COPD patients.
- Lung volume reduction surgery is a high-cost intervention, and cost-effectiveness is sensitive to the long-term clinical benefits vs best medical care. Studies modelled cost-effectiveness over 10 years, but updates using observed clinical data have only been performed after 5 years.
- A single study estimated lung transplantation in COPD was less cost-effective than in other conditions
- Despite variation in cost-effectiveness by method of delivery (telephone, layperson-delivered, professional delivered) some forms of self-management programmes are cost-effective or cost-saving.

Contributor	Comment
Maureen Rutten-van Molken Associate Professor Institute for Medical Technology Assessment Erasmus University/	The most urgent cost-effectiveness gaps in COPD are: • CEA of treatment strategies or pathways (e.g. LAMA followed by LABA+LABA in case of insufficient response, followed by triple therapy) instead of separate treatments. • CEA of triple medication therapy • CEA of biologics

Erasmus Medical Centre, Rotterdam The Netherlands	• CEA of interventions to improve medication compliance • CEA of various e-health applications in COPD • CEA of interventions to stimulate healthy behavior in everyday life • CEA of personalizing treatment (i.e. targeting integrated care programs to specific groups of COPD patients)
Melinde R.S. Boland **Health Economics-iMTA (GE-iMTA)** **institute of Health Policy & Management (iBMG)** **Erasmus University Rotterdam** **Netherlands**	There are several barriers that hamper the implementation of (cost-) effective COPD care in daily practice. Promising results, seen in controlled clinical trial settings do not directly reflect effects observed in routine daily practice, i.e. the external validity of these trials is often suboptimal (Kruis et al., 2014; Herland et al., 2005). After proven efficacy, the translation of interventions into a practical service should be evaluated in an implementation study (Pinnock, Epiphaniou & Taylor, 2014). This translation seems to result in lower but more realistic outcomes of the interventions (Pinnock et al., 2003, 2007).

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Health Economic Evidence Analysis: Management of type II diabetes and related complications

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9 Diabetes

9.1 Bibliometrics

A total of 238 economic studies were mapped to the clinical model for diabetes with the majority of studies[1] published over the last 12 years. A total of 78 reviews were identified, of which 26 were published between 2009 and 2014.

Table 9.1 Search term and bibliometric results for type I and type II diabetes

PubMed/MEDLINE	
Search term	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Diabetes Mellitus"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt]) NOT ("Diabetes Mellitus, Experimental"[MeSH Terms] NOT "Diabetes, Gestational"[MeSH Terms] NOT "Donohue Syndrome"[MeSH Terms] NOT "Prediabetic State" [MeSH Terms] NOT "Diabetes Complications"[MeSH Terms])
Number of studies	
Included in model	238 (of which type II: 192)
Included as "other"	281
Reviews	77
Excluded	611
Total	1,208
Additional studies suggested by reviewers	
Total	4

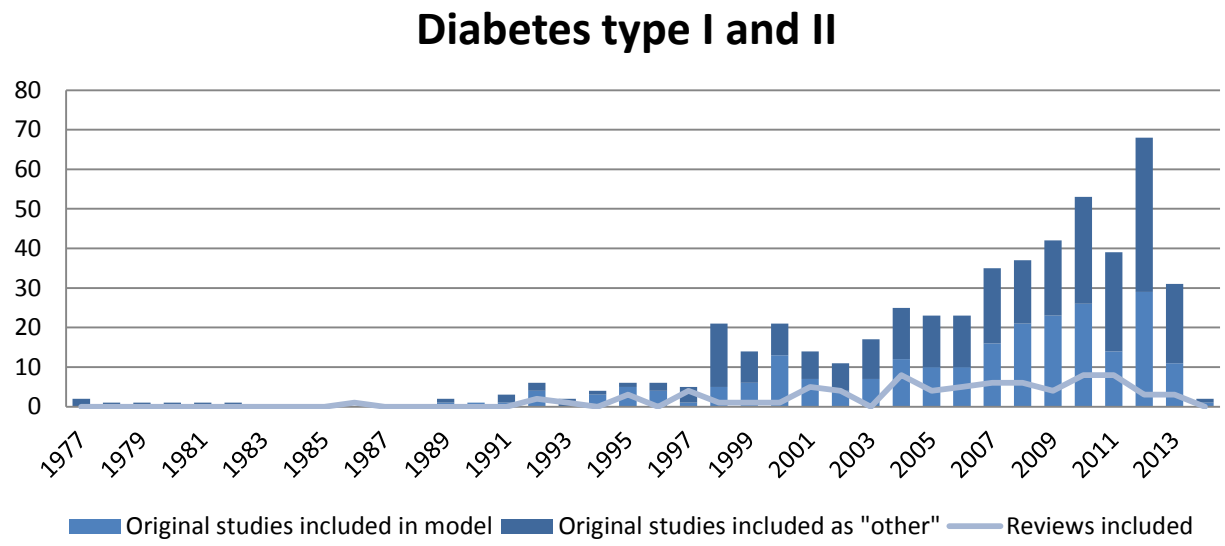

Figure 9.1 Bibliometric data for type I and type II diabetes by year

[1] 75% of studies or more

9.2 Type II diabetes mellitus

The evidence for glycemic control and for the prevention of macro- and microvascular complications in type II diabetes patients is listed in Table 9.2, Table 9.3 and Table 9.4 respectively.

Table 9.2 Primary studies and reviews identified for glycemic control in type II diabetes mellitus

Glycemic control	Number of studies	Number of reviews
Blood glucose monitoring		
HgB a1c every 3-6months	1	0
Blood glucose self-monitoring	10	2
Pharmaceuticals to improve glycemic control		
Metformin	24	2
Sulphonylureas: glipizide, gliclazide	16	2
Meglitinides: repaglinide nateglinide	1	1
Thiazolidinediones: rosiglitazone and pioglitazone	18	1
DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, alogliptin	11	2
Glucagon-like peptide 1 agonists: exenatide, liraglutide	17	2
Alpha-glucosidase inhibitors: acarbose miglitol	1	0
Insulin	28	7
Continuous insulin infusion	2	0
Weight loss to improve glycemic control		
Diet	5	0
Drugs: orlistat, loracaserin, phentermine-toprimate, diethylpropion, phentermine, benzphetamine, phendimetrazine	2	0
Bariatric surgery	9	3
Exercise	3	0
Intense lifestyle modification	2	0
Psychological interventions	0	0

9.2.1 Blood glucose monitoring

No reviews were identified on the monitoring of blood glucose by health professionals, and only a single primary study on this topic was identified (Wermeling et al., 2010). In contrast, the use of glucose self-monitoring by patients was addressed by two reviews (Li et al., 2010b; Tucker & Palmer, 2011) and 10 primary studies were identified.

The review by Li et al. covered research published until May 2008, and included only one study specifically on self-monitoring within a Health Maintenance Organization (HMO) setting in the USA. This study found the cost-effectiveness varied from USD540/QALY to USD30,300/QALY depending on monitoring frequency and time horizon (Li et al., 2010b).

The review by Tucker et al. also included studies until 2008. The authors identified a single study addressing self-monitoring using data from a clinical trial (DiGEM), associating self-monitoring with lower quality of life and significantly higher costs, leading the authors to conclude "*self-monitoring was unlikely to be cost-effective in addition to control [standardized usual care]*" (Tucker & Palmer, 2011). Ten primary studies were identified in the present work, of which 8 were published 2008 or later, suggesting the need to revisit conclusions in the two reviews.

Main findings:

- A fair body of evidence on self-monitoring of blood glucose has emerged since publication of the most recent reviews, and the cost-effectiveness of this intervention does not appear to be summarized in existing work

9.2.2 Pharmaceuticals to improve glycemic control

Metformin was covered by two reviews including studies until 2008. Tucker et al. noted "*In economic terms, metformin dominated conventional control, with increased benefits and lower overall costs, including lower costs associated with: medical consultation; and hospitalization with complications. In other words, the higher costs associated with treating and monitoring blood pressure control were found to be substantially offset by a reduction in the incidence of complications.*" The authors identified two studies of metformin in overweight patients, both showing an overall reduction in costs. Additional studies addressed a variety of other drugs as add-on to metformin, including rosiglitazone, sulphonylurea, sitagliptin and nateglinide (Tucker & Palmer, 2011). The majority of the 24 primary studies identified in the present search addressed the use of metformin in combination with other drugs or described addition of subsequent drugs to the treatment regimen after failure of metformin monotherapy.

Sulphonylurea was reviewed by the same authors. Tucker et al. stated "*Tight blood sugar control with insulin or sulphonylurea was found to be associated with an overall increase in costs, but with an ICER at a level which should be attractive to healthcare policy makers in the UK*" based on a single study. The authors also reviewed sulphonylurea in combination with metformin as reported in two studies (Tucker & Palmer, 2011). Li et al. identified three studies assessing sulphonylurea or insulin in intensive glycemic control against "conventional treatment" (mainly dietary control), with two studies reporting the intervention to be cost-saving, and one reporting the cost-effectiveness level to deteriorate significantly with age at diagnosis (Li et al., 2010b).

The meglitinide drugs were reviewed by only Tucker et al, who identified one study of nateglinide as add-on to metformin. Nateglinide was considered cost-effective at an additional GBP 4,500 per QALY gained (Tucker & Palmer, 2011).

The thiazolidinediones (rosiglitazone and pioglitazone) were reviewed by Tucker et al. As an add-on treatment, pioglitazone was reported to have an "*84.3% likelihood of being considered cost-effective vs. placebo*" according to the UK threshold of GBP 30,000 per QALY, while another study showed rosiglitazone to be less cost-effective than sitagliptin but more cost-effective than sulphonylurea as add-on to metformin. Also as add-on to metformin, a third study showed pioglitazone was slightly more cost-

effective than rosiglitazone, and a fourth study confirmed cost-effectiveness of rosiglitazone over sulphonylurea as add-on to metformin. Of the 18 primary studies identified, 8 were published in the review cutoff year (2008) or later. Though some trends can be identified, there appears to be too little evidence to determine which is the most cost-effective second-line treatment to be added to metformin (Tucker & Palmer, 2011).

The DPP-4 inhibitor sitagliptin was reviewed by Tucker et al. and Waugh et al. As an add-on to metformin, sitagliptin was found to be more cost-effective than rosiglitazone and sulphonylurea in a single study (Tucker & Palmer, 2011). Waugh et al. reviewing studies between 1990 and 2008 also cited sitagliptin as being more cost-effective than rosiglitazone, but this was attributed almost exclusively to price differences as "*the anticipated net QALY gain from sitagliptin [over rosiglitazone] is only 0.02–0.03, which is marginal and well within the bounds of error*". The conclusion was identical for vildagliptin compared with pioglitazone, where effectiveness was considered identical but the former drug cheaper. The authors concluded "*the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former have an advantage in avoidance of weight gain, which, together with their lower (at present) costs, gives them an edge. However, given the uncertainties around the ICER estimate, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins*." (Waugh et al., 2010). Of the 11 primary studies identified in the present review, only one study was included in the identified reviews, while the remaining 10 studies were published after the review cutoff dates, suggesting the need for an updated review of these drugs.

The Glucagon-like Peptide 1 (GPL 1) agonists, *exenatide* and *liraglutide*, were also reviewed by Tucker et al. and Waugh et al. As an add-on to oral therapy in patients with poorly controlled diabetes, one study published by authors from the Center for Outcomes Research, a commercial unit, and Eli Lilly associated exenatide with improved clinical outcomes over insulin (Ray et al., 2007), while another study published by researchers at Cardiff University with funding from Sanofi-Aventis reported the opposite result (Woehl et al., 2008). The review authors did not conclude which study was more reliable (Tucker & Palmer, 2011). Due to increased cost of insulin regimens for heavier patients, the fixed dose exenatide was found to be more cost-effective in higher BMI patients (Waugh et al., 2010). Since publication of the two exenatide studies, the present review has identified 14 primary studies evaluating exenatide or liraglutide, and an updated review may be prudent.

In an analysis of 15 recent (2004-2013) modelling studies assessing the cost-effectiveness of DPP-4 inhibitors and GLP-1 receptor agonists, Asche, Hippler & Eurich (2014) found 13 of the studies were based on the same three basic models (UK Prospective Diabetes Study Outcomes Model, CORE Diabetes Model, Cardiff Diabetes Model). The authors found significant variation in the range of clinical parameters modelled in each study (A1c, systolic blood pressure, lipids, weight, hypoglycaemic and "other" which included heart failure, side effects, oedema and fear of injection) and importantly that "*Only two studies [..] made the fundamental assumption that antihyperglycaemic agents were equal in terms of long-term microvascular and macrovascular endpoints—consistent with current large-scale randomized controlled trials*". In most of the studies reviewed, differences in clinical parameters between the study drugs were relatively small and would generally not be considered clinically significant, such as <0.5% difference in A1c or <5 mmHg change in systolic blood pressure. The authors

argue that the assumptions made in most of the models do not represent the available evidence from current clinical trials, and that extrapolations over 40 years to lifetime are unlikely to represent reality, particularly when based on clinical trial data with 26-52 weeks follow-up.

A single study in the German setting was identified for the use of acarbose in addition to existing treatments for the reduction of cardiovascular risk. The study found acarbose to be very cost-effective at Euro 692 per QALY gained (Roze et al., 2006), however these results do not appear to have been confirmed elsewhere.

Several types of insulin are available for the treatment of diabetes, grouped into rapid-acting (lispro, aspart, glulisine), short-acting (Regular), intermediate-acting (neutral protamine Hagedorn), long acting (detemir, glargine) and premixed (Humulin 70/30, Novolin 70/30, Novolog 70/30, Humulin 50/50, Humalog 75/25, Humalog 50/50) (NDIC, 2012). The variety of preparations and the widely varying conditions under which they are used make it impractical to summarize the evidence within this report, however it is noted that in particular the use of continuous insulin infusion (insulin pumps) is relatively sparsely studied in type II diabetes with only two primary studies and no reviews identified in the present search.

In addition, the management of type 2 diabetes typically starts with oral antidiabetics (OADs, i.e. metformin, sulfonylurea) and transitions to insulin if glycemic targets are not reached. The switch from OADs to insulin may be delayed for a number of reasons, including patient preference, weight gain and risk of hypoglycemia, however lack of adequate glycemic control eventually leads to both micro- and macrovascular complications (see sections 9.2.4 and 9.2.5). A review by Asche et al. (2012) showed that early insulin initiation was associated with improved glycemic control and no changes in quality of life or treatment satisfaction vs OADs, although insulin was associated with weight gain. The review identified four economic studies of insulin initiation published between 2000 and 2010, of which two were cost-effectiveness studies. These both addressed comparison between two insulin types (BIAsp 30/70 vs glargine) and showed ICER's for BIAsp 30/70 over glargine of USD 46,533/QALY and GBP 6,951. QALY gains were related to reduced incidence of nephropathy and retinopathy. The review identified no economic studies comparing insulin vs non-insulin therapies.

Main findings:

- Limited evidence on the use of metformin as monotherapy was identified by existing reviews, though studies appeared to find metformin consistently cost-effective and cost saving. Metformin was mostly studied in the context of combination therapy.
- Limited evidence on the use of sulphonylurea as monotherapy was identified by existing reviews, with one study reporting the drug to be cost-effective according to UK thresholds. According to reviews, sulphonylurea was studied in combination with metformin in two studies, and compared with dietary control in three studies.
- Some trends are evident in the cost-effectiveness of the thiazolidinediones (rosiglitazone and pioglitazone) as second-line therapies after metformin, though it is unclear which add-on treatment is most cost-effective.

- The thiazolidinediones and DPP-4 inhibitors can be considered clinically similar but are reported to differ in cost-effectiveness due to price. Open questions remain around associated clinical events such as weight gain, fractures and heart failure. Ten out of 11 recent primary studies identified in this work were not covered by the reviews, suggesting the need for an updated review.
- Fourteen primary studies identified in this search were published after the latest review cutoff (2008), suggesting the need for an updated review.
- Limited evidence was identified for the use of insulin infusion pumps, with no reviews addressing this area.
- A recent review including studies until 2010 identified only two studies assessing the cost-effectiveness of early insulin initiation versus continued OAD. Both studies compared different types of insulin rather than insulin vs. non-insulin therapy.

9.2.3 Weight loss to improve glycemic control

Of the interventions to stimulate weight loss in type II diabetics, only bariatric surgery was the subject of recent review (Shukla et al., 2011; Terranova et al., 2012; Nikitovic & Brener, 2013). Two single studies showed the cost-effectiveness of gastric banding and gastric bypass in the USA, and of laparoscopic adjustable gastric banding (LAGB) in Australia (dominant intervention). One study from a payer perspective found Roux-en-Y gastric bypass (RYGB) and LAGB to be dominant in Germany and France, and cost-effective in the UK, for patients with BMI > 35, and a similar study reported concordant results in Austria, Italy and Spain. The authors noted "*While the cost-effectiveness of surgical treatment of T2DM in morbidly obese patients has been fairly well established, more studies are required to determine cost-effectiveness in less obese patients*", citing in total four studies on the cost-effectiveness of various types of bariatric surgery (Shukla et al., 2011). Terranova et al. reviewed the same data (Terranova et al., 2012). In a review of Canadian HTA decisions from Ontario, Nikitovic et al. report the ICER for bariatric surgery to be under CADD 16,000/QALY (Nikitovic & Brener, 2013).

Reviews were not identified for dietary interventions, weight loss drugs, exercise, intense lifestyle modifications or psychological interventions, though primary studies were identified in all interventions except psychological interventions.

The most recent dietary evidence was published in 2010, and only two studies were published since 2009. Using data from published clinical trials, one modelling study demonstrated a meal replacement plan could be dominant or cost-effective, depending on whether the meal replacement was considered to replace an equal cost meal or constitute an added cost (Randolph et al., 2010). Another study reported a 10-year model based on an RCT of a telephone-delivered physical activity and dietary behavior intervention in Australia, the Logan Healthy Living Program, with 2.5 years follow-up. The intervention was reported to be cost-effective when compared to existing practice at AUD29,375/QALY (Graves et al., 2009).

Two studies addressed the cost-effectiveness of orlistat, no economic evidence was identified for other weight loss drugs. The cost-effectiveness of orlistat depended on the risk factors for vascular complications, varying from Euro 3,462/LYG for obese diabetics with hypertension and

hypercholesterolemia, to Euro 19,986/LYG for obese diabetics without additional risk factors in the Belgian setting. In addition, the authors of this study noted "*Evidence on longer-term benefits of orlistat (>2 years) will be of importance for future decision-making*" (Lamotte et al., 2002). From a US healthcare provider perspective, the modelled cost per event-free life year gained was USD 8,327 without stratifying patients by risk factors (Maetzel et al., 2003).

The economic evidence for exercise was recent with three studies published between 2009 and 2012. One model in the Canadian setting was based on the Diabetes Aerobic and Resistance Exercise (DARE) clinical trial. The cost-effectiveness varied between the type of exercise offered, i.e. aerobic, resistance or both. Compared with no exercise, the combined program cost CADD 37,872/QALY (Coyle et al., 2012). A protocol for the Dalby lifestyle intervention cohort (DALICO) clinical study describes the intervention as a "multi-professional physical activity referral" for newly diagnosed diabetics. The intervention is being compared against prescription of physical activity (usual care) without additional support, and cost-effectiveness and/or cost-utility analysis is planned (Stenman et al., 2012). Finally, a study modelling the cost-effectiveness of a telephone-delivered intervention for diet and exercise was cost-effective when compared to existing practice at AUD29,375/QALY (Graves et al., 2009).

Two studies reported on lifestyle interventions. For low-income Hispanic diabetics, a community healthcare worker intervention was modelled and shown to be cost-effective at USD33,319/QALY across the population. Greater cost-effectiveness was observed for the 80% of patients entering the study with A1c levels above 9% and reducing to below 9% at follow-up, resulting in an ICER of USD10,995/QALY (Brown et al., 2012). A model in the Dutch setting applied the effectiveness outcomes of several lifestyle intervention trials and assessed the cost-effectiveness. The authors remarked "*Despite prevented costs for complications, all interventions were projected to increase health care costs over a lifetime, because of increased survival*", and ICER's ranged from Euro 10,000/QALY to 39,000/QALY. In their conclusions, the authors further noted "*because of limited information about long-term maintenance of health benefits, there was substantial variability (uncertainty) in the expected long-term outcomes for each intervention*" (Jacobs-van der Bruggen et al., 2009).

The present search identified no primary studies on the use of psychological interventions in diabetic patients.

Main findings:

- Gastric surgery for obese type II diabetics is shown to be cost-effective or cost-saving across a number of countries in three studies.
- Single modelling studies suggest meal replacements and telephone interventions for diet and exercise may be cost effective.
- Two modelling studies from 2002/03 indicate orlistat is cost-effective in diabetics, however longer term real world data is lacking
- A single study has shown exercise to be cost-effective in diabetics, and a cost-effectiveness analysis of an ongoing clinical trial of professional support following exercise prescription is planned.

- Two studies in different settings report lifestyle interventions to be cost-effective, though the authors note that long-term outcomes are unknown.

9.2.4 Reducing macrovascular complications

The macrovascular complications associated with diabetes include coronary artery disease and stroke. Interventions to prevent or reduce these complications are given in Table 9.3.

Table 9.3 Primary studies and reviews identified for reduction of macrovascular complications in type II diabetes mellitus

Reducing Macrovascular Complications: Coronary Artery disease and Stroke	Number of studies	Number of reviews
Smoking cessation		
Smoking cessation	1	0
Aspirin for cardiovascular prevention		
Aspirin for cardiovascular prevention	1	0
Blood pressure control		
Pharmacology: Thiazide diuretics (hydroclorthiazide, chlorthalidone), Angiotensitin Inhibitor (aptropril), Angiotensin II receptor inhibitors (libesartan, losartan), comination renin-antiogensin system inhibition (ramipril, telmisartan), calcium channel blocker (diltizaem, verapamil), alpha blockers (atenolol, metoprolol), alpha blockers (doxazosin), combination therapy	12	2
Non-pharmacological	1	0
Dyslipidemia		
Statins	12	1
Non-pharmacological	0	0

Economic evidence for the reduction of macrovascular complications was limited in some areas. No primary studies or reviews were identified for non-pharmacological dyslipidemia management, and only a single study was identified each for aspirin, smoking cessation and non-pharmacological blood pressure control in prevention of cardiovascular disease.

The study addressing smoking cessation was a model assessing the optimal mix of four interventions to maximize health gain: intensive glycemic control, intensified hypertension control, cholesterol reduction and smoking cessation. Assuming no increase in budget, an additional 211,000 QALYs could be gained over the newly diagnosed American diabetic population using a mix of these interventions over standard care (moderate glycemic and hypertension control, no special treatment for cholesterol reduction or smoking cessation). Cost-effectiveness of smoking cessation as an isolated intervention varied by age group from USD 7,244/QALY (55-64 years) to USD 70,047/QALY (85-94 years), and was highest in the youngest and oldest age groups (Earnshaw et al., 2002).

Evaluating aspirin in reducing macrovascular complications, a cost-effectiveness model included outcomes for nephropathy, neuropathy, retinopathy, coronary heart disease and stroke, and demonstrated an ICER of USD 8,801/QALY for aspirin in prevention of these complications (Li et al., 2010a).

A review by Li et al. (2010b) identified four studies on hypertension control, which all showed intensive hypertension control to be cost saving or very cost-effective at USD1,200/LYG or less. Three studies were on ACE inhibitors and beta-blockers, the fourth did not state the medications used. Tucker et al. reviewed two additional studies, one demonstrating pharmacist-led treatment of hypertension was associated with ICERs of GBP34,078 to 63,320 per event avoided. A comparison of atenolol with captopril showed the drugs were equally effective and therefore did not report cost-effectiveness ratios, but total medication costs were much lower for atenolol (Tucker & Palmer, 2011). Four primary studies were published since the review cutoff years of 2008.

One study was identified addressing the non-pharmacological management of hypertension. An ongoing clinical study "Tailored Case Management for Diabetes and Hypertension" (TEACH-DM) is assessing the effectiveness and cost-effectiveness of a telephone delivered intervention to improve "healthful behavior", including medication adherence, weight loss, exercise, diet planning and others (Crowley et al., 2013). No interim results have been reported.

Li et al reviewed five studies for the management of cholesterol with statins. The intervention was most cost-effective in patients with previous cardiovascular events or high risk. All studies evaluated Simvastatin, Pravastatin or Atorvastatin against placebo. ICER's ranged from cost-saving in patients with previous myocardial infarction or angina, to USD 77,800/QALY in patients with no cardiovascular disease history (Li et al., 2010b). Five primary studies identified in the present search were published after the review cutoff.

No economic evidence was identified for non-pharmacological management of cholesterol.

Main findings:

- ACE inhibitors and beta-blockers for hypertension control are shown to be very cost-effective or cost saving in three studies.
- One ongoing clinical trial is assessing the effectiveness and cost-effectiveness of a telephone delivered intervention to improve blood pressure and diabetes control
- Statins are consistently reported as cost-effective in preventing macrovascular complications. Due to a good deal of evidence published since the most recent review (2008 cutoff), an updated review may be prudent.

9.2.5 Reducing microvascular complications

Interventions for the reduction of microvascular complications (diabetic retinopathy, neuropathy and renal disease/nephropathy) as well as other complications (diabetic foot ulcers and influenza) are given in Table 9.4.

Table 9.4 Primary studies and reviews identified for the reduction of microvascular complications in Type II diabetes

Reducing microvascular and other complications	Number of studies	Number of reviews
Reducing microvascular complications		
Ophthalmological exams	24	4
Neuropathy	7	0
Renal disease and nephropathy	15	4
Reducing other complications		
Influenza vaccine	0	0
Diabetic foot ulcers	16	5

Management of diabetic retinopathy, which includes screening of risk populations, is addressed by four reviews (Tucker & Palmer, 2011; Li et al., 2010b; Au & Gupta, 2011; Jones & Edwards, 2010). Li et al. reviewed early evidence from the USA (1994) where eight strategies for eye screening with 1-4 year intervals, compared to no screening, were found to be cost-saving. However, later studies generally found ICER's in the region of USD20,000-40,000/QALY depending on the frequency of screening and the comparator, i.e. no screening or 2-5 year intervals (Li et al., 2010b).

Jones et al. reviewed studies from 1998 to 2008, identifying 15 primary studies (type I and II diabetes) of which 3 were covered by Li et al. The cost-effectiveness of screening was more favorable in younger patients, with one author noting ophthalmological care has "*little additional value above even minimal glycemic control*" for patients developing type II diabetes at age 65 years. Three studies concurred that systematic screening was more cost-effective than opportunistic screening. Furthermore, telemedicine was considered in four studies for remote populations in Canada, rural populations in Norway, in an American prison and in the general American setting. Interventions were cost-effective in Canada, but only in Norway if sufficient cases were examined. In American prisons, telemedicine was found to be dominant, with cost-effectiveness improving with the size of the screening population. The intervention was also dominant in the general American setting. One author noted, however, that "*the clinical effectiveness and economic value of telemedicine has not been clearly established*" (Jones & Edwards, 2010).

Screening interval was addressed by Jones et al. Concerns have been raised that less frequent screening could lead to additional cases of blindness, however evidence from cohort studies suggests that "*because of the low risk of progression to sight-threatening diabetic retinopathy for patients with Type 1 and Type 2 diabetes without retinopathy, a 2- to 3-year screening interval could be safely adopted*". One study suggested "*for patients with good glycemic control and no background retinopathy, biennial or even triennial screening can be almost as effective as annual screening and more cost-effective*" (Jones & Edwards, 2010).

Tucker et al. reviewed one study on retinopathy evaluating automatic versus manual grading of diabetic retinopathy. This study estimated cost-savings of GBP 1,990 per additional appropriate screening outcome, assuming the automatic strategy would identify 5,560 cases versus 5,610 for the manual strategy (Tucker & Palmer, 2011).

Of the 24 studies identified in the present search, 11 were published after the review cutoff dates of the most recent reviews (2008), suggesting the need for an updated review.

No reviews were identified for the management of diabetic neuropathy. The seven primary studies identified were published between 2006 and 2012, all addressed the cost-effectiveness of pregabalin or duloxetine. In addition, gabapentin was described in two studies, one of which also assessed desipramine. Comparing duloxetine with pregabalin from a US third party payer perspective, duloxetine was dominant in the base case but cost USD16,300-20,667 more per additional QALY under "real world circumstances" in the sensitivity analysis (Bellows et al., 2012). Against "routine treatment", which included pain management, another US study showed duloxetine was dominant measured by the SF-36 bodily pain domain (Wu et al., 2006). In Mexico, duloxetine was found to be cost-effective at MXN 102,433 (slightly lower than the GDP/capita) over generic gabapentin, while pregabalin was dominated by duloxetine (Carlos et al., 2012). Along with duloxetine, desipramine was also found to be more cost-effective than gabapentin or pregabalin (O'Connor, Noyes & Holloway, 2008). In the UK, duloxetine was considered as a potential 1st to 4th line treatment and was shown to reduce costs by GBP 77,071 and add 1.88 QALY's per 1,000 patients when implemented as a second-line treatment (Beard et al., 2008).

After duloxetine, pregabalin appears to be the next most cost-effective option, showing pain relief gains over gabapentin at an additional cost of Euro 20,535/QALY (Rodríguez et al., 2007). In community treated patients in Spain, pregabalin exhibited a QALY gain over usual care and was potentially cost-effective from a societal and health system perspective, though these results were not statistically significant with the ICER 95% confidence interval ranging from dominant to Euro 144,105 from the societal perspective (de Salas-Cansado et al., 2012)

Four reviews covered the management of nephropathy, which includes renal disease. Gialama et al. reviewed eleven studies on irbesartan in hypertension management of patients with nephropathy, microalbuminuria or proteinuria. The studies mostly assessed irbesartan against standard anti-hypertensives (amlodipine, valsartan, losartan), all were modelling studies and mostly used efficacy data from two clinical trials (Irbesartan in Diabetic Nephropathy [IDNT] and Irbesartan in Reduction of Microalbuminuria-2 [IRMA-2]). The results showed irbesartan was more effective in increasing life expectancy than amlodipine, and that earlier irbesartan initiation further increased effectiveness. Several studies demonstrated delayed onset and reduced incidence of end-stage renal disease (ESRD). Four studies showed treatment with irbesartan was associated with lower per-patient costs than conventional anti-hypertensive treatment. The studies reviewed did not report ICER's based on QALY's for irbesartan against any comparators, however irbesartan was found to be cost-saving in several studies and considered cost-effective in others (Gialama & Maniadakis, 2013).

Of the 12 studies reviewed by Li et al. for ESRD, 7 were covered by Gialama et al. Treatment with ACE Inhibitors (two studies in USA) was found to be cost-saving or cost-effective, with more patients treated increasing cost-effectiveness. ACE Inhibitors were also dominant in Thailand against placebo in patients with microalbuminuria but normal blood pressure. Losartan was found to be dominant over placebo in both French and Swiss patients with nephropathy, reported in two separate studies of the same clinical trial (RENAAL) (Li et al., 2010b).

No additional studies were reviewed by Tucker et al. Gialama et al. did not state the inclusion dates for their review, but the most recent study reviewed was published in 2011. None of the primary studies identified in the present search were published after this date, suggesting the most recent review by Gialama et al. is up to date. However, three additional references were suggested by reviewers. One study assessed the optimal conditions for kidney disease screening in the UK, finding that albumin-to-creatinin ratio (ACR) screening with annual intervals is cost-effective compared with bi-annual screening at GBP 606/QALY (Farmer et al., 2014). The cost-effectiveness of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in type 2 diabetics was assessed by one modelling study and one review. The modelling study estimated the optimal time to start ACE-inhibitor therapy, simulating 50-year old patients with newly diagnosed diabetes over a lifetime from the payer perspective. Three strategies were compared: treating all patients at time of diagnosis, screening for microalbuminuria and screening for macroalbuminuria. Universal treatment at time of diagnosis was found to dominate both screening strategies (Adarkwah et al., 2011). Largely similar results were reported by the review, which identified 6 studies on ACE-inhibitors and 33 studies on ARBs. 37 out of the 39 studies indicated ACE-inhibitors or ARBs were cost-saving compared with placebo or usual treatment, however there was a lack of evidence for the direct comparison of ACE-inhibitors and ARBs (Huang et al., 2014)

The present search did not identify any economic literature on the use of influenza vaccine in type II diabetics.

Five reviews addressed the management of diabetic foot ulcers. In the most recent review, published by Buchberger et al. in 2011 and covering publications since 1990 (cut-off date not specified), nine papers addressed cost-effectiveness of diabetic foot ulcer treatments. Of these, five compared becaplermin with standard wound care (SWC), two studies each compared Dermagraft and Apligraf with SWC. The review authors note "*The quality of publications was largely acceptable. The results of all studies showed becaplermin being cost-effective or even cost saving. No obvious statement can be made regarding Dermagraft because of inconsistent cost bases and therefore incremental cost-effectiveness ratios with contrary implications. The results for Apligraf are similar: no ICER is stated in either publication, but [Redekop et al.] report that treatment with Apligraf and SWC leads to lower costs compared to SWC alone since its greater effectiveness off set the added costs of the product; [Steinberg et al.] describe, that the [sic. "their"] own findings on the incremental cost per additional ulcer healed were similar to the results of[Allenet et al.]*". The authors identify several problems with the existing effectiveness evidence, including inadequate blinding, small sample size and limited follow-up periods, leading the authors to caution "b*ecause of the small size of the studies and their poor quality with high potential of bias the*

validity of the results with regard to effectiveness and cost-effectiveness has to be considered limited." (Buchberger et al., 2011).

An additional review on becaplermin by Papanas et al. reviewed evidence until 2009. These authors identified seven studies on cost-effectiveness of becaplermin, of which five were covered by Buchberger et al. For the remaining two studies, the authors note that becaplermin gives rise to higher initial costs in the USA followed by lower costs arising from long-term treatment and reduced complications. From the patient perspective in the USA, becaplermin therapy was calculated to cost USD 42 per course of therapy over 12 months. These authors comment that the "*effectiveness of becaplermin has not been adequately confirmed in 'real-world' clinical situations"* (Papanas & Maltezos, 2010).

Li et al. identified two studies on the prevention of foot ulcers. One study from Sweden found that foot inspection, optimal footwear, treatment and education was a cost-saving intervention against usual care over a 5-year time horizon (undiscounted) in patients with previous ulcers or amputation (high risk) or neuropathy, peripheral vascular disease or foot deformity (moderate risk), but not cost-effective in low risk type II diabetics with no additional risk factors. A study from the Netherlands found intensive glycemic control plus optimal foot care was cost-effective against standard care at USD11,010-34,400/QALY according to reduction in foot lesions of 90% to 10%, respectively, over a lifetime horizon discounted at 3% (Li et al., 2010b).

White et al. reviewed eight studies on the cost-effectiveness of topical therapies for foot ulcers, of which six had been reviewed by the authors above. In the remaining two studies, the costs of topical negative pressure (TNP) therapy were considered, both finding that this technology was more expensive in material costs, but resulted in offsetting savings in staff costs (White & McIntosh, 2009).

Of the 10 economic studies reviewed by Langer et al., seven studies of becaplermin were reviewed by Buchberger et al. Of the remaining four studies, one compared saline gauze, Granuflex (DuoDERM, a hydrocolloid dressing) and Apligraf (a human skin construct) and reported cost per healed ulcer, which was lowest for Granuflex (GBP 342), followed by saline gauze (GBP 541) and Apligraf (GBP 6,741). A similar study confirmed this ranking at USD1,873 per healed patient for DuoDERM, USD2,939 for impregnated gauze dressings and USD15,053 for Apligraf. A third study confirmed these findings from a French and European perspective. These studies reported cost per healed ulcer, but no utility data.

Main findings:

- Diabetic retinopathy screening is generally cost-effective, but the cost-effectiveness ratio depends heavily on the frequency of screening and target population, limiting generalizability.
- Systematic screening for retinopathy is considered more cost-effective than opportunistic screening
- Four studies suggest retinopathy screening by telemedicine is cost-effective, however there is uncertainty about the clinical effectiveness and economic value
- Almost half of the primary studies on diabetic retinopathy (11 of 24) identified in the present search were published after the most recent reviews, suggesting the need for an updated review

- Duloxetine is consistently found to be cost-effective over pregabalin or usual care in four studies for diabetic neuropathy. Pregabalin is shown to be cost-effective over gabapentin or usual care in two studies.
- Irbesartan was shown to be cost-effective for a variety of outcomes but not for QALY's in the management of nephropathy
- Prevention of end-stage renal disease with ACE Inhibitors or Angiotensin II Receptor Antagonists (Losartan) appears to be cost-effective in patients both with and without existing nephropathy or hypertension, however studies were based on a wide range of patient populations and settings, limiting comparison among studies. The most recent review of evidence appears to be up to date. In a recent (2014) review of ACE-inhibitors and ARBs, 37 out of 39 studies found these drugs to be cost-saving compared with placebo or usual care, however the review also concluded that insufficient evidence was available to compare ACE-inhibitors and ARBs against each other.
- No economic evidence was identified on the use of influenza vaccine in type II diabetics
- Although economic studies of becaplermin in diabetic foot ulcer treatment concur the treatment is cost-effective or cost-saving, these studies are based on questionable clinical data.
- In terms of cost per wound healed, three studies concur that the hydrocolloid dressing (Granuflex) is most cost-effective, followed by saline dressings and a human cell product (Apligraf). No evidence was identified for cost-utility of these treatments.
- Two studies of different interventions suggest prevention of foot ulcers is cost saving or cost-effective, particularly in high risk groups.

9.3 Evidence gaps in the treatment of diabetes

Observations from published studies

- The most recent reviews of glucose self-monitoring do not include studies after 2008, where at least eight studies have been published.
- In existing reviews, metformin and sulphonylurea were mostly studied as combination therapies and limited economic evidence was available for monotherapy.
- Meglitinide drugs (nateglinide) were represented by a single study in the most recent reviews
- The thiazolidinediones and DPP-4 inhibitors can be considered clinically similar but are reported to differ in cost-effectiveness due to price. Open questions remain around associated clinical events such as weight gain, fractures and heart failure. Ten out of 11 recent primary studies identified in this work were not covered by the reviews, suggesting the need for an updated review.
- Limited economic evidence was identified for continuous insulin infusion (insulin pumps), covered by only two primary studies
- Bariatric surgery for morbidly obese type 2 diabetics is cost-effective or cost-saving according to available evidence, however less is known about surgery in less obese patients.
- There is limited economic evidence on dietary and exercise interventions as a type II diabetes management strategy. Existing studies of exercise programmes estimate ICER's of approx. CAD

40,000/QALY and AUD 30,000/QALY. Interventions generally exhibit better cost-effectiveness for patients at higher risk of complications, however the long-term benefits are unknown due to lack of long-term follow-up data.

- A single study was identified for smoking cessation and a single study for aspirin on the prevention of macrovascular complications in type II diabetics. Similarly only a single study, an ongoing clinical trial, was identified for non-pharmacological management of hypertension in diabetics.
- The most recent review (cutoff date in 2008) identified five studies on the management of cholesterol in diabetics with statins, which are now off-patent. Primary studies published after 2008 were all published in 2010 or earlier, largely addressing atorvastatin which was on-patent at the time. Cost-effectiveness of these drugs is likely to have changed dramatically since publication of these studies.
- Screening for diabetic retinopathy was generally well studied, and evidence suggests it is more cost-effective in younger populations and when performed systematically rather than opportunistically. There is evidence to suggest telemedical screening is cost-effective or even cost-saving, however uncertainty remains around clinical effectiveness and the cost-effectiveness appears to differ significantly between settings.
- Irbesartan appears to be cost-effective in the management of nephropathy, although none of the studies reviewed reported costs per QALY several studies reported irbesartan to be cost-saving while others concluded it was cost-effective.
- Prevention of end-stage renal disease with ACE Inhibitors or Angiotensin II Receptor Antagonists (Losartan) appears to be cost-effective in patients both with and without existing nephropathy or hypertension, however studies were based on a wide range of patient populations and settings, limiting comparison among studies
- No economic evidence was identified on the use of influenza vaccine in type II diabetics. Diabetic patients are at increased risk of complications, hospitalization and death following influenza infection, and vaccination has been shown to reduce hospitalizations during influenza epidemics (ADA, 2004), however the cost-effectiveness of vaccination in this patient group is unknown.
- Limited evidence suggests prevention of diabetic foot ulcer is cost-saving or cost-effective. For treatment of ulcers, becaplermin is reported to be cost-effective in a range of studies, however the underlying clinical evidence is reportedly of relatively poor quality. Finally, in terms of cost per healed ulcer, hydrocolloid dressing incurs the lowest cost, followed by saline gauze and Apligraf (a human skin construct), however these studies did not report cost per QALY.

Contributor	Comment
Richard Glassock Emeritus professor of medicine, University of California at Los Angeles	Areas where additional economic evidence is needed: • Limited economic evidence for use of Sodium-glucose transport proteins (SGLT2) inhibitors, alone or in combination with Metformin, in type 2 diabetes is available • Captopril (T1DM), Irbesartan (T2DM) and Losartan (T2DM)

	appear to be cost-effective in management of diabetic nephropathy, but a QALY study needs to be done directly comparing ACE vs ARB as generic drugs in T2DM with microalbuminuria only • A cost-effectiveness analysis of multi-factorial intervention in T2DM has yet to be conducted In addition, it should be emphasized that substantial data has emerged that strict glucose control slows the rate of development of end-stage renal disease (ESRD) in both T1DM and T2DM. Since one year of ESRD treatment costs about 50,000 Euros, this information must be incorporated into Markov simulations of cost-benefit (Skupien et al., 2014; Zoungas et al., 2014) Strict glycaemic control takes many years (decades) to prevent CV death, it is not likely that such control will be cost-effective in terms of preventing CV death and prolonging life expectancy late in the course of a disease might even increase the cost of care from a societal viewpoint. ACE inhibitors are preferred for treatment of DM with proteinuria to lower risk of ESRD but any anti-hypertensive drug can be used to avoid CV events in DM at comparable degrees of BP control. At comparable levels of BP control, there is no advantage to RAS inhibition over non-RAS drugs in terms of avoiding CV events or CV related mortality in patients with chronic kidney disease. This needs to be taken into account in cost-benefit analyses (Ninomiya et al., 2013). ACE inhibitors might be preferred in DM (Wu et al., 2013). These observations need to be taken into consideration in cost-benefit analysis (Markov simulations) of RAS inhibitors as a class. A favourable cost-benefit for statin use in patients with DM with ESRD treated with dialysis is highly unlikely and the cost-benefits of their use on non-dialysis chronic kidney disease in DM is highly uncertain (Upadhyay, 2014)
Rui Li Health Economist Division of Diabetes Translation Centers for Disease Control and Prevention USA	After we conducted the review published in 2010 in Diabetes Care (Li et al., 2010b), I compiled a list of evidence gaps - interventions that were recommended by 2008 ADA clinical guidelines for treating diabetes published in 2008 Diabetes Care, but where no cost-effectiveness studies were identified (the A,B, C, E in the parenthesis are the level of evidence in ADA recommendation). • Continuous monitoring of glucose (CMG) in conjunction with intensive insulin regimen (A) • CMG in children, teens, and younger adults (E) • CMG as a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic

	episodes (E) • People with type 2 diabetes should be encouraged to perform resistance training three times a week (A) • Treatment for hypoglycemia (E, E, B) • Annually provide an influenza vaccine to all diabetic patients >=6 months of age • Administer pneumococcal polysaccharide vaccine to all diabetic patients >=2 years of age (C) • Multiple drug therapy is generally required to achieve blood pressure targets (B) • Blood pressure goals of 110-129, 65-79 mmHg in pregnant patients with diabetes and chronic hypertension. ACEI and ARBs are contraindicated during pregnancy (E) • In most adult patients, measure fasting lipid profile at least annually. For low-risk adults, lipid assessments may be repeated every 2 years (E) • Lifestyle modification should be recommended to improve the lipid profile in patients with diabetes (A) • Combination therapy with ASA (75-162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after an acute coronary syndrome (B) • Coronary heart disease (CVD) screening: in asymptomatic patients, evaluate risk factors to stratify patients by 10-year risk, and treat risk factors accordingly (B) • In patients with known CVD, angiotensin-converting enzyme inhibitor (C), aspirin (A), and statin therapy (A) (if not contraindicated) should be used to reduce the risk of cardiovascular events • In patients with a prior myocardial infarction, add beta-blockers (if not contraindicated) to reduce mortality (A) • In patients >40 years with another cardiovascular risk factor, aspirin and statin therapy (if not contraindicated) should be used to reduce the risk of CVD events (B) • Metformin may be used in patients with stable congestive heart failure if renal function is normal. It should be avoided in unstable or hospitalized patients with CHF (C) • Reduction of protein intake in individuals with diabetes and chronic kidney disease (B) • Diabetes care in hospital settings (C, E) • Diabetes care in school and day care setting (E) • Diabetes care in correctional institutions (E) • Diabetes care in emergency and disaster preparedness (E)
Carl V Asche Center for Outcomes Research, University of Illinois College of Medicine at Peoria IL, USA	Although condition specific models help to guide resource allocation in health care, it is clear that a number of changes are required in the evaluation of diabetes therapies: 1) The basic models should be continually updated to include contemporary important clinical trial data that serve to assess clinical outcomes in patients with diabetes. 2) 40-year or lifetime modelling of costs and benefits of therapies is not reliable and more emphasis should be placed on short-

term (5-year) and intermediate-term (10-year) outcomes. The probability that these models provide any valid predictions beyond 10 years is remote.

3) No models should assume that small clinically inconsequential changes in A1c, Systolic Blood Pressure, lipids or weight result in major clinical improvements in patients. Numerous guidelines and consensus statements on what constitutes a clinically important difference for most of these parameters have been published.
4) Modelling transparency must be improved in the identification of data and synthesis of evidence, as well as in the selection of modelled outcomes. Future models should aim to include all relevant treatment outcomes, whether these relate to effects on underlying diabetes and its complications or to short- or long-term side effects of treatment.

The vast array of different clinical, cost and utility data used in the different models we reviewed (Asche, Hippler & Eurich, 2014) makes it apparent that a uniform methodology should be developed for diabetes economic models. In this manner, future models could be run using the same data, which would allow for more acceptable comparability between studies.

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Health Economic Evidence Analysis: Management of osteoarthritis

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10 Osteoarthritis

10.1 Bibliometrics

A total of 34 economic studies were mapped to the clinical model for osteoarthritis (Table 10.1 and Figure 10.1). The majority[1] of studies were published in 2007 or later. Of the eight reviews identified, four were published between 2009 and 2014.

Table 10.1 Bibliometric data for Osteoporosis

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Osteoarthritis"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	34
Included as "other"	57
Reviews	8
Excluded	149
Total	248

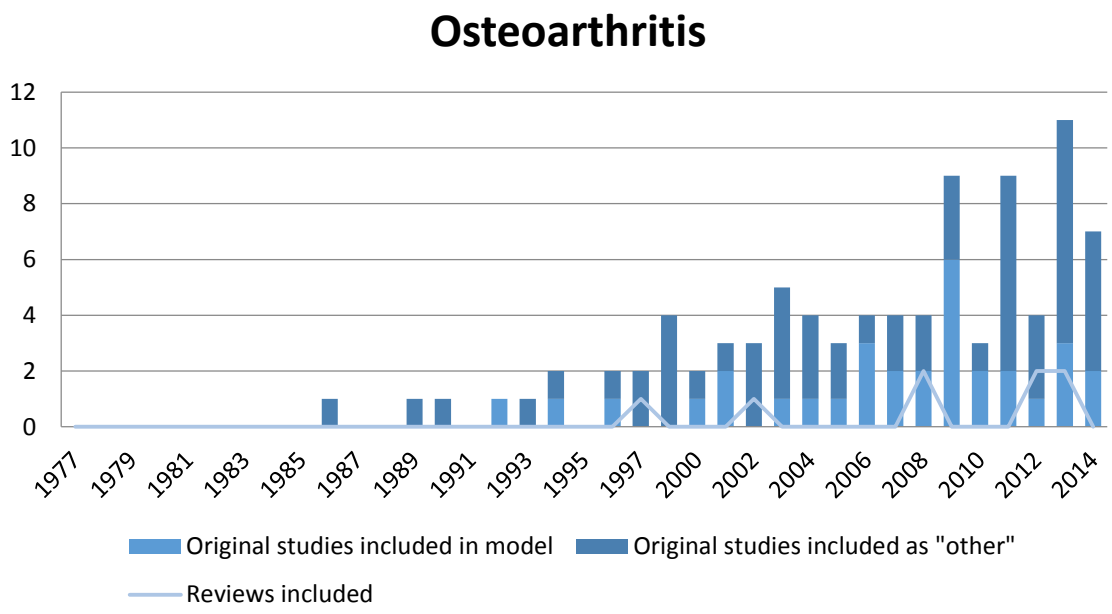

Figure 10.1 Bibliometric data for osteoarthritis by year

10.2 Review Coverage

The clinical model for osteoarthritis consists of 21 treatment modalities (Table 10.3). Of these, eight treatment modalities are lifestyle modifications, nine are medical therapies, and four are surgical therapies. Of the six reviews identified, four were published between 2009 and 2014 (Table 10.2). Five of the twenty (25%) treatment modalities are included in one or more of these four reviews.

[1] 75% of studies or more

Table 10.2 Table of reviews for osteoarthritis and associated treatment

Title and reference	Year	Treatments covered
"*Cost-effectiveness analyses of osteoarthritis oral therapies: a systematic review.*" (Wielage et al.)	2013	Medical Therapies NSAIDS Acetaminophen Opioids Proton Pump Inhibitors
"*Cost-effectiveness of pharmaceutical management for osteoarthritis pain: a systematic review of the literature and recommendations for future economic evaluation*." (Xie et al.)	2013	Medical Therapies NSAIDS
"*Cost-effectiveness of nonpharmacologic, nonsurgical interventions for hip and/or knee osteoarthritis: systematic review.*" (Pinto D, Robertson MC, Hansen P)	2012	Lifestyle Therapies Exercise programs
"*Economic outcomes for celecoxib: a systematic review of pharmacoeconomic studies*". (Huelin et al.)	2012	Medical Therapies NSAIDS

10.3 Evidence Analysis

Osteoarthritis is managed with lifestyle modification therapies such as exercise programs, weight loss, joint rest, physical therapy, braces, joint protection, heat / cold therapy, and psychological coping strategies. Osteoarthritis is also managed medical with acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid injections, opioids, hydroxyquinilone, proton pump inhibitors (for GI protection), and misoprostol (for GI protection). Osteoarthritis can also be managed surgically with arthroscopic joint irrigation, arthroscopic debridement, arthroscopic synvectomy, and total joint arthroplasty. Thirty-nine primary studies evaluating the cost-effectiveness of these treatment modalities were identified (see Table 10.3)

Table 10.3 Primary health economic evidence and reviews for the treatment of osteoarthritis

Osteoarthritis	Studies	Reviews
Lifestyle Modification Therapies		
Exercise Programs	6	1
Weight Loss	0	0
Joint Rest	0	0
Physical Therapy	0	0
Braces	0	0
Joint Protection	0	0
Heat / Cold Therapy	0	0
Psychological coping strategies – depression assessment and intervention	0	0
Medical Therapies		
Acetaminophen	1	1
NSAIDS	16	3
Intra-articular glucocorticoids	0	0
Opioids	3	1

Colchicine	0	0
Hydroxyquinilone	0	0
Proton Pump Inhibitors (for GI protection)	1	1
Misoprostol (for GI protection)	1	0
Glucosamine and Chondroitin	2	0
Surgical Therapies		
Arthroscopic joint irrigation	0	0
Arthroscopic debridement	0	0
Arthroscopic synovectomy	0	0
Total joint arthroplasty (replacement)	13	0

10.3.1 Lifestyle modification therapies

10.3.1.1 Exercise programs

Six primary studies identified evaluated the cost-effectiveness of exercise programs for treatment of osteoarthritis. Five of these six primary studies were economic evaluations in combination with a randomized controlled trial, and one utilized a model. Three studies compared an exercise program intervention to no exercise program, and three studies compared types of exercise programs.

Bulthuis Y, Mohammad S, Braakman-Jansen LM, Drossaers-Bakker KW (2008) conducted a randomized controlled trial with a concurrent economic evaluation with a one-year time horizon from a payer perspective in the Netherlands. This study found that three weeks of intensive exercise post hospital discharge for treatment of osteoarthritis (OA) when compared to usual care resulted in an ICER that was cost saving for adults with OA (Bulthuis Y, Mohammad S, Braakman-Jansen LM, Drossaers-Bakker KW, 2008). Thomas et al. (2005) conducted a randomized controlled trial with a concurrent economic evaluation with a 2-year time horizon from a NHS perspective in the UK. This study randomized adults age 45 to age 65 with OA into three categories – exercise therapy, monthly telephone contact, and exercise therapy plus monthly telephone contact (Thomas et al., 2005). The findings of this study were exercise therapy compared with monthly telephone contact resulted in an ICER of GBP 2570 per clinically significant improvement in symptoms, and resulted in GBP 8,000 per 50% improvement in symptoms of OA.

The research conducted by Patrick et al. (2001) demonstrates how sensitive the ICER is to the assessment tool utilized in the calculation of QALYs. Patrick et al. (2001) conducted a randomized controlled trial in US adults with OA age 55-75. This study evaluated aquatic exercise vs. no exercise from a societal perspective. The findings of this research were that aquatic exercise in comparison to no exercise results in an ICER of USD 205,186/QALY when using the Quality of Well-Being Scale, and of USD 32,643 when using the Current Health Desirability Rating (Patrick et al., 2001).

Richardson et al. (2006) utilized a Markov model with a payer perspective to compare the cost-effectiveness of a class-based exercise program supplementing a home-based exercise program in comparison to a home-based program alone. The findings of this study were that a class-based exercise program supplementing a home-based exercise program was dominant, both more effective and less expensive, than a home-based exercise program alone (Richardson et al., 2006).

Sevick et al. (2000) conducted a randomized controlled trial with a concurrent economic evaluation in a US population of adults greater than age 65 with OA of the knee. This study evaluated weight resistance training in comparison with an aerobic exercise-training program over an 18 month time horizon from a payer perspective (Sevick et al., 2000). In this study, weight resistance training was found to be cost saving in comparison to aerobic exercise (Sevick et al., 2000).

Sevick et al. (2009) conducted another randomized controlled trial with a concurrent economic evaluation in a US population of adults greater than age 65 with OA of the knee. In this study a diet and exercise program was compared with an exercise program alone (Sevick et al., 2009). This study found diet and exercise to be cost saving in comparison to the exercise program alone (Sevick et al., 2009).

Key Messages:

- A general exercise program for adults with OA is cost-effective in comparison to no exercise program.
- Combination interventions such as diet and exercise and class-based exercise in combination with home-based exercise are comparatively more cost-effective than single interventions.
- The ICER for exercise programs is very sensitive to the tool used to measure QALY gains with the intervention.

10.3.1.2 Other lifestyle modification therapies

No studies assessed the cost-effectiveness of joint rest, physical therapy, braces, joint protection, heat/cold therapy of psychological coping strategies for the treatment of osteoarthritis.

10.3.2 Medical Therapies

10.3.2.1 Acetaminophen

One primary study identified assessed the cost-effectiveness of acetaminophen (paracetamol) for the treatment of osteoarthritis. Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, & Cabanela RL (2003) compared acetaminophen to celecoxib, ibuprofen, ibuprofen and misoprostol, and to rofecoxib. This study utilized a decision analysis model with payer perspective, a 6-month time horizon, and a US population (Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, Cabanela RL, 2003). This study found that acetaminophen dominated, was both more effective and less expensive, than all other treatment modalities examined (Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, Cabanela RL, 2003).

Key messages:

- Acetaminophen appears to be a cost-effective treatment option for the treatment of osteoarthritis, dominating celecoxib, ibuprofen, ibuprofen plus misoprostol and rofecoxib, according to a single study.

10.3.2.2 NSAIDS

Sixteen of the primary studies identified evaluated the cost-effectiveness of NSAID therapy for osteoarthritis (summarised in Table 10.3). Two of the eighteen studies evaluated the cost-effectiveness over a lifelong time horizon, one study utilized a 5-year time horizon, and all other studies used a time horizon of one year or less.

Of these sixteen primary studies, fourteen compare a selective cox-2 inhibitor to a non-selective cox inhibitor. When cox-2 inhibitors were first released onto global markets there was no published research indicating that cox-2 inhibitor use was associated with an increased risk of adverse cardiovascular events such as myocardial infarction and stroke (Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, 2007). However, since the release of cox-2 inhibitors post-marketing research has indicated they are associated with an increased risk of serious adverse cardiovascular events, which has resulted in the voluntary recall of rofecoxib and the FDA placing a black box warning on celecoxib (Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, 2007). Three of these primary studies consider this increased risk of adverse cardiovascular events in the comparative effectiveness model, while twelve studies do not consider the increased risk of cardiovascular events in the model. One additional study evaluates oral and topical administration of non-selective cox inhibitors, and another compares utilization of selective cox-2 inhibitors as first, second, and third line therapy.

Selective cox-2 inhibitor in comparison to non-selective cox inhibitor, considering the increased risk of adverse cardiovascular events associated with cox-2 inhibitors

Three studies compared selective cox-2 inhibitors to non-selective cox inhibitors while also considering the increased risk of cardiovascular adverse events, generally finding that selective cox-2 inhibitors (celecoxib, rofecoxib) are less cost-effective than alternatives. Schaefer et al. (2005) evaluated the cost-effectiveness of diclofenac, ibuprofen, naproxen, celecoxib and rofecoxib using a decision tree model, a US veterans affairs payer perspective and a 1 year time horizon. This study found rofecoxib was dominated (less effective and more expensive) in comparison with ibuprofen or naproxen (Schaefer et al., 2005). This study also found that celecoxib in comparison to ibuprofen or naproxen resulted in an ICER of USD 42,305 / QALY.

Brennan Spiegel & Chiun-Fang Chiou (2005) compared celecoxib alone with a non-selective cox inhibitor and compared celecoxib with a non-selective cox inhibitor plus a proton pump inhibitor. This study utilized a decision analytic model with a US population, a payer perspective, and a 1 year time horizon (Brennan Spiegel, Chiun-Fang Chiou, 2005). The results of this study indicated celecoxib was dominated (both less effective and more expensive) by both the non-selective cox inhibitor and by the non-selective cox inhibitor plus the proton pump inhibitor (Brennan Spiegel & Chiun-Fang Chiou, 2005). Additionally this study found a non-selective cox inhibitor to be the most effective treatment option in a population with low risk of gastrointestinal (GI) adverse events, and found a non-selective cox inhibitor plus a proton pump inhibitor to be the most cost-effective treatment option in a population with high risk of GI adverse events (Brennan Spiegel, Chiun-Fang Chiou, 2005).

(Wielage et al., 2013b) compared celecoxib and naproxen using a decision analytic model with a US payer perspective and a lifelong time horizon. This study found that naproxen dominated (both more effective and less expensive) than celecoxib.

Selective cox-2 inhibitor in comparison to non-selective cox inhibitor, not considering the increased risk of adverse cardiovascular events associated with cox-2 inhibitors

Eleven studies do not consider the risk of adverse cardiovascular events in the comparative effectiveness model, and generally find selective cox-2 inhibitors to be more cost-effective than non-selective cox inhibitors. Chancellor et al. (2001) found celecoxib to be cost saving in comparison to diclofenac alone and with gastroprotective agents. Marshall et al. (2001), Phillips (2008), and Pellissier et al. (2001) all found rofecoxib in comparison to non-selective cox inhibitors plus gastroprotective agents to result in reduced serious adverse GI events at an ICER that is within Canadian, UK, and US willingness to pay thresholds. El-Serag et al. (2002) found the ICER for celecoxib in comparison to ibuprofen and in comparison to ibuprofen plus gastroprotective agents to be within US willingness to pay thresholds. Yen et al. (2004) found the ICER for celecoxib in comparison to naproxen to be within Taiwan's willingness to pay thresholds. Loyd, Rublee & Jacobs (2007) found celecoxib to be the most cost-effective treatment option when compared with diclofenac and naproxen. Al et al. (2008) compared diclofenac and celecoxib, and found diclofenac plus misoprostol to be the most CE option for a population at low risk of adverse GI events, and found celecoxib to be the most cost-effective option for a population at high risk for adverse GI events. Contreras-Hernández, Mould-Quevedo JF, Torres-González R, Goycochea-Robles MV, Pacheco-Domínguez RL, Sánchez-García S, & Mejía-Aranguré JM (2008) compared the cost-effectiveness of acetaminophen, celecoxib, diclofenac, naproxen, and piroxicam; and found celecoxib to dominate all other treatment options.

Only one of the eleven studies that did not consider the risk of adverse cardiovascular events when comparing a selective cox-2 inhibitor to a non-selective cox inhibitor found the non-selective cox inhibitor to be more cost effective. Brown et al. (2006) compared a non-selective cox inhibitor to Rofecoxib, and found a non-selective cox inhibitor plus a gastroprotective agent to be the most cost-effective in terms of cost per endoscopic ulcer prevented, in terms of cost per serious GI event avoided, and in terms of cost per life year gained.

Topical compared with oral administration

One study compared oral administration of ibuprofen to topical administration of ibuprofen. Castelnuovo et al. (2008) conducted a randomized control trial over a 2-year period in the UK, utilizing an NHS perspective. This study found that oral ibuprofen compared with topical ibuprofen resulted in an ICER of GBP 12,000QALY (Castelnuovo et al., 2008), which is within UK willingness to pay thresholds. It is not clear in this research how adverse GI events were accounted for with oral ibuprofen administration (Castelnuovo et al., 2008).

Utilization of selective cox-2 inhibitors as first, second, and third line therapy.

One study examined the cost-effectiveness of 1) utilizing celecoxib in the general population as first line therapy compared with 2) using a non-selective cox inhibitor as first line therapy and celecoxib as a second line therapy for individuals that develop GI complication, and compared with 3) using a non-selective cox inhibitor as first line therapy for OA, non-selective cox inhibitor plus a proton pump inhibitor as second line therapy for individuals that develop GI complication, and then using celecoxib as a third line therapy for individuals that continue to develop GI complications (Bessette et al., 2009). This study utilized a Markov model with a provincial drug program perspective in a Canadian population over a 5-year time horizon (Bessette et al., 2009). This study found utilization of celecoxib as a first line therapy for the entire general population resulted in an ICER of CAD 54,696 QALY, which is greater than typical Canadian willingness to pay thresholds (Bessette et al., 2009).

Key Messages:

- The ICER is very sensitive to estimations of risk of cardiovascular adverse events associated with selective cox-2 inhibitors.
- When elevated risk of cardiovascular adverse events are considered in the economic model, then non-selective cox inhibitors are dominant (both more effective and less expensive) in comparison with selective cox-2 inhibitors.
- The ICER is also sensitive to risk of GI adverse events, with non-selective cox inhibitors plus a gastroprotective agent being a more cost-effective option in populations at high-risk for GI adverse events, and non-selective cox inhibitors alone being the more cost-effective option in populations at low risk for GI adverse events.

Table 10.3 Primary studies identified for NSAIDs

Author (year)	Perspective/ Design / Time Horizon	Comparators	Results	Increased risk of CV AEs with selective Cox2 inhibitors considered.
Chancellor (2001)	Switzerland. Payer. Decision Analytic Model. 6 months.	Celecoxib Diclofenac alone Diclofenac + H2RA Diclofenac + misoprostol Diclofenac + PPI	Celecoxib is cost saving compared to all others.	No
Marshall (2001)	Canada. Payer. Decision Analytic Model. 1 year	Rofecoxib Non-selective cox inhibitor + gastro protective agent	Rofecoxib reduces serious GI events at an ICER that is acceptable.	No

Phillips (2008)	UK. Payer. Decision Tree Model. 1 year.	Rofecoxib Non-selective cox inhibitor + gastroprotective agent	Rofecoxib reduces serious GI events at an ICER that is acceptable.	No
Pellissier (2001)	US. Payer. Decision Analytic Model. 1 year.	Rofecoxib Non-selective cox inhibitor + gastroprotective agent	Rofecoxib results in a cost / life year saved within US WTP threshold.	No
El-Serag (2002)	US. Payer. Decision Tree Model. 1 year.	Celecoxib Ibuprofen Ibuprofen + PPI Ibuprofen + misoprostol	Celecoxib compared with ibuprofen monotherapy is within US WTP thresholds. NSAID + PPI compared with ibuprofen monotherapy is within US WTP threshold.	No
Yen (2004)	Taiwan. Societal. Decision Tree Model. 4 months.	Celecoxib Hyaluronan Naproxen	Hyaluronan is not CE. Celecoxib compared with naproxen is within Taiwan WTP thresholds, and becomes more CE with greater GI risk.	No
Brown (2006)	UK. NHS. Stochastic decision analytic model. 6 months.	Non-selective cox inhibitor alone Non-selective cox inhibitor + H2RA Non-selective cox inhibitor + misoprostol Non-selective cox inhibitor + PPI Meloxicam Rofecoxib	Non-selective cox inhibitor + H2RA is most CE in terms of cost/ endoscopic ulcer prevented and in terms of cost/ serious GI event and in terms of cost / life year gained.	No
Loyd, Rublee & Jacobs (2007)	US. Societal. Decision Tree Model. Lifetime.	Celecoxib Diclofenac Naproxen	Celecoxib is most CE, and more cost-effective with increasing age and increasing CV risk.	No
Catelnuelvo (2008)	UK. NHS. RCT. 2 year.	Oral ibuprofen Topical ibuprofen	Oral ibuprofen compared with topical ibuprofen results in an ICER of GBP 12,000 /QALY	n/a
Al (2008)	Netherlands. Societal. Decision Analytic Model. 1 year.	Celecoxib Diclofenac alone Diclofenac + H2RA Diclofenac + misoprostol Diclofenac + PPI	Diclofenac + misoprostol is the most CE option for low-GI risk population. Celecoxib is the most CE option for high-GI risk	No

			population.	
Contreras-Hernandez (2008)	Mexico. Social Security Institution. Decision Tree model. 6 months.	Acetaminophen Celecoxib Diclofenac Naproxen Piroxicam	Celecoxib dominates	No
Brereton (2012)	UK. NHS. Markov model. Lifetime.	Celecoxib + PPI Diclofenac + PPI	Celecoxib + PPI; GBP 4,773 / QALY	No
Schaefer et al. (2005)	US. Veterans affairs. Decision Tree Model. 1 year.	Diclofenac Ibuprofen Naproxen Celecoxib Rofecoxib	Rofecoxib is dominated. Celecoxib is within US WTP thresholds for a population at high GI risk.	Yes. Risk of: HTN. CHF. MI.
Spigel (2005).	US. Payer. Decision Analytic Model. 1 year.	Celecoxib alone NSAID alone NSAID + PPI	NSAID most CE in patients with low GI risk. NSAID + PPI most CE in patients with high GI risk. Celecoxib was dominated by both.	Yes. Risk of MI.
Bessette (2009)	Canada. Provincial drug program. Markov model. 5 years.	Celecoxib as first line Non-selective cox inhibitor as first line and Celecoxib as second line Non-selective cox inhibitor as first line, Non-selective cox inhibitor + PPI as second line, and Celecoxib as third line.	Celecoxib as first line results in an ICER of CAD 54,696 /QALY	Yes. Risk of: MI. Stroke.
Wielage (2013)	US. Payer. Markov Model. Lifetime.	Celecoxib Naproxen	Celecoxib was dominated.	Yes. Risk of: CHF. MI. Stroke.

10.3.2.3 Intra-articular glucocorticoid injections

No studies assessed the cost-effectiveness of intra-articular glucocorticoid injections for the treatment of osteoarthritis.

10.3.2.4 Opioids

Three of the primary studies identified evaluated the cost-effectiveness of opioids for pain management in adult with osteoarthritis. Marshall et al. (2006) conducted an open-label active-controlled randomized naturalistic 4-month study with a concurrent economic evaluation. Two perspectives were evaluated in this study, a societal perspective and a payer perspective in the evaluation of oxycodone in comparison to a combination of oxycodone-acetaminophen (Marshall et al., 2006). This study found oxycodone to be dominant, both more effective and less expensive, than combination of oxycodone-acetaminophen from a societal perspective, and within US willingness to pay thresholds from a payer perspective, with an ICER of 50,000-100,000 USD/QALY (Marshall et al., 2006).

A second study also evaluated the cost-effectiveness of opioids in the management of pain in adults with osteoarthritis. Ward et al. (2007) utilized a discrete event simulation model with one year time horizon from a payer perspective to evaluate once-daily hydromorphone in comparison to two to three times daily dosing of

extended-release (ER) oxycodone. This study found that once daily hydromorphone resulted in an ICER of 8,343 Euro/QALY.

A third study evaluated the cost-effectiveness of tramadol extended release in comparison to tramadol regular release (AD Patkar, P Langley, C Janagap, K Meyer, A Grogg, 2007). This study utilized a model from a US managed care perspective with a one year time horizon (AD Patkar, P Langley, C Janagap, K Meyer, A Grogg, 2007). The findings of this study found the ICER for tramadol extended release in comparison to tramadol regular release to be within US willingness to pay thresholds.

Key Messages:

- The cost-effectiveness of opioids in the management of osteoarthritis pain is sensitive to the dosing regimen.
- The cost-perspective utilized in the study greatly influences the ICER.
- Opioid drugs are only compared with other opioids (or combinations with non-opioids), consequently the relative cost-effectiveness of opioids versus other classes of painkillers is not known.

10.3.2.5 Hydroxychloroquine

No studies assessed the cost-effectiveness of hydroxychloroquine for the treatment of osteoarthritis.

10.3.2.6 Proton Pump Inhibitors (for GI protection)

One of the primary studies identified assessed the cost-effectiveness of proton pump inhibitors (for GI protection) for the treatment of osteoarthritis. Latimer et al. (2009) isolated the cost-effectiveness of proton pump inhibitors (PPI) through a Markov model with a UK population of adults with OA, taking an NHS perspective and utilizing a lifelong time horizon. Latimer et al. (2009) compared celecoxib plus a PPI to celecoxib, diclofenac plus a PPI to diclofenac, ibuprofen plus a PPI to ibuprofen, naproxen plus a PPI to naproxen, and paracetamol plus a PPI to paracetamol. The results of this study indicated that the addition of a PPI to a treatment regimen of celecoxib, diclofenac, ibuprofen, naproxen or paracetamol resulted in an ICER less than 1,000 GBP / QALY.

Key Messages:

- Proton pump inhibitors appear to be a cost-effective treatment option for GI protection in combination with a range of pain medications, as evidenced by a single study

10.3.2.7 Misoprostol (for GI protection)

One primary study evaluated the cost-effectiveness of misoprostol for GI protection in patients with osteoarthritis taking NSAIDs for pain management. Jönsson & Haglund (1992) utilized a Markov model with a 3-month time horizon from a societal perspective. This study found that misoprostol in comparison to no prophylactic treatment was cost-effective in a Swedish population of patients with osteoarthritis and NSAID-associated abdominal pain. The ICER in this study was found to be sensitive to the estimated frequency of ulcer development (Jönsson & Haglund, 1992).

Key Messages:

- Misoprostol appears to be a cost-effective treatment option for GI protection during NSAID treatment (one study).
- The economic model evaluating the cost-effectiveness of prophylactic medical treatment for NSAID associated abdominal pain is sensitive to the estimation of ulcer development frequency.

10.3.2.8 Glucosamine and Chondroitin

Glucosamine and chondroitin, although not treatment modalities currently recommended for the treatment of OA, deserve special consideration. These studies deserve special consideration because evidence suggests glucosamine is as safe as placebo (Towheed et al, 2005), and because a Cochrane review with pooled results suggests that the variation in the effectiveness research may be due to differences in preparation (Towheed et al, 2005). Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function but studies evaluating the Rotta preparation show that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA (Towheed et al, 2005).

Two studies were found to evaluate the cost-effectiveness of glucosamine. Scholtissen et al (2010) evaluated the cost-effectiveness of glucosamine sulphate in comparison to paracetamol and placebo (PBO) for the treatment of knee OA. This study utilized a 6 month time horizon and a payer perspective (Scholtissen et al, 2010). This study found glucosamine sulfate to be dominant, both more effective and less expensive, in comparison to paracetamol (Scholtissen et al, 2010).

Black et al (2009) evaluated the cost-effectiveness of glucosamine sulfate in addition to current care in comparison to current care for adults with knee OA. This study utilized a cohort simulation model and a lifelong time horizon (Black et al, 2009). The addition of glucosamine sulfate to current care was found to result in an ICER of 21,335 GBP / QALY (Black et al, 2009).

10.3.3 Surgical Therapies

No studies assessed the cost-effectiveness of arthroscopic joint irrigation, arthroscopic debridement or arthroscopic synovectomy for the treatment of osteoarthritis.

10.3.3.1 Total joint arthroplasty

Thirteen primary studies evaluated the cost-effectiveness of total joint arthroplasty for osteoarthritis (SeeTable 10.4). Each of these thirteen studies evaluates total joint arthroplasty in a population of adults with osteoarthritis. Six evaluated the cost-effectiveness of total joint arthroplasty in comparison to non-surgical management; three compared the cost-effectiveness of one type of prosthesis utilization to a different type of prosthesis utilization; three evaluated the cost-effectiveness of total joint arthroplasty to hemi-arthroplasty and one evaluated the cost-effectiveness of total joint arthroplasty relative to joint fusion surgery.

Total joint arthroplasty in comparison to non-surgical management

Of the six primary studies evaluating total joint arthroplasty vs non-surgical management, four studies evaluated the hip joint (Chang RW & Pellisier JM, 1996; Bourne RB, Rorabeck CH, Laupacis A, Feeny D, Wong C, Tugwell P, Leslie K, 1994; Higashi & Barendregt, 2011; and Jenkins et al., 2013) and four studies evaluated the knee joint (Losina et al., 2009; Waimann et al., 2014; Higashi & Barendregt, 2011; and Jenkins et al., 2013).

Chang RW & Pellisier JM (1996) found total hip arthroplasty to be cost saving in a modelled comparison to non-surgical management in a US population. Conversely, the other three studies evaluating the hip joint did not find total hip arthroplasty to be cost saving in comparison to non-surgical management. Higashi & Barendregt (2011) modelled a comparison of total hip arthroplasty to non-surgical management from a payer perspective. Higashi & Barendregt (2011) found total hip arthroplasty to result in an ICER of AUD 5,000 /QALY in an Australian population when compared to non-surgical management. Bourne RB, Rorabeck CH, Laupacis A, Feeny D, Wong C, Tugwell P, & Leslie K (1994) conducted an RCT with an economic evaluation from a payer perspective over a 2 year time horizon in the UK, and found total hip arthroplasty to result in an ICER of GBP 27,139/QALY. Jenkins et al. (2013) conducted a prospective cohort study with a one-year time horizon in the UK, and found total hip arthroplasty to result in an ICER of GBP 1,372/QALY in a UK population in comparison to non-surgical management.

Two of these studies (Chang RW & Pellisier JM, 1996 and Jenkins et al., 2013) found the ICER to be sensitive to the age of the patient, with older age resulting in a larger ICER than younger age at the time of the surgical intervention. The ICER was also found to be sensitive to revision rate (Bourne RB, Rorabeck CH, Laupacis A,

Feeny D, Wong C, Tugwell P, & Leslie K, 1994), inclusion of future unrelated healthcare costs (Higashi & Barendregt, 2011), sex of the patient (Chang RW, Pellisier JM, 1996), and health of the patient before surgery (Jenkins et al., 2013).

Of the four studies evaluating the cost-effectiveness of total knee replacement in comparison to non-surgical management, none were found to be cost saving. Two of the studies were modelled studies, and two were prospective cohort studies.

Losina et al. (2009) conducted a study modelling the cost-effectiveness of total knee replacement to non-surgical management in the US from a payer perspective with a lifelong time horizon. This study found total knee replacement to result in an ICER of $28,100 / QALY (Losina et al., 2009). Higashi & Barendregt (2011) conducted a study modelling the cost-effectiveness of total knee replacement to non-surgical management in Australia from a payer perspective with a lifelong time horizon. This study found total knee replacement to result in an ICER of AUD 12,000/QALY (Higashi & Barendregt, 2011).

Waimann et al. (2014) conducted a prospective cohort study comparing total knee replacement to non-surgical management from a societal perspective with a 6-month time horizon. This study found total knee replacement to result in an ICER of USD 20,133 / QALY (Waimann et al., 2014). Jenkins et al. (2013) also conducted a prospective cohort study comparing total knee replacement to non-surgical management from a payer perspective in the UK with a 1-year time horizon. This study found total knee replacement to result in an ICER of GBP 2,101/QALY (Jenkins et al., 2013).

The ICER for total knee replacement in comparison to non-surgical management was found to be sensitive to a variety of factors. Higashi (2011) found the ICER to be sensitive to inclusion of future unrelated healthcare costs, Losina et al. (2009) to differences in cost inputs from low-volume and high-volume medical canters, Waimann et al. (2014) found the ICER to be sensitive to the tool used to measure utility in the evaluated population, and Jenkins et al. (2013) to the age and the overall health of the patient at the time of the surgical intervention.

Comparison of cemented, cement-less and hybrid prosthesis in total joint arthroplasty

Three studies compared the cost-effectiveness of utilization of cemented, cement-less, and hybrid prosthetic devices in total joint arthroplasty (Di Tanna et al., 2011; Pennington et al., 2013; Cummins et al., 2009).. All three of these studies used a model to evaluate cost-effectiveness, and all three modelled the cost-effectiveness of each prosthetic device in total hip replacement procedures (Di Tanna et al., 2011; Pennington et al., 2013; Cummins et al., 2009).

Di Tanna et al. (2011) compared cement-less prosthesis to hybrid prosthesis in an Italian population and utilized a payer perspective with a lifelong time horizon. This study found cement-less prosthesis to result in an ICER of EUR 2,401/QALY when compared to hybrid prosthesis (Di Tanna et al., 2011). Pennington et al. (2013) compared cemented, cement-less and hybrid prosthesis in a UK population and utilized a payer perspective with a lifelong time horizon. This study found the hybrid prosthesis to be the most cost-effective option in a population of adults at age 70 with 75% probability (Pennington et al., 2013). However, Pennington et al. (2013) was unable to determine a statistically significant difference in the cost-effectiveness of any of the three prosthetic devices in adults at age 60 and adults at age 80. Both of these studies found the ICER to be sensitive to the age of the patient (Di Tanna et al., 2011; Pennington et al., 2013).

Cummins et al. (2009) compared the cost-effectiveness of two types of cemented prosthesis – cemented prosthetics with antibiotics and cemented prosthetics without antibiotics. Cummins et al. (2009) studied a US population from a payer perspective. This study found cemented prosthetics with antibiotics in comparison to cemented prosthetics without antibiotics to result in an ICER of USD 37,355 / QALY (Cummins et al., 2009).

Total joint arthroplasty in comparison to hemiarthroplasty

Three studies compared total joint arthroplasty to hemi-arthroplasty. One of these compared total shoulder arthroplasty to hemiarthroplasty, and two compared total knee replacement to unicompartmental hemiarthroplasty of the knee.

Mather 3rd et al. (2010) utilized a model to compare total shoulder arthroplasty to hemi- arthroplasty of the shoulder from a societal perspective in the US. This study found total shoulder arthroplasty to be dominant (more effective and less costly) than hemiarthroplasty of the shoulder (Mather 3rd et al., 2010). This study also found the ICER to be sensitive to the revision rate and utility measures.

However, the two studies that evaluated total knee arthroplasty in comparison to hemi-arthroplasty of the knee had conflicting results. Soohoo et al. (2006) compared unicompartmental hemiarthroplasty of the knee to total knee arthroplasty in the US with a model from a payer perspective. Soohoo et al. (2006) found unicompartmental hemiarthroplasty of the knee to in comparison to total knee arthroplasty to result in an ICER <$50,000 / QALY. Xie et al. (2010) utilized a prospective cohort study to compare total knee arthroplasty to unicompartmental hemiarthroplasty of the knee in a US population from both a societal perspective and a payer perspective. (Xie et al., 2010) found total knee arthroplasty in comparison to unicompartmental hemiarthroplasty of the knee to result in an ICER of $65,245 / QALY from a societal perspective, and an ICER of $4,860/QALY from a payer perspective.

Total joint arthroplasty in comparison to joint fusion surgery

Only one study evaluated total joint arthroplasty in comparison to joint fusion surgery. SooHoo et al. (2004) compared total ankle arthroplasty to ankle fusion surgery for treatment of ankle OA. SooHoo et al. (2004) utilized a model with a 10-year time horizon from a payer perspective for a US population in this research. The findings of this study were that ankle arthroplasty results in an ICER of $18,149 / QALY, and is sensitive to the theoretical functional advantages of arthroplasty over ankle fusion surgery.
Key Messages:

- The ICER for total joint replacement ranges from cost-saving to $37,000 / QALY, and is sensitive to the age of the patient, the sex of the patient, the overall health status of the patient, assumptions regarding revision rates, perspective, and methodology for measurement of utilities.
- Hybrid prosthetics may be slightly more cost-effective than cement-less prosthesis. However, the difference in ICER is quite small and is sensitive to the age of the patient.
- Cemented prosthetics with antibiotics appears to not be a cost-effective option in comparison with cemented prosthetics without antibiotics in a general population of adults with OA.
- It is not possible to determine if total arthroplasty, hemi-arthroplasty or joint fusion therapy is a more cost-effective treatment option for OA. The ICER in these comparisons appears to be sensitive to perspective, the joint being evaluated, and the assumptions made regarding the theoretical benefits of one procedure over another procedure.

1 Table 10.4 Primary studies identified for total joint arthroplasty

	Design Perspective Country Time Horizon	Population	Comparators	Results	Sensitivity
Chang (1996)	Model. Societal. US. Unknown.	Adults with hip OA	Total hip arthroplasty vs. non-surgical management	Cost saving for 60-year-old women.	Sex (male ICER > Female ICER), age (older ICER > younger ICER)
Bourne (1994)	RCT. Payer. UK. 2 years.	Adults with hip OA.	Total hip arthroplasty vs. non-surgical management	ICER = GBP 27,139/QALY	Revision rate
Higashi (2011)	Model. Payer. Australia. Lifetime.	Adults with hip OA or knee OA.	Total hip arthroplasty vs. non-surgical management, total knee arthroplasty vs. non-surgical management.	Hip: AUD 5,000/ QALY, Knee: AUD 12,000/ QALY	Inclusion of future unrelated healthcare costs.
Losina (2009)	Model. Payer. US. Lifetime.	Adults with knee OA.	Total knee arthroplasty vs. non-surgical management	USD 28,100 / QALY	Sensitive to cost inputs from low volume vs high volume centers.
Waimann (2014)	Prospective cohort. Societal. US. 6-months	Adults with knee OA.	Total knee arthroplasty vs. non-surgical management.	USD 20,133/ QALY	Tool to measure utility.
Jenkins (2013)	Prospective cohort. Payer. UK. 1-year.	Adults with hip OA or knee OA.	Total hip arthroplasty vs. non-surgical management. Total knee arthroplasty vs. non-surgical management.	Total hip arthroplasty: GBP 1,372/ QALY. Total knee arthroplasty: GBP 2101 / QALY	Health before surgery, age.
Cummins (2009)	Model. Payer.	Adults with hip OA.	Cemented total hip arthroplasty with antibiotics vs. cemented total hip	USD 37,355 / QALY	Cost of cement, and age of patient.

	US. Unknown.		arthroplasty without antibiotics.		
diTianna (2011)	Model. Payer perspective. Italy. Lifetime.	Adults with hip OA.	Cement-less versus hybrid prostheses in total hip replacement	EUR 2,401 per revision-free life year	Age.
Pennington (2013)	Model. Payer. UK. Lifetime.	Adults with hip OA.	HA with cement-less prosthesis, with hybrid prosthesis, and with cemented	Hybrid most CE option for age 70 (75% probability). Age 60 and 80, unable to determine.	Sensitive to age (older ICER > younger ICER)
Mather (2010)	Model. Societal. US. Unknown.	Adults with shoulder OA.	Total shoulder arthroplasty vs. hemi-arthroplasty.	Total shoulder arthroplasty was dominant	Sensitive to revision rate, and utility measures.
SooHoo (2006)	Model. Payer. US. Unknown.	Adults with knee OA	Unicompartmental knee arthroplasty vs. total knee arthroplasty	<USD 50,000 / QALY	Revision rate
Xie (2010)	Prospective cohort. Societal & Payer US. 2-years.	Adults with knee OA.	Total knee arthroplasty vs. unicompartmental arthroplasty.	Societal: USD 65,245 / QALY Payer: USD 4,860/QALY	Perspective.
SooHoo (2004)	Model. Payer. US. 10 years.	Adults with ankle OA.	Ankle arthroplasty vs. ankle fusion	USD 18,419 / QALY	Theoretical functional advantages of arthroplasty.

10.4 Evidence gaps in osteoarthritis

Observations from published studies

- The ICER was shown to differ markedly when the choice of quality of life assessment tool was changed, from USD 205,186/QALY using the Quality of Well-Being Scale to USD 32,643 using the Current Health Desirability Rating.
- The cost-effectiveness of the cox-2 inhibitor drugs was significantly affected by the safety profile, with decreased cost-effectiveness of celecoxib and rofecoxib when adverse cardiovascular events were modelled.
- The cost-effectiveness of opioids has only been compared with other opioids (or combinations with non-opioids), consequently the relative cost-effectiveness of opioids versus other classes of painkillers is not known
- Single studies suggest proton pump inhibitors and misoprostol are cost-effective additions to pain relief medications in patients experiencing gastrointestinal side-effects.
- Total joint arthroplasty was studied against both non-surgical interventions (6 studies) and other surgical interventions (7 studies), however the range of joints examined (knee, hip, shoulder, ankle) meant few studies were available for each specific intervention and evaluations tended to be sensitive to perspective, age, overall health, utility measures etc.

There are four general categories under which evidence gaps develop in the research on cost-effective treatment options for osteoarthritis: choice of treatment modality evaluated in cost-effectiveness research, choice of comparator, long time horizons, and lack of a breadth of research based upon assumptions with a strong evidence base.

10.4.1 Choice of treatment modality evaluated

The primary studies identified in this review are heavily skewed towards conducting cost-effectiveness analysis on a couple of treatment modalities, while the majority treatment modalities have very limited cost-effectiveness research. Sixteen primary studies were identified that evaluate NSAIDs in the treatment of osteoarthritis, of which fifteen focused on the evaluation of two specific medications – Celecoxib and Rofecoxib (a medication that has subsequently been withdrawn from international markets). Additionally thirteen primary studies were identified that examined the cost-effectiveness of total joint replacement surgery, of which eleven focused on evaluation of only the knee joint or the hip joint. Meanwhile no primary studies were identified that evaluated the cost-effectiveness of joint rest, physical therapy, braces, joint protection, heat / cold therapy, psychological coping strategies, intra-articular glucocorticoid injections, hydroxyquinilone, arthroscopic joint irrigations, arthroscopic debridement, or arthroscopic synovectomy. Additionally there is only very limited research on the cost-effectiveness of acetaminophen in the treatment of osteoarthritis, despite the only primary study identified demonstrating that acetaminophen is likely a cost-effective treatment option for osteoarthritis.

The research gap that exists is a lack of cost-effectiveness research on joint rest, physical therapy, braces, joint protection, heat / cold therapy, psychological coping strategies, intra-articular glucocorticoid injections, hydroxyquinilone, arthroscopic joint irrigations, arthroscopic debridement, and arthroscopic synovectomy; and only limited cost-effectiveness research on acetaminophens use in osteoarthritis.

10.4.2 Choice of comparator

There are two gaps in the research in regards to choice of comparator – the first is in the breadth of comparators and the second is in the definition of the comparator. There are three general classes of treatment modalities for osteoarthritis – lifestyle modification therapies, medical therapies, and surgical therapies. None of the primary studies identified compared lifestyle modification therapies to either medical therapies or surgical therapies, and none of the primary studies identified compared medical therapies to surgical therapies. Additionally there was very little breadth of choice of comparator in the cost-effectiveness research within the three general classes of treatment modalities for osteoarthritis. Of the thirteen primary studies evaluating surgical procedures, only three made comparisons to different surgical procedures. Of the sixteen primary studies evaluating NSAIDs, only two of these studies compared NSAIDs to a different class of drugs. Furthermore there was no comparison of opioids to different classes of drugs, and there was no comparison of the two types of gastroprotective agents – proton pump inhibitors and misoprostol.

Six of the thirteen primary studies evaluating total joint arthroplasty used the comparator of non-surgical management. However, non-surgical management was not clearly defined in any of these six studies and could have constituted medical therapies, lifestyle modification therapies or a combination of both.

The research gap that is identified is lack of a clear comparison of lifestyle modification therapies with either medical therapies or surgical therapies, and lack of a clear comparison of medical therapies to surgical therapies.

10.4.3 Short time horizon

Osteoarthritis, once it develops in older adults, tends to be progressive and unremitting. However, the majority of the cost-effectiveness research identified evaluating treatment modalities for osteoarthritis had comparatively short time horizons. Twenty-one of the primary studies, more than 66% of all of the primary studies, utilized a time horizon of one year or less.

The evidence gap that exists here is an understanding of the cost-effectiveness of treatment modalities over the duration of the illness.

10.4.4 Strength of research supporting model assumptions

Twelve of the sixteen primary studies evaluating NSAIDs as a treatment modality for osteoarthritis base their assumptions regarding the risk of cardiovascular adverse events associated with selective cox-2 inhibitors on out-dated research. Only four of the sixteen studies evaluating the cost-effectiveness of NSAIDs utilize the most current research indicating that cox-2 inhibitors are associated with an elevated risk of adverse cardiovascular events, including myocardial infarction and stroke. The modelled risk of adverse cardiovascular events profoundly impacts the ICER –the majority of the cost-effectiveness with cardiovascular adverse event risk assumptions based upon out-dated research finds selective cox-2 inhibitors to be cost-effective in comparison to non-selective cox inhibitors; and all of the research that utilizes cardiovascular adverse event risk assumptions based upon the most recent research finds non-selective cox inhibitors to be dominant over selective cox-2 inhibitors.

The research gap identified is that numerous studies use out-dated research to support assumptions in the comparative effectiveness models, and only a few cost-effectiveness studies use the most recent

research to support assumptions regarding cardiovascular risk associated with selective cox-2 inhibitors. This bias is not abundantly clear in all of the primary studies, and can create confusion when making policy decisions.

Contributor	Comment
Dr. Jean-Yves Reginster University of Liege, Liege, Belgium	1) Very few drugs are licensed for the treatment of OA and none of them were given a marketing authorisation by multi-national agencies (FDA or EMA), particularly when it comes to the long-term structural prevention of the disease 2) There is an important distinction to be made between symptomatic (reduction of pain and improvement of function) and structural (prevention of progression) of osteoarthritis 3) The hard clinical endpoints to be considered as the relevant outcomes may vary from one location to another (i.e. total joint replacement, which is relevant for lower limbs osteoarthritis is probably meaningless for spinal or hand osteoarthritis) 4) The pathophysiological process and subsequently the clinical pattern of osteoarthritis at different locations might be substantially different (e.g. flares at the hands or at the knee, much less frequent at the spine) 5) When considering, as most health economic researches do, osteoarthritis of the knee and of the hip, the hard clinical endpoint (i.e. the relevant outcomes) is the reduction in the rate of total joint replacement. However, since total joint replacement induces a major and immediate benefit in terms of quality of life (lasting for several years), it might be difficult to demonstrate any cost-efficiency for medications that delay or prevent total joint replacement.

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Health Economic Evidence Analysis: Management of osteoporosis

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11 Osteoporosis

11.1 Bibliometrics

A total of 71 economic studies were mapped to the clinical model for osteoporosis (Table 11.1 and Figure 11.1). The majority[1] of studies (75%) were published in 2006 or later. Of the 11 reviews identified, five were published between 2009 and 2014.

Table 11.1 Bibliometric data for Osteoporosis

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Bone Diseases, Metabolic"[MeSH Terms] NOT ("mucolipidosis" [MeSH Terms]) NOT (pseudohypoparthyroidism [MeSH Terms]) NOT ("renal osteodystrophy" [MeSH Terms] NOT ("Rickets" [MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	71
Included as "other"	74
Reviews	11
Excluded	196
Total	352

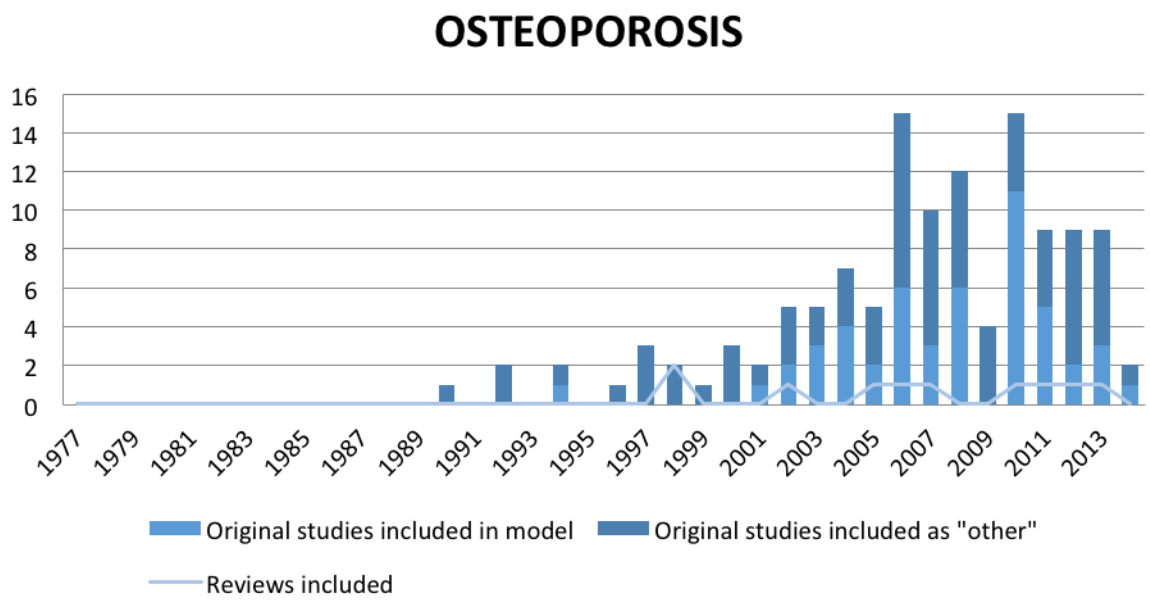

Figure 11.1 Bibliometric data for Osteoporosis by year

[1] 75% of studies or more

11.2 Review Coverage

The clinical model for osteoporosis consists of twelve treatment modalities (Table 11.3). Of these, three treatment modalities are lifestyle modifications, and nine are medical therapies. Zero of three (0%) of the lifestyle modification therapies are addressed by a least one of the four reviews published between 2009 and 2014. Seven of nine (78%) of the medical therapies are addressed by a least one of the four reviews published between 2009 and 2014.

Table 11.2 Table of reviews for osteoporosis and associated treatment

Title and reference	Year	Treatments covered
"A systematic review of cost-effectiveness of drugs for postmenopausal osteoporosis." (Hiligsmann M, Evers S, Sedrine W, Kanis J, Ramaekers B, Reginster J, Silverman S, Wyers C, & Boonen A)	2015	**Medical Therapies** Denosumab, Bisphosphonates, Hormone Replacement Therapy, Selective estrogen receptor modulators, Strontium Ranelate
"Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporotic women." (Hiligsmann M, Boonen A, Dirksen CD, Ben Sedrine W)	2013	**Medical Therapies** Denosumab
"Pharmacoeconomic analysis of strategies to treat postmenopausal osteoporosis: a systematic review". (Brandão, Machado & Acurcio)	2012	**Medical Therapies** Calcium and Vitamin D Supplement, Parathyroid hormone, Bisphosphonates, Hormone Replacement Therapy, Selective estrogen receptor modulators, Strontium ranelate, Desonuab,
"A review of the cost effectiveness of bisphosphonates in the treatment of post-menopausal osteoporosis in Switzerland." (Lippuner et al., 2011)	2011	**Medical Therapies** Bisphosphonates
"Cost-effectiveness of strontium ranelate for the prevention and treatment of osteoporosis." (Hiligsmann et al., 2010)	2010	**Medical Therapies** Strontium Ranelate

11.3 Evidence Analysis

11.3.1 Treatment of osteoporosis

Osteoporosis is managed with lifestyle modification therapies such as a diet that includes adequate calcium and vitamin D intake, exercise, and smoking cessation. Osteoporosis is also managed medically with supplemental calcium and vitamin D, bisphosphonates, denosumab, strontium ranelate, selective estrogen receptor modulators (in females only), parathyroid hormone, hormone replacement therapy (in females only), calcitonin, and testosterone therapy (in hypogonadal males only). Fifty-three primary studies evaluating the cost-effectiveness of these treatment modalities were identified (See Table 11.3). Fifty of fifty-three identified primary studies were based on a Markov model and one was based on a clinical trial. Thirty-four of the fifty primary studies utilized a payer perspective, eleven studies utilized a societal perspective, and five utilized an unknown perspective. Thirty-eight of fifty-three primary studies utilized a lifelong time horizon, and twelve utilized a time horizon between one year and thirteen years.

Table 11.3 Primary health economic evidence and reviews for the treatment of osteoporosis

Osteoporosis	Studies	Reviews
Lifestyle Modification Therapies		
Diet – adequate intake of calcium and vitamin D	0	0
Exercise	0	0
Smoking Cessation	0	0
Medical Therapies		
Supplemental Calcium and Vitamin D	4	1
Bisphosphonates (alendronate, risedronate, zoledronic acid, ibandronate)	34	3
Denosumab	6	3
Strontium ranelate	7	3
Selective estrogen receptor modulators (raloxifene, tamoxifen)	8	2
Parathyroid hormone	6	1
Hormone Replacement Therapy	4	2
Calcitonin	2	0
Testosterone therapy	0	0

11.3.1.1 Lifestyle modification therapies

No studies assessed the cost-effectiveness of adequate dietary intake of calcium and vitamin d, exercise or smoking cessation for the treatment of osteoporosis.

11.3.1.2 Medical Therapies

11.3.1.2.1 Supplemental calcium and vitamin D

Four of the primary studies identified evaluated the cost-effectiveness of supplemental calcium and vitamin D for the treatment of osteoporosis. One study (Willis, 2002) compared combined calcium and vitamin D3 supplementation with no drug treatment in a population of women with osteoporosis with fractures at the age 70 in Sweden. This study was based on a Markov model from a national health system perspective with a lifetime time horizon. The ICER for this study was sensitive to the efficacy of calcium and vitamin D3 supplementation. If calcium and vitamin D3 supplementation have a 27% efficacy or 20% efficacy in reducing fractures, then calcium and vitamin D3 is cost saving. If calcium and vitamin D3 supplementation only have 15% efficacy, then supplementation results in an ICER of SEK 74,000/QALY.

A second study (LK., 2003a) compared universal calcium and vitamin D supplementation with no drug treatment; osteoporosis screening followed by treatment with alendronate for those diagnosed compared with no drug treatment; and osteoporosis screening followed by treatment with hormone replacement therapy for those diagnosed compared with no drug treatment in women at age 50 and 65 both with and without osteoporosis in Brazil. This study was a 1-year clinical trial and utilized a Unified Health Care System perspective. The study indicated calcium and vitamin D supplementation cost BRL 12,673 (approx. EUR 4,000)/femoral fracture prevented for women age 50, and BRL 12,408 /femoral fracture prevented in women age 65. Universal calcium and vitamin D supplementation were found to be more cost-effective than screening + alendronate, which cost BRL 136,217/femoral fracture prevented in women age 50 and BRL 101,181/femoral fracture prevented in women age 65. Additionally universal calcium and vitamin D supplementation were found to be more cost effective than screening + hormone replacement therapy, which cost BRL 1,479,504/femoral fracture prevented for women age 50 and BRL 1,389,939/femoral fracture prevented in women age 65.

A third study (Geelhoed, Harris & Prince, 1994) compared calcium supplementation and exercise to no treatment for peri-menopausal women in Australia without osteoporosis. This study is based on a Markov model from a payer perspective with a lifelong time horizon, and an outcome of osteoporotic hip fractures determined by estimated bone density. The ICER for calcium supplementation and exercise was found to be AUD 28,500/QALY in this study.

A forth study (Hiligsmann et al., 2014) compared supplemental calcium and vitamin D to no treatment in Belgian men and women with osteoporosis at age 60 and age 70. The study is based on a Markov model from a payer perspective. The ICER is this study was found to be sensitive both to age and sex. The ICER in this study was found to be EUR 40,578 / QALY for women at age 60, Euro 7,912 / QALY for women age 70, Euro 23,477 / QALY for men age 60, and Euro 10,250 for men age 70.

Main findings:

- Calcium and vitamin D supplementation appears to be a cost effective treatment for postmenopausal women and men with osteoporosis.
- Universal calcium and vitamin D supplementation in postmenopausal women over age 50 appears to be a cost-effective treatment option for prevention of osteoporotic fracture in comparison to screening for osteoporosis and subsequent medical treatment as indicated.
- Calcium supplementation and exercise appears to be a cost-effective option for osteoporotic fracture prevention in peri-menopausal women without osteoporosis.
- The ICER for calcium and vitamin D supplementation in comparison to no treatment is sensitive to age and sex of the population.
- Results are likely to be sensitive to the efficacy of calcium and vitamin D supplementation in preventing fractures.

11.3.1.2.2 Bisphosphonates

Twenty-nine of the primary studies identified evaluated the cost-effectiveness of bisphosphonate therapy for osteoporosis. Central characteristics of these studies are reproduced in Table 11.4 and each drug is discussed in turn below.

Alendronate

Twelve studies identified specifically examined the cost-effectiveness of alendronate therapy. Of these twelve studies eleven were conducted in postmenopausal women, eight of which were conducted in European populations. Johnell O, Jönsson B, and Jönsson L (2003) found from a healthcare provider perspective in Sweden that alendronate when compared to no treatment resulted in an ICER of SEK 76,384/QALY. This finding was reiterated by research conducted by Jönsson L, Borgström F (2003) finding that alendronate in comparison to no treatment for a population of postmenopausal women in Sweden from a healthcare payer perspective resulted in an ICER of SEK 68,428/QALY. Borgström et al. (2004) also examined postmenopausal women in Sweden and found alendronate in comparison to no treatment to have an ICER of EUR 14,483 /QALY from a societal perspective. However, when the cost-effectiveness of alendronate use was examined in a similar Swedish population of postmenopausal women, but in comparison to calcium and vitamin D supplementation rather than in comparison to no treatment, the ICER was found to be less favorable. For this comparator, Christensen et al. (2005) estimated the ICER for alendronate at SEK 125,000/QALY. Kanis et al (2006) found from a payer perspective in the UK that generic alendronate in comparison to no treatment resulted in an ICER of < GBP 20,000/QALY in women over age 50.

Ström et al., (2007) conducted a multinational study examining alendronate in comparison to no treatment for postmenopausal women. The study was conducted from a societal perspective in the following European countries: Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, and the UK. The results for

women with a history of previous osteoporotic fractures were ICERs of EUR 6,461/QALY in Belgium, cost saving in Denmark, EUR 4,670/QALY in France, EUR 7,658/QALY in Germany, EUR 15,489/QALY in Italy, cost saving in Norway, EUR 13,193/QALY in Spain, cost saving in Sweden, and EUR 1,356/QALY in the UK. For women without a history of fractures ICERs were EUR 23,684/QALY in Belgium, EUR 6,201/QALY in Denmark, EUR 27,419/QALY in France, EUR 27,821/QALY in Germany, EUR 39,712/QALY in Italy, cost saving in Norway, EUR 32,943/QALY in Spain, cost saving in Sweden, and EUR 11,849/QALY in the UK (Ström et al., 2007).

Two of the studies examining the cost-effectiveness of alendronate in a European population, specifically conducted sensitivity analysis on the effect patient adherence with the prescribed medication have on the ICER. Hiligsmann et al (2006) found from a payer perspective in Belgium that alendronate in comparison to no treatment resulted in an ICER of EUR 9,105/QALY with full medication adherence, and resulted in an ICER of EUR 15,325/QALY with realistic adherence assumptions. Additionally Hiligsmann et al (2006) found from a payer perspective in Belgium that generic alendronate in comparison to no treatment results in an ICER of EUR 4,871/QALY when patients are assumed to take all medication prescribed, EUR 11,985/QALY when patients are assumed to take 80% of prescribed medications, and EUR 30,181/QALY when patients are assumed to take only 60% of prescribed medications.

Three studies identified examined the cost-effectiveness of alendronate in the US population. One study compared alendronate to no treatment from a societal perspective in men age 71 with osteoporosis that also have locally advanced or high-risk localized prostate cancer in the US. This study found alendronate to have an ICER of USD 66,800/QALY in comparison with no treatment (Ito et al., 2010). Another study compared alendronate with calcium supplementation in postmenopausal women with osteoporosis from a societal perspective in the US. This study found alendronate in comparison to calcium supplementation and vitamin D supplementation to result in an ICER of USD 11,600/QALY (Liu et al., 2006). Nayak et al (2012) examined the cost-effectiveness of screening for osteoporosis and subsequently treating with alendronate as needed in comparison to no treatment in US women age 65 and older. This study found alendronate to be cost-effective if it was priced at USD 20/ year to USD 800/ year, and found alendronate to be cost-saving if it was priced from USD 20/ year to USD 200 / year.

One study identified examined the cost-effectiveness of alendronate was conducted in Japan. Moriwaki et al. (2013) studied alendronate in a Japanese population of postmenopausal women from a societal perspective. This study found the ICER for alendronate compared to no treatment to be much greater in women with smoking history or high alcohol intake in comparison to women with a family history of hip fractures s conducted (Moriwaki et al., 2013).

Risedronate

Thirteen identified studies examined the cost-effectiveness of risedronate. Of these thirteen studies, eight compared risedronate to no treatment and six studies compared risedronate to alendronate. Of the eight the studies comparing risedronate to no treatment, all were conducted in a population of postmenopausal women with osteoporosis, and seven were conducted in EU countries while one was conducted in Japan.

Kanis et al. (2004), Brecht et al. (2003), and Wasserfallen et al. (2008) all found risedronate to be cost saving in comparison to no treatment in women age 70 with osteoporosis and with fractures. Kanis et al. (2004) evaluated a UK population, Brecht et al. (2003) a German population, and Wasserfallen et al. (2008) a Swiss population. Kanis et al. (2004) and Wasserfallen et al. (2008) utilized a payer perspective, while Brecht et al. (2003) utilized a societal perspective. Additionally, Iglesias et al. (2002) compared risedronate to no treatment in a population of slightly older (75 year old) women in the UK from a payer perspective, and also found risedronate to be cost saving.

Conversely, a large multinational study comparing risedronate to no therapy found risedronate to be cost-effective, but not cost saving, from a societal perspective. Borgström et al. (2006) compared risedronate to no treatment in a population of women with osteoporosis at age 70 from a societal perspective in Sweden, Finland, Spain, and Belgium. Borgström et al. (2006) found the ICER for women with a history of previous fractures to be EUR 1,176/QALY in Sweden, EUR 28,377, EUR 55,026/QALY in Spain, and EUR 18,020/QALY in Belgium. This study also found the ICER for women without a history of previous fracture to be EUR 30,062/QALY in Sweden, EUR 82,000/QALY in Finland, EUR 141,353/QALY in Spain, and EUR 66,857/QALY in Belgium (Borgström et al., 2006a). Additionally Ding et al (2002) found risendronate in comparison to no treatment to result in an ICER of < USD 100,000 only for postmenopausal women 70+ with a history of previous vertebral fracture in Japan from a payer perspective.

Five studies compared risedronate to alendronate from a payer perspective. Of these five studies, Thompson et al. (2010) and Brecht et al. (2003) both found risedronate to be cost saving compared to alendronate in a population of German postmenopausal women with osteoporosis. Additionally, Tosteson et al. (2008) compared risedronate, alendronate, and ibandronate for the treatment of osteoporosis in a population of postmenopausal women in the US from a payer perspective. Tosteson et al. (2008) found in this evaluation that risedronate was dominant (more effective and less expensive) than both alendronate and ibandronate.

Conversely, Grima et al. (2008) found treatment of osteoporosis in postmenopausal women in Canada with risedronate in comparison with alendronate resulted in an ICER of CAD 3,877/QALY. Berto et al. (2010) found treatment of osteoporosis in postmenopausal women in Italy to result in an ICER of EUR 36,099/QALY for women age 65-69, EUR 9,737/QALY for women age 70-74, and for risedronate to be dominant in women age >75.

Ibandronate, etidronate, and zoledronic acid

Only one study evaluated ibandronate, one study evaluated etidronate and two studies evaluated zoledronic acid. Jansen JP, Gaugris S, and Bergman G (2008) compared ibandronate with alendronate and vitamin D3 supplementation in a population of postmenopausal women in the UK and Netherlands, and found ibandronate was dominated by alendronate and vitamin D3 supplementation in women age greater than 60.

Goeree, Blackhouse & Adachi (2006) evaluated etidronate and risedronate in a population of Canadian women with osteoporosis without fractures at age 65 from a payer perspective. Goeree, Blackhouse & Adachi (2006) found risedronate in comparison to no treatment resulted in an ICER of CAD 78,274/QALY, while etidronate in comparison to no treatment resulted in an ICER of CAD 32,571/QALY.

Akehurst et al. (2011) evaluated zoledronic acid in comparison with calcium and vitamin D supplements in women with osteoporosis from a payer perspective in Finland, Norway, and Netherlands. This study found zoledronic acid in comparison with calcium and vitamin D supplementation to be cost saving in Norway, have an ICER of EUR 19,000/QALY in Finland, and an ICER of EUR 22,300/QALY in the Netherlands (Akehurst et al., 2011). Additionally Fardellone et al. (2007) evaluated zoledronic acid in comparison to current treatment strategies in France. This study found zoledronic acid to result in a cost of EURO 1,497 per a fracture avoided, while current treatment strategies resulted in a cost of EURO 1,685 per a fracture avoided (Faradellone, 2007).

Bisphosphonates use in patients with glucocorticoid induced osteoporosis

Two of the twenty-nine studies identified as evaluating bisphosphonate therapy specifically examine the cost-effectiveness of bisphosphonate therapy in glucocorticoid-induced osteoporosis. One study evaluated the cost-effectiveness of ibandronate in comparison with calcium supplementation in a German population of men and women with osteopenia or osteoporosis due to inflammatory bowel disease at age 36 and 65 (Kreck S, Klaus J, Leidl R, von Tirpitz C, Konnopka A, Matschinger H, 2008). This study found ibandronate in comparison

with calcium supplementation results in an ICER of EUR 407,375/QALY in adults age 36, and EUR 6,516,345/QALY in adults age 65.

A second study conducted in the UK examined bisphosphonate therapy for glucocorticoid-induced osteoporosis from a payer perspective. This study found the ICER for bisphosphonate therapy in women (5 mg of prednisone a day) compared with no therapy to be GBP 41,000/QALY for age 40-59, GBP 17,000/QALY for age 60-79, and GBP 5,000/QALY for age 80+. The same study found the ICER for men to be GBP 40,000/QALY for age 40-59, GBP 43,000/QALY for age 60-79, and GBP 35,000/QALY for age 80+ (van Staa et al., 2007).

Dosing of bisphosphonates

One study examined how the dosing schedule of bisphosphonates impacts the ICER. Earnshaw et al. (2007) evaluated a population of postmenopausal women in the US from a payer perspective. This study found that bisphosphonates therapy results in an ICER of EUR 407,375/QALY for monthly dosing and USD 9,476/QALY for weekly dosing.

Main findings:

- Bisphosphonates, particularly alendronate and risedronate, appear to be a cost-effective treatment option for osteoporosis in postmenopausal women in comparison to no therapy.
- Bisphosphonates, specifically alendronate and risedronate, appear to be a less cost-effective treatment for osteoporosis in postmenopausal women than calcium supplementation and vitamin d supplementation.
- Bisphosphonates appear to not be a cost-effective treatment option in patients with glucocorticoid induced osteoporosis.
- The ICER for bisphosphonates is sensitive to history of previous fractures, history of high alcohol intake, and smoking history, dosing regimen, patient age, underlying medical conditions, medication adherence, and comparative generic drug pricing. Several studies support improved cost-effectiveness ratios for older patients, and for patients with previous fractures.

Table 11.4 Primary studies identified for bisphosphonates

Author (year)	Population	Study design	Results
Johnell et al (2003)	Women with osteoporosis with fractures at age 71. Sweden.	Markov model with health care provider perspective and lifelong time horizon.	Alendronate vs no treatment = SEK 76,384/ QALY
Strom et al (2007)	Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, and UK. Women with osteoporosis .	Markov model with Societal perspective and lifelong time horizon.	Alendronate vs no treatment: With previous fracture: BE = EUR 6,461/QALY, DK = cost saving, FR = EUR 4,670/QALY, Germany = EUR 7,658/QALY, IT = EUR 15,489/QALY, NO = cost saving, ES = EUR 13,193/QALY, SI = cost saving, UK = EUR 1,356/QALY. Without previous fracture: BE = EUR 23,684/QALY, DK = EUR 6,201/QALY, FR = EUR 27,419/QALY, Germany = EUR 27,821/QALY, IT = EUR 39,712/QALY, NO = cost saving, ES = EUR 32,943/QALY, SI = cost saving, UK = EUR 11,849/QALY.

Jonsson et al (2003)	Sweden. Women with osteoporosis with fracture at age 71.	Markov model with a payer perspective and a lifelong time horizon.	alendronate vs no treatment: SEK 68,428/QALY
Hiligsmann et al. (2006)	Belgium. Women age 70 with osteoporosis and with a two-fold increase in fracture risk of the average population.	Markov microsimulation model with a payer perspective and a lifelong time horizon.	Alendronate vs. no treatment: full medication adherence = EUR 9,105/QALY, realistic medication adherence = EURO 15,325/QALY.
Hilligsmann et al (2006)	Belgium. Women age 65 with T-score of -2.5	Markov microsimulation model with a payer perspective and lifetime time horizon.	Generic alendronate vs. no treatment: 100% compliance with medication prescribed = EUR 4,871/QALY, 80% = EUR 11,985/QALY, 60% = EUR 30,181/QALY.
Kanis et al (2006)	UK. Women age 50 with osteoporosis.	Markov cohort model with a payer perspective and a lifetime time horizon.	Generic alendronate vs no treatment: using a WTP threshold of GBP 20,000/QALY alendronate was cost-effective for primary fracture prevention in women with osteoporosis at age 50 or greater.
Borgstrom et al (2004)	Sweden. Men with osteoporosis at age 71.	Markov model with a societal perspective and a lifelong time horizon.	Alendronate vs no treatment: EUR 14,483/QALY
Ito et al (2010)	US. Men with osteoporosis with locally advanced or high risk localized prostate cancer.	Markov cohort model societal perspective and with lifetime time horizon.	Alendronate vs no intervention = USD 66,800/QALY
Nayak et al. (2012)	US. Women age 65 screened for osteoporosis then treated with alendronate as needed.	Microsimulation model. Payer perspective. Lifetime time horizon.	Alendronate (at prices of USD 20 / year to USD 800 / year) vs no intervention = Alendronate is cost-effective at all costs, and is cost-saving at a cost of < USD 200 / year.
Moriwaki et al (2013)	Japan. Women with ostepenia and age 70 with a family history of hip fracture, a high alcohol in take, or smoking history.	Markov model with a societal perspective a lifetime time horizon.	Alendronate vs no treatment: family history of hip fracture = USD 92,937/QALY, High alcohol intake = USD 126,251/QALY, smoking history = USD 129,067/QALY.
Christensen et al (2005)	Sweden. Women with osteoporosis at age 71.	Markov model with a societal perspective and a 29-year time horizon.	Alendronate + calcium supplement + vit D supplement vs calcium supplement + vit D supplement = SEK 125,000/QALY
Liu et al (2006)	US. Women with osteoporosis with fractures at age 70.	Markov model with societal perspective and lifelong time	Alendronate vs calcium supplement + Vit D supplement = USD 11,600/QALY.

		horizon.	
Kreck et al (2008)	Germany. Men and women with ostepenia or osteoporosis due to inflammatory bowel disease at age 36 and 65.	Markov model with a societal perspective with 6-year time horizon.	Ibandronate vs Calcium supplement: Age 36: EUR 407,375/QALY. Age 65: EUR 6,516,345/QALY
Akehurst et al (2011)	Finland, Norway, Netherlands. Women with osteoporosis (no age specified).	Markov model with a payer perspective and an unknown time horizon.	Zoledronic acid vs Ca and Vit D supplements: NO = cost saving, FI = EUR 19,000/QALY, NL = EUR 22,300/QALY.
Fardellone et al (2007)	France. Women with postmenopausal osteoporosis.	Simulation based model from a healthcare payer perspective with a lifetime time horizon.	Zoledronic acid vs current treatment strategies: Cost per a vertebral fracture avoided was EUR 1,479.
Iglesias et al (2002)	UK. Women with osteoporosis with fractures at age 75 years	Markov model with a NHS perspective and lifelong time horizon.	Risedronate vs no treatment: risedronate Dominant
Borgstrom et al (2006)	Sweden, Finland, Spain, Belgium. Women with osteoporosis at age 70.	Markov model with a societal Perspective and a lifelong time horizon.	Risedronate vs no treatment: Without Previous Fracture: SE = EUR 1,176/QALY, FI = EUR 28,377/QALY, ES = EUR 55,026/QALY, BE = EUR 18,020/QALY. With previous fracture: SE = EUR 30,062/QALY, FI = EUR 82,000/QALY, ES = EUR 141,353/QALY, BE = EUR 66,857/QALY.
Kanis et al (2004)	UK. Women with osteoporosis with fractures at age 70.	Markov model with a payer perspective and a time horizon of 5 years.	Risedronate vs no treatment = Cost saving
Brect et al (2003)	Germany. Women with osteoporosis with fractures at age 70.	Markov model with German Social Insurance perspective and a 13-year time horizon.	Risedronate vs no treatment = Cost Saving
Wasserfallen et al (2008)	Switzerland. Women with osteoporosis with fractures at age 70.	Markov model with a payer perspective and a 5-year time horizon.	Risedronate vs no treatment = cost saving
Ding et al (2002)	Japan. Women age 55+.	State transition model with a payer perspective and 3 year time horizon.	Risendronate vs. no treatment: < USD 100,000 for women age 70+ with a history of previous vertebral fracture.

Grima et al. (2006)	Canada. Postmenopausal women age 65+.	Markov cohort model with a payer perspective and 5 year time horizon.	Risendronate vs. alendronate: Can 3,877/QALY
Kanis & Borgstrom (2004)	UK. Women age 60-80 with osteoporosis stratified by prior fracture or no prior fracture, and stratified by T-scores.	Markov model with payer perspective and an unknown time horizon.	Risedronate vs no treatment: Women >70 with prior vertebral fracture = cost saving, Women >65 with osteoporosis established by T-score = cost-effective
Goree et al (2006)	Canada. Women with osteoporosis without fractures at age 65.	Markov model with a Provincial Government perspective and lifelong time horizon.	No treatment = base, Etidronate = CAD 32,571/QALY, risedronate = CAD 78,274/QALY.
Grima et al (2008)	Canada. Women with osteoporosis with or without fractures at age 65 or over.	Clinical trial with a Health ministry perspective and a 5 year time horizon.	Risedronate (brand) vs. alendronate (brand or generic) = CAD 3,877/QALY
Berto et al (2010)	Italy. Women with osteoporosis with fractures at age >65.	Clinical trial with a Italian a National Health System perspective and a 5 year time horizon.	Risedronate /alendronate: age 65-69 = EUR 36,099/QALY, 70-74 = EUR 9,737/QALY, >75 = risedronate dominant
Brect et al (2004)	Germany. Women with osteoporosis with fractures at age 70.	Markov model with German Social Insurance perspective and 13-year time horizon.	No drug treatment = base, risedronate = EUR 32,092/QALY, Alendronate = EUR 41,302/QALY
Thompson et al (2010)	Germany. Women with osteoporosis at age 65 or older.	Markov model with a payer perspective and a lifelong time horizon.	Risedronate vs alendronate: risedronate is dominant.
Jansen et al (2008)	UK and Netherlands. Women with osteoporosis at age 80 and women with osteoporosis and vertebral fractures at age 50.	Markov model with a healthcare payer perspective and a 10-year time horizon.	Age 80: Alendronate + D3 vs no treatment = GBP 5,887/QALY, alendronate + D3 vs ibandronate = GBP 128/QALY Age 50: Alendronate + D3 vs no treatment = GBP 340,981/QALY, alendronate + D3 vs ibandronate = cost saving

Tosetson et al (2008)	US. Treating all women with osteoporosis with and without fractures at ages 65 and 75.	Markov model with third-party payer perspective and 10 year time horizon.	No treatment = base. 65 years with fractures: risedronate = USD 22,068/QALY, alendronate = USD 362,845/QALY, ibandronate = dominated. 65 years without fractures: risedronate = USD 66,722/QALY, alendronate = dominated, ibandronate = dominated. 75 years with fractures: risedronate = dominated, alendronate = dominated, ibandronate = dominated. 75 years without fractures: risedronate = USD 991/QALY, alendronate = dominated, ibandronate = dominated.
Pham et al (2011)	US. Women with osteoporosis >50 years stratified by health life expectancy: sick, average, healthy.	Markov model with unknown perspective and lifelong time horizon.	Oral bisphosphonate therapy vs. no intervention: Sick = USD 18,000/QALY, average = USD 27,000/QALY, healthy = USD 43,000/QALY
Pister et al (2006)	US. Women with osteoporosis age >65.	Markov model with unknown perspective and unknown time horizon.	Bisphosphonates vs no treatment <USD 100,000/QALY,
Earnashaw et al (2007)	US. Women with osteoporosis with fractures at age > 50 years.	Markov model with third-party payer perspective and a 5-year time horizon.	Bisphosphonates monthly vs bisphosphonates weekly = USD 9,476/QALY
van Staa et al (2007)	UK. Men and women age 40-60, age 60-79, and age 80+ taking oral glucocortioids 5 mg/day, and 15 mg/day.	Markov model with payer perspective and a 5 year time horizon.	Bisphosphonates vs no treatment 5md prednisone daily: Women: age 40-60 = GBP 41,000/QALY, age 60-79 = GBP 17,000/QALY, and age 80+ = GBP 5,000/QALY. Men age 40-60 = GBP 40,000/QALY, age 60-79 = GBP 43,000/QALY, and age 80+ = GBP 35,000/QALY. 15mg of prednisone daily: Women: age 40-60 = GBP 17,000/QALY, age 60-79 = GBP 13,000/QALY, and age 80+ = GBP 15,000/QALY. Men age 40-60 = GBP 22,000/QALY, age 60-79 = GBP 34,000/QALY, and age 80+ = GBP 33,000/QALY.

Denosumab

Six of the primary studies identified evaluated the cost-effectiveness of denosumab therapy for osteoporosis. Two of these compared denosumab to no therapy as well as other comparators. Chau D, Becker DL, Coombes ME, Ioannidis G, & Adachi JD (2012) studied a population of women with osteoporosis and fractures at age 72 in Canada. This study utilized a Markov model with a public payer perspective and a lifelong time horizon. In this study denosumab was dominant over no therapy (Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, 2012). Jönsson et al. (2011) also compared denosumab with no therapy in a population of women with osteoporosis at age 71 in Sweden. This study utilized a Markov model with a societal perspective and a

lifelong time horizon. The ICER was EUR 14,120/QALY for denosumab compared with no therapy (Jönsson et al., 2011).

All of the six primary studies compared denosumab to bisphosphonates. Parthan et al. (2013) compared denosumab with generic alendronate, with risedronate, and with ibandronate in a population of postmenopausal women with osteoporosis in the US. This study utilized a Markov model with a third-party payer perspective and a lifelong time horizon. Comparing denosumab with generic alendronate resulted in an ICER of USD 85,100/QALY, and desonumab dominated both risedronate and ibandronate (Parthan et al., 2013).

Chau D, Becker DL, Coombes ME, Ioannidis G, & Adachi JD (2012) also compared denosumab with alendronate, risedronate and ibandronate in a population of women with osteoporosis and fractures at age 72 in Canada. This study utilized a Markov model with a public payer perspective and a lifelong time horizon. Denosumab compared with alendronate resulted in an ICER of CAD 27,287/QALY in this study, and denosumab dominated risedronate and ibandronate (Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, 2012).

Additionally, Parthan et al. (2013) compared denosumab with alendronate, zoledronate, risedronate and ibandronate in a population of men with osteoporosis aged 75+ in Sweden. This study utilized a Markov model with a payer perspective and a lifelong time horizon which found denosumab dominated alendronate, zoledronic acid, risedronate and ibandronate (Parthan et al., 2013).

Hiligsmann & Reginster (2011) also compared denosumab with branded and generic alendronate and risedronate in a population of women with osteoporosis with or without fractures at age 70 in Belgium. This study utilized a Markov model with a payer perspective and a lifelong time horizon. The ICER for women with no history of fractures for denosumab compared with branded alendronate was EUR 14,120/QALY, and EUR 22,220/QALY compared with generic alendronate. Denosumab dominated risedronate. For women with a history of fractures, denosumab compared with branded alendronate incurred an additional EUR 14,155/QALY, compared with generic alendronate the ICER was EUR 19,718/QALY, and compared with risedronate it was EUR 4,456/QALY (Hiligsmann & Reginster, 2011).

Jönsson et al. (2011) compared denosumab with alendronate and risedronate in a population of women with osteoporosis at age 71 in Sweden. This study utilized a Markov model with a societal perspective and a lifelong time horizon. The ICERs for this study are EUR 22,220/QALY for denosumab compared to alendronate and EUR 27,062/QALY for denosumab compared with risedronate (Jönsson et al., 2011).

Hiligsmann & Reginster (2010) compared denosumab with alendronate in a population of postmenopausal women with osteoporosis in Belgium using a Markov model with a payer perspective and a lifelong time horizon. For postmenopausal women with a history of fracture the ICER for denosumab was found to be EUR 38,514/QALY, EUR 22,270/QALY and EUR 27,802/QALY for women aged 60, 70, and 80. In postmenopausal women without a history of fracture the ICER was found to be EUR 37,167/QALY, EUR 19,718/QALY and EUR 19,368/QALY for women aged 60, 70 and 80 (Hiligsmann & Reginster, 2010).

One of the six primary studies compared denosumab to raloxifene. Chau D, Becker DL, Coombes ME, Ioannidis G, & Adachi JD (2012) studied a population of women with osteoporosis and fractures at age 72 in Canada. This study utilized a Markov model with a public payer perspective and a lifelong time horizon. Denosumab dominated raloxifene (Chau D, Becker DL, Coombes ME, Ioannidis G, Adachi JD, 2012).

One study compared denosumab with teriparatide in a population of men with osteoporosis greater than age 75 in Sweden. This study utilized a Markov model with a payer perspective and a lifelong time horizon. In this study denosumab was found to dominate teriparatide (Parthan et al., 2014).

Two of the six primary studies compared denosumab to strontium ranelate. Parthan et al. (2014) studied a population of men with osteoporosis greater than age 75 in Sweden. This study utilized a Markov model with a payer perspective and a lifelong time horizon. In this study denosumab was found to dominate strontium ranelate (Parthan et al., 2014). Jönsson et al. (2011) also compared denosumab with strontium ranelate in a population of women with osteoporosis at age 71 in Sweden using a Markov model with a societal perspective and a lifelong time horizon. The ICER for this study was found to be EUR 5,000/QALY for denosumab compared with strontium ranelate (Jönsson et al., 2011).

Main findings:

- For postmenopausal women denosumab appears to be a cost-effective option in comparison to no therapy, to have a comparable cost-effectiveness as bisphosphonates and strontium ranelate, and appears to be a more effective and less costly treatment option than raloxifene and teriparatide.
- For men older than age 75 with osteoporosis denosumab appears to be more effective and less costly than bisphosphonates.
- The ICER is sensitive to the age of the population being treated, sex, and presence of previous fractures.

11.3.1.2.3 Strontium ranelate

Seven of the primary studies evaluated the cost-effectiveness of strontium ranelate therapy for osteoporosis. Five of these studies examined the cost-effectiveness of strontium ranelate therapy in postmenopausal women in comparison with no therapy. Borgström et al. (2006b) studied a population of women with osteoporosis with fractures at age 69 and without fractures at age 77 in Sweden. A Markov model from a societal perspective with a lifetime time horizon estimated the ICER to be SEK 472,586/QALY for women age 69 with fractures, and SEK 259,643/QALY for women age 77 without fractures (Borgström et al., 2006b).

Borgström et al. (2010) also compared strontium ranelate to no treatment in a population of postmenopausal women at age 65 with clinical risk factors for fractures in the UK. This study was based on a Markov model from a NHS perspective and a lifelong time horizon and found that at a WTP threshold at GBP 30,000/QALY strontium ranelate was a cost-effective treatment option for osteoporosis in comparison with no treatment (Borgström et al., 2010a).

Hiligsmann, Bruyère & Reginster (2010b) compared strontium ranelate to no therapy in women with osteoporosis both with and without fractures at the ages of 70, 75, and 80. This study utilized a Markov model with a payer perspective and a lifelong time horizon Hiligsmann, Bruyère & Reginster (2010b). The ICER for the population of postmenopausal women without fractures was found to be EUR 15,069/QALY at age 70, EUR 6,913/QALY at age 75, and cost saving at age 80. With fractures the ICERs were found to be EUR 23,426/QALY at age 70, EUR 9,698/QALY at age 75, and cost saving at age 80 (Hiligsmann, Bruyère & Reginster, 2010b).

Hiligsmann, Bruyère & Reginster (2010) also compared strontium ranelate to no treatment or risedronate in a population of postmenopausal women at age 75 and 80. This study utilized a Markov model with a payer perspective and a lifelong time horizon. The ICER for strontium ranelate over no therapy at age 75 was found to be EUR 16,418/QALY, and strontium ranelate in comparison to risedronate was found to be dominant. The ICER for strontium ranelate in comparison to no therapy for postmenopausal women at age 80 was found to be EUR 6,025/QALY.

Conversely, one study compared strontium ranelate to no treatment and found strontium ranelate to be cost saving. Seeman et al. (2010) compared strontium ranelate to no treatment in a population of postmenopausal women age 80+ in Sweden using a Markov cohort model with a societal perspective and a lifelong time horizon. This study found strontium ranelate to be both more effective and less expensive than no treatment (Seeman et al., 2010).

Only one study evaluated the cost-effectiveness of strontium ranelate compared with no treatment in men. Hiligsmann et al. (2013) studied a population of men with osteoporosis with a mean age of 73 in Belgium using a Markov model from a payer perspective with a lifelong time horizon. This study found strontium ranelate has an ICER of EUR 49,798/QALY compared to no treatment (Hiligsmann et al., 2013).

One study compared strontium ranelate to risedronate. Hiligsmann, Bruyère & Reginster (2010) compared these drugs in a population of postmenopausal women at age 75 and 80 utilizing a Markov model with a payer perspective and a lifelong time horizon. Strontium ranelate was found to be dominant over risedronate (Hiligsmann, Bruyère & Reginster, 2010a).

Main findings:

- In postmenopausal women strontium ranelate appears to be a cost-effective treatment option in comparison to no treatment, and appears to be more cost-effective than risedronate.
- In men age 73, strontium ranelate appears to be a less cost-effective treatment option than in women compared with no treatment.
- The ICER appears to be sensitive to presence or absence of osteoporotic fractures (more cost-effective without fractures), age of the patient (more cost-effective with older age), and sex of the patient (more cost-effective in women).

11.3.1.2.4 Selective estrogen receptor modulators

Eight of the primary studies identified evaluated the cost-effectiveness of selective estrogen receptor modulator therapy for osteoporosis. All nine primary studies were conducted in postmenopausal women. Six of the studies and compared raloxifene to no treatment, and two studies compared bazedoxifene to raloxifene The ICER values reported for the six studies varied widely.

Kanis et al. (2005) compared raloxifene to no treatment in a population of women in the UK using a Markov model from a NHS perspective but did not specify the time horizon. For women with no prior vertebral fracture the ICER for raloxifene over no treatment was GBP 18,000/QALY, GBP 23,000/QALY, GBP 18,000/QALY and GBP 21,000/QALY for women aged 50, 60, 70 and 80. For women with a history of vertebral fracture the ICER was GBP 10,000/QALY, GBP 24,000/QALY, GBP 18,000/QALY, and GBP 20,000/QALY for women aged 50, 60, 70, and 80 (Kanis et al., 2005).

Pfister et al. (2006) compared raloxifene to no treatment in a population of postmenopausal women with osteoporosis greater than age 65 in the US but did not specify the perspective or time horizon adopted in their Markov model. The ICER for raloxifene over no treatment was found to be >USD 100,000/QALY (Pfister et al., 2006).

Brecht et al. (2004) compared raloxifene to no treatment in a population of women with osteoporosis and fractures at the age of 70 in Germany. This study utilized a Markov model with a payer perspective and a 13-year time horizon. The ICER for raloxifene in comparison to no treatment in this study was found to be EUR 1,249,119/QALY (Brecht et al., 2004).

Goeree, Blackhouse & Adachi (2006) compared raloxifene, etidronate and risedronate separately to no treatment in a population of postmenopausal women with osteoporosis with fractures at the age of 65. A Markov model with a provincial government perspective and a lifelong time horizon was used. The ICERs for raloxifene compared with no treatment was found to be CAD 49,279/QALY, for etidronate compared with no treatment CAD 32,571/QALY and for risedronate compared with no treatment CAD 78,274/QALY (Goeree, Blackhouse & Adachi, 2006).

Borgström et al. (2004b) also evaluated the cost-effectiveness of raloxifene in comparison to no treatment for osteoporosis in women in Sweden. In this study the ICER was found to vary by the age of the women.

Raloxifene in comparison to no treatment was found to have an ICER of EUR 40,213/QALY in 60-year-old women, EUR 32,776/QALY in 70-year-old women, and EUR 28,477/QALY in 80-year-old women (Borgström et al., 2004b).

Darba et al. (2013) evaluated the cost-effectiveness of bazedoxifene in comparison to raloxifene for women age 55+ with osteoporosis and high risk of fracture in the Spain. A Markov cohort model from a payer perspective with a time horizon of 82 years of age was used (Darba et al., 2013). This study found bazedoxifene to be dominant, both more effective and less expensive, than raloxifene (Darba et al., 2013).

Hiligsmann et al. (2013) evaluated the cost-effectiveness of bazedoxifene in comparison to Raloxifene for osteoporosis in post-menopausal women in Belgium. This study utilized a Markov micosimulation model, populated with effectiveness data from a single randomized control trial, and used a Belgian payer perspective and 3-year time horizon. The study found bazedoxifene and raloxifene to be equally cost-effective. However, subgroup analysis of women at higher risk for fractures found bazedoxifene to be dominant, both more effective and less expensive, than raloxifene in 84% of the simulations (Hiligsmann et al. 2013).

The widely varying ICERs found when comparing raloxifene to no treament may be a result of the assumptions used or the outcomes considered in the model. Raloxifene is known to reduce vertebral fracture risk, but not to reduce non-vertebral fracture risk (Seeman et al., 2006). There is also some conflicting evidence regarding the long term effects of Raloxifene, with some research suggesting that over a 4 year time horizon Raloxifene is no more effective than placebo (Delmas et al., 2002).

Main findings:

- Research examining the cost-effectiveness of raloxifene compared with no treatment in postmenopausal women has reported widely differing ICER values in the range GBP 18,000 (approx. EUR 23,000)/QALY to EUR 1,249,119/QALY.
- Raloxifene and bazedoxifene appear to have similar cost-effectiveness in comparison to each other for the general population of postmenopausal women with osteoporosis.
- Bazedoxifene appears to be both more effective and less expensive than raloxifene for treatment of postmenopausal women with osteoporosis at high risk for fracture.

11.3.1.2.5 Parathyroid hormone

Six of the primary studies identified evaluated the cost-effectiveness of parathyroid hormone therapy for osteoporosis. Of these two studies compared parathyroid hormone therapy to no therapy. (Pfister et al., 2006) modelled a population of women with osteoporosis aged 65+ in the US with a Markov model with an unknown perspective and unknown time horizon. This study found parathyroid hormone to have an ICER >USD 100,000/QALY when compared with no treatment (Pfister et al., 2006). Additionally, Borgström et al. (2010b) compared two different brands of parathyroid hormone, teriparatide and PHT (1-84), to no treatment in a population of women with osteoporosis with fractures at age 70 in Sweden. This study was based on a Markov model with a societal perspective and a lifetime time horizon. The ICER for teriparatide compared with no therapy was EUR 43,473/QALY, and for PHT (1-84) EUR 20,300/QALY.

Of the six primary studies two compared parathyroid hormone therapy to bisphosphonates. Tosteson et al. (2008) modelled parathyroid hormone against risedronate, ibandronate and alendronate in a population of women with osteoporosis with and without fractures at ages of 65 and 70 in the US. The Markov model adopted a third party payer perspective and a 10-year time horizon. This study found that parathyroid hormone was dominated by risedronate, ibandronate and alendronate for women age 65 and women age 70 both with and without a history of previous fractures (Tosteson et al., 2008). Murphy et al. (2012) compared teriparatide to bisphosphonate therapy in two populations in Sweden: a population of postmenopausal women with osteoporosis (PMO) and a population of men and women with glucocorticoid induced osteoporosis (GIO). This study was based on a Markov model with a payer perspective and a lifetime time

horizon. The ICER for teriparatide compared to bisphosphonate therapy in the PMO population was EUR 36,995/QALY if the patient had a history of 1 fracture, and EUR 19,371/QALY if the patient had a history of 2 fractures. The ICER in the GIO population was EUR 20,826/QALY if the patient had a history of one fracture, and EUR 15,155/QALY if the patient had a history of two fractures (Murphy et al., 2012).

Liu et al. (2006) compared parathyroid hormone to calcium and vitamin D supplementation; parathyroid hormone plus alendronate to calcium and vitamin D supplementation; and alendronate to calcium and vitamin D supplementation in a population of women at age 70 with osteoporosis and fractures in the US. The study was based on a Markov model with a societal perspective and a lifetime time horizon. This study found the ICER for parathyroid hormone alone compared with calcium and vitamin D supplementation to be USD 173,300/QALY, the ICER for parathyroid hormone and alendronate compared to calcium and vitamin D supplementation to be USD 156,500/QALY, and the ICER for alendronate compared with calcium and vitamin D supplementation to be USD 11,600/QALY (Liu et al., 2006).

One study compared parathyroid hormone plus calcium and vitamin D supplementation to no therapy. Lundkvist et al. (2006) modelled teriparatide plus calcium and vitamin D supplementation against no therapy in a population of women with osteoporosis with fractures at age 69 in Sweden. The Markov model adopted a societal perspective and a lifetime time horizon. The ICER for teriparatide plus calcium and vitamin D supplementation was found to be EUR 20,300/QALY if the patient had a recent fracture, and EUR 64,432/QALY if the patient had an old fracture (Lundkvist et al., 2006).

Main findings:

- The cost-effectiveness of parathyroid hormone varies significantly with the comparator and by study. Compared with bisphosphonates, parathyroid hormone was dominated by risedronate, ibandronate and alendronate in one study, but incurred relatively low ICER's in another study of EUR 15,555 to 36,995/QALY depending on the patient group. Compared with calcium and vitamin D supplementation, the ICER for parathyroid hormone was over USD 100,000/QALY. Compared with no treatment, the ICER ranged from EUR 20,300/QALY to over USD 100,000/QALY. Consequently, there appears to be some uncertainty surrounding the cost-effectiveness of parathyroid hormone compared with other therapies.
- The ICER for parathyroid hormone therapy is sensitive to number of osteoporotic fractures, and the timing of osteoporotic fractures.

11.3.1.2.6 Hormone replacement therapy (females only)

Four of the primary studies identified evaluated the cost-effectiveness of hormone replacement therapy (HRT) for the treatment of osteoporosis. One study (Lekander I, Borgström F, Ström O, Zethraeus N, 2008) compared HRT to no treatment in a population of postmenopausal women with osteoporosis at age 50 in Sweden, UK, and US. This study was based on a Markov state transition model from a societal perspective with a lifetime horizon. The model considered risk of the following associated conditions: hip fracture, vertebral fracture, wrist fracture, breast cancer, colorectal cancer, coronary heart disease, stroke and venous thromboembolic events. In this study no drug therapy was dominant over HRT in Sweden, UK, and US for women without previous fractures and without a hysterectomy. In the population of women without previous fractures and with a hysterectomy the ICER was found to be USD 26,644/QALY, USD 19,265/QALY, and USD 16,059/QALY in Sweden, UK and US. In the population of women with previous fractures and without hysterectomy the ICER was found to be USD 16,660/QALY, USD 29,132/QALY, and USD 49,532/QALY in Sweden, UK, and US. In the population of women with previous fractures and with a hysterectomy the ICER was found to be USD 14,163/QALY, USD 2,054/QALY, and USD 3,326/QALY in Sweden, UK, and US (Lekander I, Borgström F, Ström O, Zethraeus N, 2008).

A second study (Geelhoed, Harris & Prince, 1994) compared lifelong HRT beginning at age 50 to no drug treatment and lifelong HRT beginning at age 65 to no drug treatment for peri-menopausal women in Australia. This study is based on a Markov model from a payer perspective with a lifelong time horizon. This study is limited by the fact that is does not consider the increased risk of venous thrombotic events and increased risk of breast cancer with HRT. This study finds lifelong HRT at age 50 to have an ICER of AUD 8,830/QALY, and lifelong HRT at age 65 to have an ICER of AUD 8,504/QALY.

A third study (LK., 2003b) compared screening for osteoporosis followed by HRT to no drug treatment, and screening for osteoporosis followed by lendronate in a population of women age 50 and age 65 both with and without osteoporosis in Brazil. This study was a 1-year clinical trial and utilized a Unified Health Care System perspective. Universal screening of women for osteoporosis with a bone mineral density test followed by HRT in individuals with osteoporosis was estimated to incur an ICER of BRL 1,479,504 (approx. EUR 470,000)/femoral fracture prevented for women age 50 and BRL 1,389,939 (approx. EUR 440,000)/femoral fracture prevented in women age 65. In contrast, screening all women for osteoporosis with a bone mineral density test and then treating individuals with diagnosed osteoporosis with alendronate incurred ICER of BRL 136,217 (approx. EUR 43,000)/femoral fracture prevented in women age 50 and an ICER of BRL 101,181 (approx. EUR 32,000)/femoral fracture prevented in women age 65. This study is limited by the short, 1-year time horizon (LK., 2003b).

A forth study, Salpeter et al. (2009) evaluated the cost effectiveness of hormone replacement therapy in 50 and 65 year old postmenopausal women in the US. A Markov cohort model with a societal perspective and a lifelong time horizon was used (Salpeter et al., 2009). This study found hormone replacement therapy to result in an ICER of USD 2,438/QALY for women at age 50, and an ICER of USD 27,000/QALY for women at age 65 (Salpeter et al., 2009).

Main findings:

- Hormone replacement therapy appears to be more cost-effective in postmenopausal women with a history of hysterectomy and a diagnosis of osteoporosis
- The ICER for hormone replacement therapy is sensitive to history of osteoporotic fractures (more cost-effective with presence) and history of hysterectomy (more cost-effective with history of hysterectomy)
- One early study that did not incorporate the risk of adverse effects of HRT (risk of breast cancer, venous thrombotic events) estimated HRT to be more cost-effective than when such risks are included

11.3.1.2.7 Calcitonin

Two of the primary studies identified evaluated the cost-effectiveness of calcitonin for the treatment of osteoporosis. One study (Coyle et al., 2001) compared calcitonin to no drug treatment and to etidrondate in a population of women with osteoporosis in Canada. This study was based on a Markov model from a Health Ministry perspective with an unknown time horizon. The ICER for calcitonin compared with no drug therapy was CAD 46,500/QALY, and for calcitonin compared with etidronate CAD 32,600/QALY.

The second study (Pfister et al., 2006) compared calcitonin to no drug treatment in a population of postmenopausal women with osteoporosis in the US. This study was based on a Markov model from an unknown perspective and with an unknown time horizon. The ICER for calcitonin compared no drug treatment was found to be >USD 100,000/QALY.

Main findings:

- Calcitonin appears not to be a cost-effective option for treatment of osteoporosis of postmenopausal women in comparison to no therapy.

11.3.1.2.8 Testosterone therapy (for hypogonadal males only)

No studies assessed the cost-effectiveness of testosterone therapy in hypogonadal males for the treatment of osteoporosis.

11.4 Evidence gaps in osteoporosis

There are three general categories under which evidence gaps develop in the research on cost-effective treatment options for osteoporosis: choice of treatment modality evaluated in cost-effectiveness research, choice of study population to be evaluated, and the robustness of the sensitivity analysis.

11.4.1 Choice of treatment modality evaluated

The cost-effectiveness literature for osteoporosis is heavily skewed towards evaluation of a select few treatment modalities, while other treatment modalities have had little to no cost-effectiveness research conducted. This review found thirty-four of the seventy-one primary studies (47%) were evaluating one class of drugs - bisphosphonates. Furthermore, twenty-five of these thirty-four primary studies were evaluating two drugs (alendronate and risedronate), which means 35% (25/71) of all research identified on cost-effective treatment of osteoporosis was conducted on only two drugs. Meanwhile, there is no cost-effectiveness research conducted on lifestyle modifications, such as a diet adequate in calcium and vitamin D, exercise and smoking cessation, and there is no cost-effectiveness research conducted on testosterone therapy for males. Additionally there is very limited research on hormone replacement therapy, with only one study being conducted that considers the risks of thromboembolic events and breast cancer in the evaluation model. Furthermore, despite calcium and vitamin D supplementation frequently being used as a comparator for other medical therapies, and the evidence that these supplements are likely to be cost-effective treatment options for osteoporosis, there is very limited cost-effectiveness research – only four of seventy-one (6%) of the identified primary studies evaluate calcium and vitamin D supplementation.

The evidence gap in osteoporosis cost-effectiveness research in regards to choice of treatment modality for evaluation are 1) four of the thirteen treatment modalities currently have no evidence basis identified for making cost-effectiveness decisions - adequate dietary intake of calcium and vitamin D, exercise, smoking cessation, and testosterone therapy and 2) two of the thirteen treatment modalities have very limited research basis for making cost-effectiveness decisions – hormone replacement therapy and supplemental calcium and vitamin D.

11.4.2 Study population evaluated

This review found that six of seventy-one (8%) primary studies on cost-effective treatment of osteoporosis considered a male population, while the remaining 92% considered a female population. Additionally this review found that one of the seventy-one (1%) identified primary studies considered a population less than age 60, and the remaining studies (99%) evaluated a population greater than age 60.

The risk of osteoporosis does increases with age, with a population prevalence of about 5% from age 50-59, and a prevalence rate closer to 20% from age 80; and women do have an approximately two to three times greater risk of developing osteoporosis than men (Cummings 2002). However, populations less than age 60 that are known to be at high risk of developing osteoporosis are not well represented in the current cost-effectiveness literature.

There is currently a research gap in the cost-effective treatment of 1) males with osteoporosis, and 2) adults less than age 60 with osteoporosis and with the following high risk conditions: anorexia nervosa, celiac disease, hyperthyroidism, hyperparathyroidism, hypogonadism, hypercalceruria, rheumatoid arthritis, alcoholism, renal disease, liver disease, HIV, diabetes, and in individuals with regular intake of glucocorticoids.

11.4.3 Sensitivity analysis

The final research gap rests in the robustness of the sensitivity analysis conducted for each study. Every study that conducted sensitivity analysis on the age of the patient population, disease severity as measured by number of previous osteoporotic fractures, and on risk factors for development of osteoporosis, such as history of high alcohol intake and smoking history, found the ICER to be quite sensitive to each of these parameters. This sensitivity is expected given that osteoporosis is a disease with a predictable and well-understood timeline for presentation and progression. However, only eleven of seventy-one primary studies (15%) identified reported a sensitivity analysis by age (albeit all only between the ages of 65 and 85). Seven of seventy-one primary studies (10%) reported sensitivity analysis results according to disease severity as measured by number of previous osteoporotic fractures. Only one of seventy-one primary studies (1%) reported sensitivity analysis results regarding the impact of the presence or absence of known risk factors for osteoporosis.

There is currently a research gap in more finely examining the impact age, risk factors, and disease severity have on the ICER when making a comparative analysis between two treatment regimens for osteoporosis.

Contributor	Comment
Dr. Jean-Yves Reginster University of Liege, Liege, Belgium	Micro-simulation models, rather than cohort models, are important to use in cost-effectiveness research evaluating osteoporosis treatment. One of the major advantages of micro-simulation models is to input an increased risk for future fractures in patients who already experienced one fracture event. Poor adherence is also one of the major issues currently faced in the management of osteoporosis and neglecting this particular aspect leads to an overestimation of the cost-efficiency of medications. It is also of prime importance to provide country-specific analyses since the data obtained in one particular setting can hardly be extrapolated to other health systems or country specificities.

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Health Economic Evidence Analysis: Treatment of Neck Pain

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12 Neck Pain

12.1 Bibliometrics

A total of 15 economic studies were mapped to the clinical model for neck pain (Table 12.1 and Figure 12.1). The majority of studies (80%) were published in 2006 or later. Both reviews identified were published in the year 2012.

Table 12.1 Bibliometric data for Neck Pain

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Neck Pain"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	15
Included as "other"	6
Reviews	2
Excluded	12
Total	35
Additional references from reviewers	
Total	0

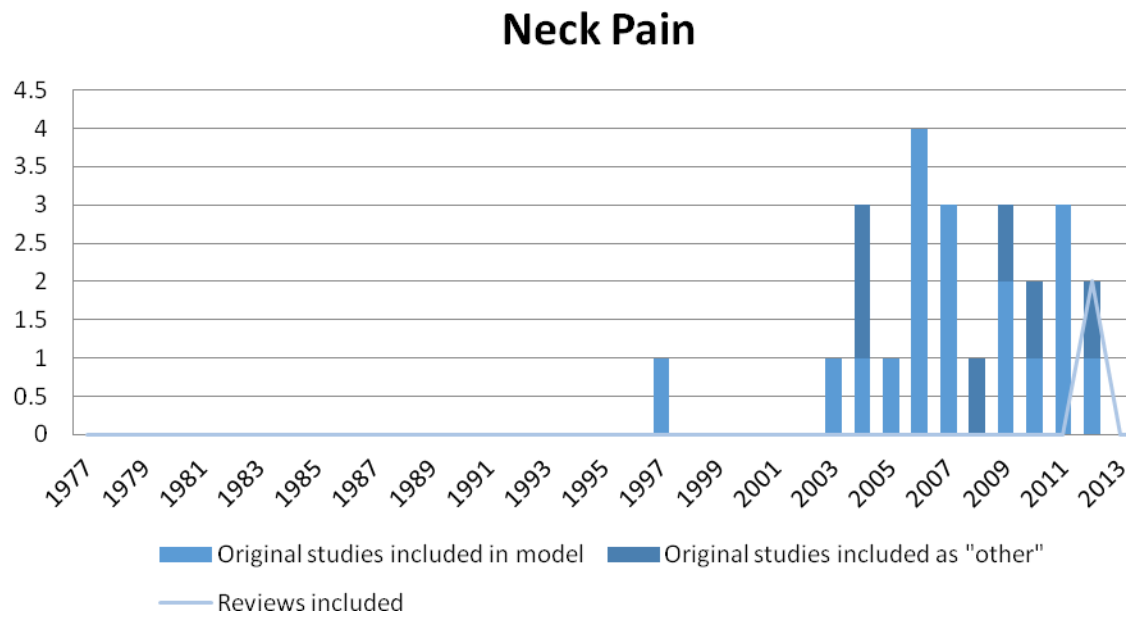

Figure 12.1 Bibliometric data for Neck Pain by year

12.2 Review Coverage

The clinical model for neck pain consists of 24 treatment modalities (Table 12.3). Of these, three treatment modalities are identified for the treatment of acute neck pain, i.e. neck pain lasting less

than three months, and 21 treatment modalities are identified for the treatment of persistent neck pain, i.e. neck pain lasting more than three months.

Of these treatment modalities, four are covered by the two reviews. The reviews included a total of 5 (Driessen, Lin & van Tulder, 2012) and 6 (Michaleff et al., 2012) primary studies, all of which were identified in the present search. The review by Michaleff et al. evaluated the cost effectiveness of spinal manipulation therapy and included studies on both neck pain (3 studies), low back pain (2 studies) and one study which recruited a mixed neck and low back pain population.

Table 12.2 Table of reviews for neck pain and associated treatment

Title and reference	Year	Treatments covered
"*Spinal manipulation epidemiology: systematic review of cost effectiveness studies*" (Michaleff et al., 2012)	2012	**Acute and Sub-Acute Neck Pain** Spinal Manipulation Therapy (SMT) General Practice (GP) (Advice, education and drug prescription) Physical therapy/ Exercise programme Combination therapy – SMT+GP
"*Cost-effectiveness of conservative treatments for neck pain: a systematic review on economic evaluations*" (Driessen, Lin & van Tulder, 2012)	2012	**Acute and Persistent Neck Pain** Spinal Manipulation Therapy Physical Therapy/ Exercise programme General Practice Behavioural Graded Activity Acupuncture – Brief acupuncture and delayed acupuncture (after 3 months) Combination therapies: Advice + Exercise Advise + Exercise + SMT Advice + Exercise +pulsed short wave diathermy (electromagnetic therapy) SMT + GP

12.3 Evidence Analysis

The following sections present the information gathered from recent (2009-2014) reviews when available and from essential information on primary evidence where no reviews are available. Table 12.3 summarises the volume of health economic studies and reviews identified according to each treatment modality.

The treatment options for acute neck pain are not specifically covered in any of the studies. Most of the studies reviewed in this model had sampled patients with neck pain for at least two weeks or more, which includes patients with both acute and persistent neck pain. The same applies to the studies reviewed in the two systematic reviews.

Table 12.3 Primary health economic evidence and reviews for the treatment of neck pain

Axial Neck Pain	Studies	Reviews
Posture and home exercise		
Posture Modification	1	0
Home Exercise: Neck rotation, Neck tilting, Neck bending, Shoulder rolls	1	0
Activity and Physical Treatments		
Physical therapy/Exercise programme	8	2
Traction	0	0
Cervical collar	0	0
Massage therapy	0	0
Spinal Manipulation	9	2
Acupuncture	2	1
Qigong	0	0
Pharmacology		
Acute pain: Acetaminophen, Tramadol, Cyclobenzaprine, Oxazepram, Ibuprofen	0	0
Chronic pain: Amytriptyline, Nortriptyline, Duloxetine, Venlafaxine, Gabepentine	0	0
Surgical procedures and injections		
Surgery	0	0
Trigger Point Injection with Lidocaine	0	0
Botulinum Toxin Injections	0	0
Electromagenetic and radiofrequency therapies		
Electromagnetic therapy	1	1
Percutaneous radiofrequency neurotomy	0	0
Transcutaneous Electrical Nerve Stimulation	0	0
Low level laser therapy	0	0
Cognitive Behavioural Therapy (CBT)	2	1

12.3.1 Posture and home exercise

12.3.1.1 Posture Modification

A Randomised Controlled Trial (RCT) conducted in Netherlands (Bernaards, Ariëns & Hildebrandt, 2006; Bernaards et al., 2011) assessed the added value of lifestyle physical activity in addition to a Work Style (WS) intervention vs the WS alone in computer workers. The two groups were compared with each other and with a control group receiving usual care, according to the outcomes recovery from neck and upper limb symptoms using a 7-point scale, and pain intensity using an 11-point scale. The cost-effectiveness was analysed from the employer's perspective. Neither the WS nor the WS+physical activity intervention was more effective than usual care in improving overall recovery, and consequently these interventions were not considered cost-effective.

Main findings:

- A work style intervention with or without lifestyle physical activity was not effective (or cost-effective) compared with usual care in improving overall recovery from neck pain (one study).

12.3.1.2 Home Exercise

One RCT has compared spinal manipulation therapy (SMT) plus home exercise, supervised rehabilitative exercise plus home exercise, and home exercise alone. The study collected data on direct and indirect costs, as well as EQ-5D data, and a cost-utility analysis was planned (Maiers et al., 2007). No economic results have been reported to date (Maiers et al., 2013).

Main findings:

- A cost-effectiveness analysis has not yet been reported from a single clinical trial comparing spinal manipulation therapy plus home exercise, rehabilitative exercise plus home exercise, and home exercise alone.

12.3.2 Activity and Physical Treatments

Three activity and physical measures were studied in the literature, namely Physical Therapy (PT) with exercise programmes, Spinal Manipulation Therapy (SMT) and acupuncture.

12.3.2.1 Physical therapy/ Exercise programme

Evidence was published in eight RCTs, in which PT was compared with SMT (5 studies), CBT (one study), and with a different PT technique (one study). Graded Behavioral Activity was compared with SMT in one study.

Economic evidence was published in three of the five RCTs comparing PT with SMT, while the remaining two were published as study protocols.

The earliest study compared chiropractic treatment with physiotherapy in a primary care setting in Sweden involving 323 patients (Skargren et al., 1997). The results showed no difference in outcomes or costs, and consequently neither physiotherapy nor SMT can be considered more cost-effective based on this data.

One RCT was conducted in the Netherlands comparing PT with SMT and with GP care (Korthals-de Bos et al. 2003). Clinical outcomes included improvement in pain intensity, functional disability, recovery level, and quality of life. Cost-effectiveness and cost-utility analyses were performed from the societal perspective. It was found that PT was not cost-effective (more costly and less effective) compared with SMT. There were no significant differences in costs or effects between PT and GP care, and consequently neither could be considered cost-effective over the other.

Another RCT in the UK involved 350 participants referred to physiotherapists by GPs (Lewis et al., 2007). Three comparison groups were studied: Advice and Exercise (A&E) with SMT, A&E with Pulsed Short Wave Diathermy (PSWD), and A&E alone. Clinical outcomes included the improvement in neck pain and disability as well as Quality Adjusted Life Years (QALYs) gained. The economic evaluation included a cost-effectiveness and a cost-utility analysis, both of which were conducted from the healthcare and societal perspective. According to the societal perspective, SMT+A&E was most likely to be cost-effective in terms of cost/QALY gained across all Willingness-to-Pay (WTP) thresholds, however at a threshold of GBP 30,000/QALY the probably of SMT+A&E being cost-effective was only

44%. When a healthcare perspective was applied, SMT+A&E was also most likely to be cost-effective across most WTP thresholds, except at lower thresholds (<GBP 7,000/QALY) where A&E alone had the greatest probability of being cost-effective. At a WTP of GBP 30,000/QALY, the probability of SMT+A&E being cost-effective from the healthcare perspective was 37%. The low probabilities of SMT+A&E being cost-effective (44% and 37% according to societal and healthcare perspective, respectively) reflect the lack of statistically significant differences in costs and outcomes. A&E plus PSWD was consistently the least cost-effective intervention.

The fourth study was published as an RCT protocol (Groeneweg et al., 2010) for investigating the Utrecht School of Manual Therapy approach versus usual physiotherapy in patients with neck pain for more than two weeks. A cost-effectiveness analysis will be carried out alongside the trial, and EQ-5D utilities are also collected, suggesting a potential cost-utility analysis. No economic results have been published to date.

The final study is an RCT comparing SMT plus home exercise, supervised rehabilitative exercise plus home exercise, and home exercise alone. The study has collected data on direct and indirect costs, as well as EQ-5D data, and a cost-utility analysis was planned (Maiers et al., 2007). No economic results have been reported to date (Maiers et al., 2013).

PT was compared with CBT techniques in one study analysing a combination of CBT and PT (Solution Finding Approach, SFA) compared with usual PT techniques (Manca et al., 2007) over a one year follow-up period. Analysis was performed from the NHS perspective. The results showed that the usual PT technique was more effective and more costly than SFA, with an ICER of GBP 1,220/QALY gained from the NHS perspective over SFA.

A study conducted in the UK (Manca et al., 2006) with 168 patients compared a brief PT intervention with usual PT among patients with neck pain for more than 2 weeks. This RCT showed the brief PT intervention to have lower costs and marginally lower QALYs compared to usual PT, resulting in an ICER of GBP 68,000/QALY for usual PT over brief PT.

An RCT conducted in Netherlands (Bosmans et al., 2011) involving 146 patients compared behavioural graded activity (BGA) with SMT. Both a cost-effectiveness and cost-utility analysis were performed from the societal perspective. The study found that BGA had no significant effect on recovery or QALYs gained compared with SMT, though pain and disability were significantly improved with BGA, and societal costs for BGA vs SMT did not significantly differ. The authors concluded that BGA was not cost-effective compared with SMT considering recovery, QALY's gained, pain or disability.

Key Massages:

- Physical therapy was less effective and more costly than spinal manipulation in one study, but did not differ in terms of costs or effects in a second study. Two trials have yet to report cost-effectiveness results for physical therapy/exercise versus spinal manipulation therapy.
- Advice and exercise alone was less cost-effective than advice and exercise in combination with manual therapy in one study.
- Usual PT appeared more cost-effective than PT plus CBT in one study with an ICER of GBP 1,220/QALY gained.

- Spinal manipulation therapy according to the Utrecht School of Manual Therapy (MTU) is being compared with usual physiotherapy in one ongoing clinical trial.
- A brief PT intervention was found to be less costly but less effective than usual PT. Usual PT was associated with an ICER of GBP 68,000/QALY gained over brief PT.
- Behavioural graded activity was not found to be cost-effective over SMT in one study.

12.3.2.2 Spinal Manipulation Therapy

The cost-effectiveness of spinal manipulation therapy (SMT) was studied in nine primary studies, some of which were reviewed in the two systematic reviews and discussed above. In these nine studies, SMT was compared with Graded Behavioural Activity (GBA; 1 study), with PT (4 studies), or with different techniques of SMT such as osteopathy, chiropractics or new techniques of SMT compared to the usual technique of SMT or PT (3 studies). In one study, SMT plus advice & exercise (A&E) was compared with physiotherapy plus A&E and A&E alone.

An RCT conducted in the Netherlands comparing Graded Behavioural Activity with SMT was discussed in section 12.3.2.1 above (Bosmans et al., 2011). Briefly, GBA had no significant effect on recovery or QALY's gained, and consequently SMT was found to be cost-effective compared with GBA.

Economic evidence on SMT compared with PT was reported in one study (Korthals-de Bos et al., 2003) discussed in the previous section (12.3.2.1). Moreover, two clinical trial protocols have been published, one described in section 12.3.2.1 (Groeneweg et al., 2010) and one in section 12.3.1.2 (Maiers et al., 2007, 2013), neither of which have reported economic evaluations to date. Korthals-de Bos et al. (2003) presented evidence on SMT compared with PT or GP care. The economic evaluation was performed from a societal perspective and showed SMT to be dominant (more effective and less costly) over both PT and GP care with respect to perceived recovery, pain intensity and utility. For functional disability (Neck Disability Index), SMT was dominant over PT but associated with an ICER of EUR 682/QALY over GP care.

Three studies were identified assessing different types of SMT techniques. A RCT conducted in Wales (Williams et al., 2004) compared osteopathy plus usual GP care with usual GP care alone. The study was performed in a single centre and recruited patients with neck, upper or lower back pain. A cost-utility analysis was performed from the healthcare perspective. The results showed osteopathy and GP care combined to be more costly and more effective than usual GP care alone. The point-estimate of the ICER was GBP 3,560 per QALY gained, however the authors reported an 80% CI of GBP 542 to 77,100 per QALY gained (1000 replication bootstrap) and noted that the groups did not differ significantly in terms of costs or QALY's. The uncertainty is likely to be compounded by the inclusion of a wide range of patients with either neck, upper or lower back pain. Another RCT (Reid et al., 2012) has proposed to compare two SMT techniques (Maitland mobilisations plus range-of-motion exercises, Mulligan SNAGs plus self-SNAG exercises) with placebo. A cost-effectiveness analysis is planned though details apart from the analysis type (cost-effectiveness, -utility or –minimisation depending on the efficacy results) were not disclosed. To date no economic evidence has been published. The final study, an RCT, compared chiropractic with physiotherapy treatment in a primary care setting in Sweden involving 323 patients (Skargren et al., 1997). The results showed

no difference in outcomes or costs, and consequently neither can be considered more cost-effective based on this data.

The RCT by Lewis et al. (2007) comparing advice and Exercise (A&E) with SMT, A&E with Pulsed Short Wave Diathermy (PSWD) and A&E alone was discussed in section 12.3.2.1. Briefly, according to the societal perspective, SMT+A&E was most likely to be cost-effective in terms of cost/QALY gained across all WTP thresholds. When a healthcare perspective was applied, SMT+A&E was also most likely to be cost-effective across most WTP thresholds, except at lower thresholds (<GBP 7,000/QALY) where A&E alone had the greatest probability of being cost-effective.

Key massages:

- Spinal manipulation therapy was cost saving compared to physiotherapy in one study but no differences in costs or effects were observed in another study (see also section 12.3.2.1). Two economic evaluations are anticipated.
- Osteopathy plus GP care appeared to be cost-effective in comparison with GP care alone, however this analysis was surrounded by a high degree of uncertainty (one study).
- One ongoing clinical trial is assessing different SMT techniques (Maitland mobilisations plus range-of-motion exercises, Mulligan SNAGs plus self-SNAG exercises) compared with placebo. An economic evaluation is planned.
- Chiropractic care showed no difference in costs or effects compared to usual GP care, consequently neither could be considered more cost-effective.
- Advice and exercise (A&E) in combination with manual therapy was more cost-effective than A&E with Pulsed Short Wave Diathermy or A&E alone according to one study

12.3.2.3 Acupuncture

Two primary studies were identified for acupuncture. The cost-effectiveness of acupuncture in addition to usual care was assessed against usual care alone in one RCT (Willich et al., 2006). The study was performed in Germany from the societal perspective, and included 3,451 persistent neck pain patients. Acupuncture plus usual care yielded a statistically significant QALY gain and cost increase vs usual care alone, resulting in an ICER of EUR 12,469/QALY at 3 months. The probability of acupuncture plus usual care being cost-effective, based on bootstrapping, approached 100% at a threshold of EUR 5,400/QALY if the treatment effect was assumed to last for 4 years. In contrast, the probability was 99.5% at a threshold of EUR 50,000/QALY if the treatment effect was assumed to be 6 months only.

Another observational study (Witt et al., 2011) assessed the additional societal cost due to adverse effects arising from acupuncture treatment. It showed that about 7% of patients developed adverse effects following acupuncture, most of whom treated themselves. Among those who sought medical care it resulted in an additional cost of USD 125 at 3 months and of USD 285 at 12 months following treatment.

Key Massages:

- Acupuncture in addition to routine care yielded better quality of life at a higher cost. The ICER was EUR 12,469/QALY at 3 months. Despite being sensitive to the duration of

treatment effect, the probability of being cost-effective was high (99.5%) in the most pessimistic case of 6 months at a WTP of EUR 50,000/QALY (one study).

- In one study, adverse effects due to acupuncture occurred in 7% of patients. The majority did not need medical care, but for those who sought medical care a significant additional cost was incurred.

12.3.3 Pharmacology

No studies assessed the cost-effectiveness of pharmacological treatment of acute or chronic neck pain.

12.3.4 Surgical Procedures and Injections

No studies assessed the cost-effectiveness of surgical procedures or injections.

12.3.5 Electromagnetic and Radiofrequency Therapies

The cost-effectiveness of PT plus Pulsed Short Wave Diathermy (PSWD) was analysed by Lewis et al (2007) as discussed in section 12.3.2.1. The results indicated that PSWD was not cost-effective compared to PT or SMT in combination with advice and exercise.

Main findings:

- Compared with physiotherapy and spinal manipulation therapy, in combination with advice and exercise PSWD is the least cost-effective intervention.

12.3.6 Cognitive Behavioural Therapy

CBT was assessed in two primary studies, one of which was discussed in section 12.3.2.1: Manca et al. (2007) compared a group receiving brief PT sessions based on CBT techniques (Solution Finding Approach) with a group receiving traditional PT. Analysis was performed from the NHS perspective. The usual PT technique was found to be more effective and more costly than SFA, with an ICER of GBP 1,220/QALY gained from the NHS perspective over SFA.

The protocol for an RCT comparing SMT with CBT was reported (Pool et al., 2006) including plans for an economic evaluation from the societal perspective. Follow-up for costs and effects were undertaken at 6 and 12 weeks after randomisation for short-term effects, and at 6 and 12 months for long-term effects. As discussed in section 12.3.2.2, the study found that BGA had no significant effect on recovery or QALYs gained compared with SMT, and societal costs for BGA vs SMT did not significantly differ. The authors concluded that BGA was not cost-effective compared with SMT considering recovery, QALY's gained, pain or disability.

Key massages:

- Brief physiotherapy based on cognitive behavioural therapy (Solution Finding Approach) is not cost-effective compared with usual physiotherapy (one study).
- Cognitive behavioural therapy (Behavioural Graded Activity) is not cost-effective compared with spinal manipulation therapy (one study)

12.4 Evidence gaps in interventions to treat neck pain

- The economic evidence for the treatment of neck pain is almost exclusively centred on physical therapy/exercise and spinal manipulation. Limited evidence exists for acupuncture and cognitive behavioural therapy.
- In particular, no studies were identified on the optimal management of acute neck pain in primary care, specifically whether it can/should be managed with pharmaceuticals or referred to specialist care.
- No economic evidence was identified for surgical interventions or trigger point injections.
- Economic evidence on electromagnetic and radiofrequency therapies was severely limited.
- Modifications to physiotherapy interventions studied here, ie. brief intervention or addition of cognitive behavioural elements, appear to be non-cost-effective. Alternative approaches to improving physiotherapy regimens could be considered.
- The economic evidence for spinal manipulation therapy appears to generally favour the intervention, although conclusions presented here are based on single study evidence and require substantiation.
- Limited evidence was identified on acupuncture. Although acupuncture was reportedly cost-effective in one study, this did not take into account costs of adverse outcomes.

Contributor	Comment
Dr Zoe Michaleff **Honorary Research Fellow,** **Musculoskeletal Division** **The George Institute for** **Global Health** **Sydney** **Australia**	To date there is a limited number of studies which evaluate the cost-effectiveness of guideline recommended treatments for neck pain. Many of the economic conclusions are based on the results of a single study and there is a need for additional high quality economic evaluations to be conducted alongside trials of effectiveness in order to improve the robustness and generalisability of the conclusions made. Future studies need to be carried out in a variety of health care systems and perspectives and there is a need to adequately define treatment approaches and delivery. For example, SMT is a treatment technique frequently used by a number of health professionals and the method, delivery, costs and outcomes may not be equivalent or comparable.

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Health Economic Evidence Analysis: Screening and prevention of Lung Cancer

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13 Screening and Prevention of Lung Cancer

This report outlines the available health economic evidence for the early detection through screening and primary prevention of lung cancer in healthy, potentially high risk, individuals.

13.1 Bibliometrics

As illustrated in Table 13.1 and Table 13.2 below, 19 primary studies and no reviews were identified for the prevention of lung cancer, in addition two studies were added by reviewers. The majority (76%) of primary studies were published between 2001 and 2014.

Table 13.1 Bibliometric data for lung cancer prevention

PubMed/MEDLINE	
Search terms	lung neoplasms[MeSH Terms] AND ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	19
Included as "other"	0
Reviews	0
Excluded	667
Total	686
Additional references from reviewers	
Total	2

13.2 Evidence analysis

This section presents primary studies reporting health economic evaluations of interventions to prevent lung cancer. The number of studies according to intervention type is presented in Table 13.2 below.

Table 13.2 Health economic evidence for screening and prevention of lung cancer

Prevention of Lung Cancer	**Studies**	**Reviews**
Primary Prevention		
Smoking cessation	6	0
Smoking reduction	0	0
Reduction of second hand smoke	0	0
Decreased exposure to asbestos	0	0
Decreased exposure to radon	7	0
Decreased exposure from indoor smoke from coal	0	0
Decreased exposure to diesel exhaust	0	0
Cautionary exposure to radiation therapy	0	0
Screening – all types	8	0
Total	**19**	**0**

13.2.1 Primary prevention

13.2.1.1 Smoking cessation

Six primary studies were identified assessing the cost-effectiveness of smoking cessation in reducing the incidence of lung cancer.

Bolin et al. (2009) aimed to compare the cost-effectiveness of varenicline with nicotine replacement therapy (NRT) for smoking cessation in four European countries (Belgium, France, Sweden and the UK). The impact of smoking cessation on four conditions was estimated: lung cancer, chronic obstructive pulmonary disease, coronary heart disease and stroke, and costs and benefits were estimated over a lifetime perspective. The study found that smoking cessation using varenicline versus NRT was associated with reduced smoking-related morbidity and mortality. The number of morbidities avoided, per 1000 smokers attempting to quit, ranged from 9.7 in Belgium to 6.5 in the UK. The number of QALYs gained, per 1000 smokers, was 23 (Belgium); 19.5 (France); 29.9 (Sweden); and 23.7 (UK). In all base-case simulations (except France), varenicline dominated (more effective and less costly) NRT regarding costs per QALY gained; for France the Incremental Cost-Effectiveness Ratio (ICER) was EUR 2,803/QALY.

In a similar study, Lutz, Lovato and Cuesta (2012) assess the cost-effectiveness of varenicline compared with buproprion, NRT and unaided cessation for smoking cessation with a 10-year time horizon in an adult population cohort from Central American and Caribbean countries (Costa Rica, Panama, Nicaragua, El Salvador, Dominican Republic) using the health care payer's perspective. The Benefits of Smoking Cessation on Outcomes simulation model was used, which includes morbidity and mortality from lung cancer, chronic obstructive pulmonary disorder (COPD), coronary heart disease, stroke and asthma exacerbations, and a 5% discount rate for costs and health outcomes was applied. The study found that varenicline obtained the greatest number of QALYs and LYs in the 10 year time horizon in each country, while unaided cessation obtained the fewest. Varenicline was found to be the dominant strategy in all countries examined.

Thavorn and Chaiyakunapruk (2008) found that, from a health system perspective, a community pharmacist-based smoking cessation programme in Thailand resulted in cost savings of THB 17,503 (approx. EUR 430) to the health system and life year gains of 0.18 years for men and; costs savings of THB 21,499 (approx. EUR 530) and life year gains of 0.24 years for women.

Villanti et al. (2013) found that repeat annual lung cancer screening in a high risk cohort of adults aged 50-64 is cost-effective in the US setting at USD 28,240/QALY gained. When smoking cessation interventions were offered with the annual screening program, the combined cost-effectiveness improved despite increases in costs, due to higher increases in QALYs saved. Cost-utility ratios in the combined intervention ranged from USD 16,198 to USD 23,185 per QALY gained depending on the intervention and assumptions. QALYs were estimated by using quality of life data in healthy individuals and lung cancer patients.

A study by Bolin, Lindgren & Willers (2006) reported the ICER in terms of cost per QALY gained for bupropion compared with NRT in smoking cessation programs for a follow-up period of 20 years using the Global Health Outcomes simulation model, which is based on the Health Economic Consequences of

Smoking Model. The model included morbidity/mortality data for five conditions: Chronic obstructive pulmonary disorder, asthma, coronary heart disease, stroke and lung cancer. The authors found that when the indirect effects on production and consumption were taken into account, bupropion was cost saving in comparison to both nicotine gum and patches. When limiting costs to direct costs, bupropion was still dominant compared to nicotine gum but incurred additional costs in comparison with nicotine patches, resulting in an ICER of SEK 6,600 (approx. EUR 725)/QALY for men and SEK 4,900 (approx. EUR 535)/QALY for women.

Finally, a study considering both smoking cessation and radon remediation (see section 13.2.1.2) found that the cost per life year saved was around GBP 2,000 for smoking cessation at various locations in the UK, while the cost was 3-5 times higher for radon remediation. The authors note "*smoking cessation programmes have significant added value in reducing the incidence of lung-cancer in radon Affected Areas, and contribute a substantially greater health benefit at a lower cost than the alternative strategy of reducing radon levels in the smokers' homes, while they remain smokers*" (Groves-Kirkby et al., 2011).

Main findings:

- The nicotine receptor partial agonist varenicline and the antidepressant buproprion were both shown to dominate or exhibit attractive ICER's compared with nicotine replacement therapy (three studies).
- Annual lung cancer screening, particularly in combination with smoking cessation programmes, appears to be cost-effective in preventing lung cancer in high risk individuals (one study)
- Community pharmacy-based smoking cessation programmes are cost-saving (one study)
- Smoking cessation is 3-5 times more cost-effective than radon remediation in the UK (one study)

13.2.1.2 Radon

Seven primary studies were identified assessing interventions to limit radon exposure in domestic settings. Gray et al. (2009) found that a UK policy requiring basic measures to prevent radon in new homes in selected areas was highly cost effective, and that such measures would remain cost effective if applied on a national level, with a cost per QALY gained of GBP 11,400. However, the study also found that a policy aiming to identify and remediate existing homes with high radon levels is neither cost-effective (GBP 36,800/QALY gained) nor effective in reducing lung cancer mortality.

Conversely, Petersen and Larsen (2006) present a cost-benefit analysis seeking to determine whether it is socio-economically worthwhile to avert lung cancer deaths by reducing radon levels in the most exposed dwellings. These results are based on a discount rate of 6%, a value of preventing a statistical fatality of EUR 1.4 million, and the relatively high cost of remediation in Denmark compared to other countries. Petersen and Larsen (2006) find that the total costs of implementation exceed the valuated health benefits by EUR 62 million, and conclude that it is not socio-economically favourable to reduce radon levels in existing Danish one-family houses.

Coskeran et al. (2005) examined the cost-effectiveness of radon remediation programmes in four Primary Care Trusts (PCTs). PCTs (now Clinical Commission Groups) play a key public health policy role in the UK's National Health Service. The authors compare the cost-effectiveness of radon remediation with

other interventions that can avert and treat lung cancer. The study found that cost-effectiveness is better in PCTs where a higher percentage of properties above the National Radiological Protection Board's Action Level (200 Bq m^{-3}) is found and where a greater percentage of householders remediate. The study concludes that current remediation programmes in these PCTs, where between 5.1% and 9.0% of existing houses had excessive radon levels and 10% of those finding high levels went on to remediate, are cost-effective at GBP 9,002 to 16,880 per LYG at a 3% discount rate, though programmes to cut smoking remain highly cost-effective approaches for reducing lung cancers. They concluded that, with the current UK public response rate, radon remediation programmes in areas where over 5% of existing houses had radon levels which were above the Action Level were cost-effective compared to other health interventions.

In (Coskeran et al., 2006) the analysis was extended to include Quality of Life estimates, the authors found estimates ranged from GBP 6,143 to GBP 10,323 per QALY in the same four PCTs suggesting the Trust-run remediation programmes were cost-effective against the UK's willingness to pay threshold. In the most recent paper by these researchers (Denman et al., 2013) it is noted that finer grained mapping of radon affected homes, from UK County level prior to 1999 to 1 km grid squares in 2007, has identified small areas of raised radon levels within regions where previously no risk was identified. Conversely, areas that were previously considered radon affected were subsequently considered low- or no risk. The net result has been an increase in the number of affected houses, which would increase the total cost of remediation. The authors estimate that remediation of all homes identified above the action level in newly identified radon Affected Areas would incur costs of GBP 156,350,000 and avert 160 lung cancers annually, resulting in GBP 980,000 per lung cancer averted annually. Assuming each lung cancer results in the loss of 13.51 years and is associated with reduced quality of life, the authors estimate a cost per QALY gained of GBP 4,110 for existing homes in newly identified radon Affected Areas if all householders measured and remediated their homes. At the current response rates in the originally declared radon Affected Areas (now up to 15%) the cost would be GBP 18,400 per QALY. Denman et al., (2013) also concluded that protection of all new homes in England and Wales had now risen to GBP 24,000 per QALY, and would rise further as smoking prevalence declined, but in newly identified radon Affected Areas was GBP 7,460 per QALY.

Stigum et al. (2003) assess the cost-effectiveness of an intervention to locate and improve homes with high radon exposure (above 200 Bq m^{-3}) as well as protecting future houses. The authors report the preventable attributable fraction of radon on lung cancer to be 3.8% (95% uncertainty interval: 0.6%, 8.3%), and that in cumulative present values the intervention would cost USD 238 million and save 892 lives; a cost per life saved of USD 0.27 million which is less than the USD 1 million Norwegian society is willing to pay to save a life.

Ford et al. (1999) explored the cost-effectiveness of three possibilities for focusing radon screening efforts: screening all homes vs. screening homes in geographically defined high radon risk areas; screening homes of smokers vs. those of nonsmokers; screening homes of all age groups vs. those of selected age groups. They found that when best estimates of compliance were used, taking a geographical approach to screening about one third of the country with predicted elevated radon levels, produced a more favorable cost-effectiveness estimate than a universal approach. They also found that

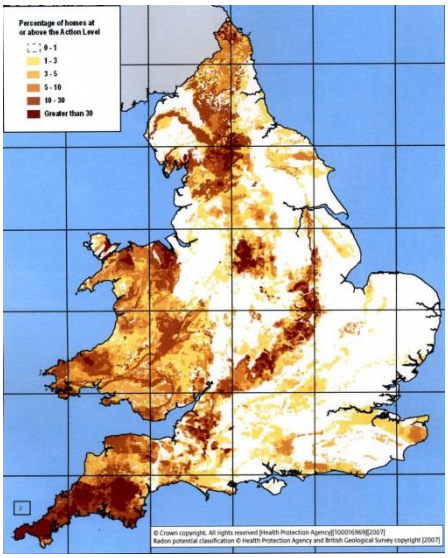
targeted approaches prevent 50% to 80% of predicted lung cancer deaths of comparable universal approaches. Finally, from a public health perspective it is more cost-effective to prevent radon-associated lung cancer deaths among people who smoke, although smoking cessation programs in isolation are more cost-effective.

Box 1 Trends in radon remediation and factors affecting cost-effectiveness

Trends in radon remediation and factors affecting cost-effectiveness

One significant feature of radon remediation programmes is the low percentage of people who take action to reduce radon risk. For example, only around 40% of householders in Northamptonshire, UK, a known radon affected area since 1992, have so far tested their homes, and only around 15% of those finding raised radon levels do anything about it. This is in contrast to public reaction to Nuclear Accidents and Nuclear Power. This has been the subject of a number of studies, including the current EU FP7 Eagle project http://eagle.sckcen.be.

Cost-effectiveness of radon remediation depends on a number of factors including the radon potential of an area, the climate, the percentage of householders who decide to remediate their homes, and the smoking prevalence in the area. This is a challenge for the comparison of various studies. Radon has a very variable geographical distribution, and in a number of countries detailed radon maps are being developed – see Figures a and b.



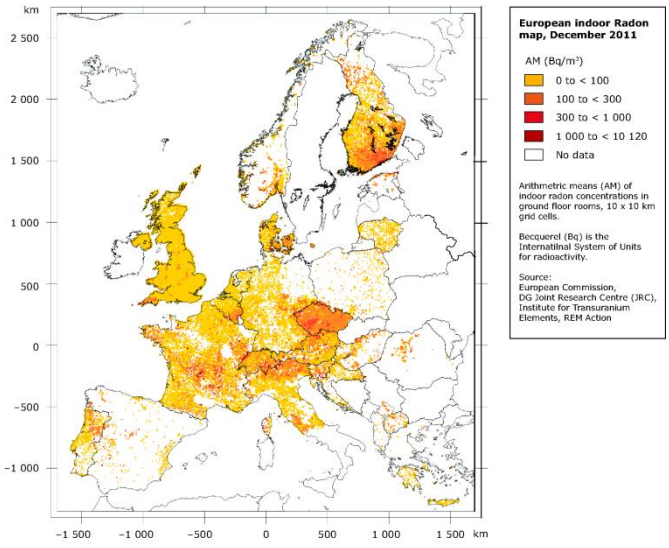


Figure a – Radon in England & Wales (2007)

Figure b – Radon in Europe (2011)

Radon is more of a problem where houses are well-sealed to prevent heat-loss, and less of a problem in warm Mediterranean countries where windows are often open. Each EU country should be able to report on radon distribution and the scale of the risk, although some are more advanced in mapping (Austria, Germany, France) than others.

The variation in cost-effectiveness with radon potential has been studied by Denman et al, as has the

variation of cost-effectiveness with the percentage involvement of house-holders. These authors originally reported that smokers are less likely to take action to reduce radon levels (Denman et al., 2004), and compared the characteristics of those who take action to reduce radon levels in their homes to those who join smoking cessation programmes (Denman et al., 2009). These studies are significant as the lung-cancer risk from radon and smoking is considered to be multiplicative, with a smoker being 25 times more at risk from radon than a non-smoker. The research regarding characteristics of those who remediate has been replicated by the National Radiological Protection Board (now Public Health England) (Zhang et al., 2011).

The issue of who responds to a radon remediation programme significantly affects the cost-effectiveness of a programme. Firstly, in a programme for existing homes, costs are incurred to no benefit if radon detectors are issued but house-holders do not respond if the level is high. But more significantly, if smokers do not respond, then the health benefits are far less than would be expected from the population-average risk (Denman et al., 2004).

According to a single variant analysis the cost of treating lung cancer, the cost of remediating and the discount rates for maintenance have little effect on cost effectiveness of domestic radon remediation programmes. However, the percentage of houses over the Action Level, the percentage of householders remediating, the lifetime risk of lung cancer, the discount rate for life-years gained, and the life expectancy have a considerable effect (Denman et al., 2008a).

The underlying smoking prevalence of an area will affect the number of lung cancers averted, and hence the cost-effectiveness of a radon remediation programme. Smoking prevalence in UK is reducing in response to government initiatives, as discussed by (Denman et al., 2014). Their recent conclusions are at variance with those of Gray et al., (2009), finding that protection of all new houses in the UK is borderline cost-effective and reducing in value as smoking prevalence drops, but targeting high radon areas for both new and existing homes is cost-effective (Denman et al., 2014).

There are discussions about the correct radon level above which remediation action should be taken, and a revision to the Basic Safety Standards is being suggested. On this topic, the work by Denman et al. suggesting the cost-effectiveness in domestic housing may be optimal around 200 $Bq.m^{-3}$ may be worth replicating in other EU countries (Denman et al., 2008b).

Groves-Kirkby et al., (2011) published a study showing that smoking cessation is more effective than radon remediation in a radon affected area, but arguably as the two campaigns target different population groups, and either campaign would leave some residual risk, a mixed and localised approach could be best (Denman et al., 2014). In this work it is suggested that, in the UK at least, there is little correlation between radon potential and smoking prevalence at Primary Care Trust level, because most of major conurbations in the UK are in low radon areas – this, of course, may not be true in the rest of Europe.

Main findings:

- A policy to protect all new homes in England and Wales, where 0.5% of homes have radon levels over 200 Bq m^{-3}, may be cost-effective (two studies), with ICER's estimated at GBP 11,400/QALY and GBP 24,000/QALY. Protection of new homes in radon Affected Areas is more cost-effective (GBP 7,460 per QALY in one UK study.)
- Remediation of existing homes is studied with a variety of methodologies and different settings, with estimates in the region of GBP 36,800/QALY gained, GBP 6,143 to 10,323/QALY gained, and a cost per life saved of USD 0.27 million. These estimates are likely to be highly sensitive to local factors, including the local radon exposure levels and types of dwelling. In addition there are significant challenges relating to house-holder involvement.
- Smoking cessation programmes can have the added value of reducing radon-induced lung cancers, and are more cost-effective than radon remediation programmes in the same locality. However, as each initiative reaches somewhat different target audiences, there is some value in a mixed and localised approach.

13.2.1.3 Smoking reduction; reduction of second hand smoke; reduced exposure to asbestos, indoor pollution from coal, diesel exhaust, and; cautionary exposure to radiation therapy

The present search did not identify any studies addressing the reduction of smoking, second hand smoke exposure, asbestos exposure, indoor pollution from coal, diesel exhaust or cautionary exposure to radiation therapy.

Exposure to asbestos causes mesothelioma , a specific type of lung cancer (Kanarek, 2011) which is primarily an occupational hazard in certain industries.

13.2.1.4 Screening

Screening for lung cancer aims to diagnose lung cancer at an early stage, when treatment has a better prognosis, with the hope of lower mortality. Trials of lung cancer screening began in the 1970s with regular sputum cytology and latterly Chest X-Rays (Diederich et al., 2002). Caro et al. (2000) produced an economic model to compare lung cancer mortality in male smokers aged 45-80 years, screened with chest X-Rays versus unscreened. Their base case analysis (mortality reduction of 18%) estimates that nearly 3,000 deaths would be avoided in a population of 100,000 male smokers age 40-80 years, at a cost-effectiveness of USD 9,000 per undiscounted life year gained; and a program resulting in only 6% mortality reduction would increase the ratio to USD 25,000 per undiscounted life year gained.

The advent of Computed Tomography (CT), and, in particular, the lower dose technique of Helical Chest CT, which has a much higher sensitivity for detecting small pulmonary nodules, has resulted in many research groups considering the value of Helical CT as the method of choice for screening, despite delivering 10 times the radiation dose of a chest X-Ray. Screening is only valuable in high risk groups (ie older heavy smokers). In addition, as 95% of the detected nodules are benign, a careful protocol for investigating nodules and establishing which are false positives is critical (Diederich et al., 2002).

Wisnivesky et al. (2003) aimed to evaluate the cost-effectiveness of a single baseline low-dose CT scan for lung cancer screening in high-risk individuals, defined as those > or = 60 years with at least 10 pack-years of cigarette smoking and no other malignancies. Their analysis adopted the health-care system's perspective, and he base-case analysis was conducted under the assumption of similar aggressiveness of screen-detected and incidentally discovered lung cancers and then was followed by multiple sensitivity analyses to relax their assumptions. They found that the incremental cost-effectiveness ratio of a single baseline low-dose CT scan was USD 2,500 per year of life saved. The base-case analysis showed that screening would be expected to increase survival by 0.1 year at an incremental cost of approximately USD 230. Only when the likelihood of over-diagnosis was > 50% did the cost effectiveness ratio exceed USD 50, 000 per year of life saved. Wisnivesky et al. (2003) concluded that baseline low-dose CT scanning for lung cancer screening is potentially highly cost-effective and compares favourably to the cost-effectiveness ratios of other screening programs.

Similarly, Marshall et al. (2001a) study found that in a very high-risk cohort (LC prevalence of 2.7%) of patients between 60 and 74 years of age, a one-time screen using helical computed tomography (CT) was cost-effective at USD 5,940 per life year saved. Likewise, in a lower risk general population of smokers (LC prevalence of 0.7%), a one-time screen was also cost-effective at USD 23,100 per life year saved.

The study of Marshall et al., (2001) examined the implications of an annual lung cancer screening programme using CT. They found that under optimal conditions in a high risk cohort of patients between 60 and 74 years of age, annual lung cancer screening over a period of 5 years appears to be cost effective at approximately USD 19,000 per life year saved. A sensitivity analysis generated estimates from approximately USD 10,800 to 62,000 per life year saved. The authors concluded that annual screening of high risk elderly patients for lung cancer may be cost effective under optimal conditions, but longer term data are needed to confirm if this will be reflected in real-life settings.

The final study producing favorable cost-effectiveness results was conducted by Chirikos et al. (2002). These authors compared one cohort that was screened using low-dose CT over the first 5 years of the study period, with the other cohort that received usual care. Chirikos et al. (2002) found that even under a "worst-case" scenario (highest cost and lowest yield assumptions), screening with CT costs approximately USD 48,000 per life-year saved assuming screening results in 50% of lung cancers detected at localized stage. They found that lower rates of cancer detection at a localized stage resulted in higher cost-effectiveness ratios, and vice versa. They concluded that if screening for lung cancer is effective, it is likely to be cost-effective if the screening process can detect > 50% of cancers at localized stage.

McMahon et al. (2011) sought to identify which participant and program characteristics influence the cost-effectiveness of lung cancer screening. They simulated six US cohorts (men and women aged 50, 60 or 70 years) in an existing patient-level lung cancer model. They found that annual screening of current and former smokers aged 50 to 74 years costs between USD 126,000 and USD 169,000/QALY (minimum 20 pack-years of smoking) or between USD 110,000 and USD 166,000/QALY (40 pack-year minimum), when compared with no screening and assuming background quit rates. Further findings suggested that

screening was beneficial but had a higher cost per QALY when the model included radiation-induced lung cancers from the initial helical CT screening and subsequent CT examinations during the diagnostic phase. If screen participation doubled background quit rates, the cost of annual screening (at age 50 years, 20 pack-year minimum) was below USD 75,000/QALY. If screen participation halved background quit rates, benefits from screening were nearly erased. And finally, if screening had no effect on quit rates, annual screening costs increased but provided fewer QALYs than annual cessation therapies (which, at age 50 years cost USD 130,500 to USD 159,700/QALY), when compared with annual stand-alone cessation. McMahon et al. (2011) concluded that the cost-effectiveness of CT screening is strongly linked to smoking cessation rates, and recommended that future trials and further modeling explore the consequences of relationships between smoking behaviours and screen participation.

The Manser et al. (2005) and Mahadevia et al. (2003) studies both found screening to be non-cost-effective. Manser at al. (2005) compared two alternatives in the Australian setting: screening for lung cancer with annual CT for 5 years starting at age 60 followed by treatment of those diagnosed with cancer; or no screening and only treatment of those who present with symptomatic cancer. They found that for male smokers aged 60-64 years, with an annual incidence of lung cancer of 552 per 100,000, the incremental cost-effectiveness ratio was AUD 57,325[1] per life-year saved and AUD 105,090 per QALY saved. For females aged 60-64 years with the same annual incidence of lung cancer, the cost-effectiveness ratio was $51,001 per life-year saved and $88,583 per QALY saved. Using a willingness to pay threshold of $50,000, they found even under favourable assumptions, reductions in lung cancer mortality of less than 20% are unlikely to be cost-effective. They concluded that the most feasible scenario under which CT screening for lung cancer could be cost-effective would be if very high-risk individuals are targeted and screening is either highly effective or CT screening costs fall substantially.

Similarly, Mahadevia et al. (2003) examined the potential benefits, harms, and cost- effectiveness of lung cancer screening with CT in various efficacy scenarios. Mahadevia et al. (2003) found that, over a 20-year period, assuming a 50% stage shift, their current heavy smoker cohort had 553 fewer lung cancer deaths (13% lung cancer-specific mortality reduction) and 1,186 false- positive invasive procedures per 100,000 persons. The incremental cost-effectiveness for their cohorts were listed as:

- current smokers: USD 116,300 per QALY gained
- quitting smokers: USD 558,600 per QALY gained
- former smokers: USD 2,322,700 per QALY gained

Mahadevia et al. (2003) found the most influential parameters to be: the degree of stage shift; adherence to screening; degree of length or over-diagnosis bias in the first year of screening; quality of life of persons with screen-detected localized lung cancers; cost of CT, and anxiety about indeterminate nodule diagnoses. However, in a one-way sensitivity analysis, none of these parameters were sufficient to make screening highly cost-effective for any of the cohorts. In multi-way sensitivity analyses, a program screening current smokers was USD 42,500 per QALY gained if extremely favourable estimates were used for all of the influential parameters simultaneously. Mahadevia et al. (2003) concluded that

[1] Manser et al. (2005) did not specify whether costs were expressed in US dollars or Australian dollars.

even if effectiveness is eventually proven, screening must overcome existing barriers to be highly cost-effective. They also recommended that, given the current uncertainty of benefits, the harms from invasive testing, and the high costs associated with screening, direct-to-consumer marketing for lung cancer screening using CT is not advisable.

There are currently two major research trials underway to further investigate the value of low-dose CT screening for high risk groups. One, the NLST trail in US is comparing Chest X-Ray screening to helical CT screening (Aberle et al., 2011) and the other is a European study, the NELSON trial (Mulshine & Henschke, 2014).

Jonnalagadda et al. (2012) have reported that their research suggests that some high-risk patient groups are less likely to present for lung cancer screening, and that lung cancer screening programmes should address these factors to ensure broad participation, particularly among minorities. These findings are similar to those in studies of symptomatic patients (see box below)

Main findings:

- Using low-dose helical CT as a tool for lung cancer screening in populations at very high risk is widely (though not unanimously) accepted to be cost-effective, though smoking cessation and screening effectiveness play a decisive role in the level of cost-effectiveness.
- Cost per life year saved ranges from USD 2,500 to USD 19,000 for various implementations of helical CT scan screening in high risk populations. In lower risk populations, the incremental costs are generally seen to be higher. Some estimates from the literature are well above thresholds normally considered cost-effective.
- Cost-effectiveness ratios are sensitive to the effectiveness of screening (proportion of cancers detected at localized stage) and the spontaneous smoking cessation rates during screening programmes.
- It is expected that two major trials will report soon on the value, parameters, and operational methods of screening high risk populations for lung cancer.

13.3 Evidence gaps for the prevention of lung cancer

Observations from published studies

- Smoking cessation with nicotine receptor partial agonists (varenicline) or antidepressants (buproprion) appear to be cost-effective compared with nicotine replacement therapy according to three studies.
- Policies to prevent radon exposure in newly built homes may be cost-effective (one study), remediation of existing homes appears to be less cost-effective per QALY but may still be within acceptable thresholds. Estimates tended to vary significantly between studies, and cost-effectiveness is sensitive to the proportion of dwellings over the radiation limit, smoking prevalence, the proportion of the population participating and to a lesser extent to the cost of remediation, which may differ significantly between settings and dwelling types.”Using helical CT as a tool for lung cancer screening in populations at very high risk is widely (though not

unanimously) accepted to be cost-effective, though smoking cessation and screening effectiveness play a decisive role in the level of cost-effectiveness. In addition, screening studies did not consider adverse events related to screening/testing (radiation, invasive procedures etc.)

- Cost per life year saved ranges from USD 2,500 to USD 19,000 for various implementations of CT scan screening in high risk populations. In lower risk populations, the incremental costs are generally seen to be higher. Some estimates from the literature are well above thresholds normally considered cost-effective.
- Two major trials, one in US and one in Europe, are underway and should provide better evidence of the value of helical CT screening in high risk groups.
- There was no HEE literature exploring the reduction of smoking, second hand smoke exposure, asbestos exposure, indoor pollution from coal, diesel exhaust or cautionary exposure to radiation therapy.
- A significant body of literature examines smoking cessation as an isolated intervention, reporting cost-effectiveness eg. as cost per quitter, but without taking into account the economic benefits associated with reduced incidence of lung cancer and other health consequences of smoking (Essex et al., 2014)

Contributor	Comment
Dr. Tim Coleman Professor of Primary Care Faculty of Medicine & Health Sciences University of Nottingham UK	<u>Lung cancer prevention as outcome:</u> As smoking cessation reduces the risk of lung cancer, any effective smoking cessation intervention could potentially have economic benefits by preventing the development of this morbidity. Estimates for the efficacy of many different cessation interventions are available from Cochrane reviews and some of these interventions (e.g. brief advice from a GP) could be much cheaper in cost terms than NRT, bupropion or varenicline (interventions tested in identified studies). However, for most types of smoking cessation interventions, no studies modelling effects on lung cancer were identified, so there is an absence of evidence about economic effectiveness for majority of effective cessation interventions.
Dr. Antony R Denman Emeritus Professor of Medical Physics, School of Science and Technology, The University of Northampton	One significant feature of radon remediation programmes is the low percentage of people who take action to reduce radon risk. For example, only around 40% of householders in Northamptonshire, UK, a known radon affected area since 1992, have so far tested their homes, and only around 15% of those finding raised radon levels do anything about it. This is in contrast to public reaction to Nuclear Accidents and Nuclear Power. This has been the subject of a number of studies, including the current EC Framework 7 Eagle project http://eagle.sckcen.be. It will be interesting to learn if this project comes up with any recommendations about informing the general public about radiation risks, and why the public do not consider radon a risk despite the radiation dose delivered being much higher than many artificial sources which cause public concern, and whether there are specific differences between EC countries and population groupings.

Regarding smoking, we have found that there is some correlation between the number of quitters and the smoking prevalence in an area in the UK (Denman et al., 2014) – as might be expected, this implies it is more difficult to encourage the remaining smokers in a low smoking prevalence area to give up.
There can be geographic variation in smoking prevalence, and there is a link (certainly in the UK) with social deprivation, with higher smoking prevalence in the major conurbations (Denman et al., 2014). This introduces the potential for targeted smoking cessation programmes, which should be more cost-effective than national schemes. In terms of the EU, this also suggests targeting of member countries where smoking prevalence is higher.
Smoking Prevalence across the EU countries varies widely, from 45% in Bulgaria, and 40% in Greece down to UK 22% and Portugal 20% . The cost-effectiveness analyses for smoking cessation programmes is robust enough to justify smoking cessation programmes as a primary health initiative in European Countries, with expertise from those countries who have reduced smoking prevalence informing initiatives elsewhere. There would be scope to evaluate specific interventions, and the best ways of informing and engaging the public in different countries, as cultural differences may impact on the effectiveness of cessation programmes.

Regarding detection of lung cancer, in the UK the concern has been that high risk patients with possible symptoms are not presenting to their GP as soon as they could. Two research trials have taken place, one in Leeds and the other in Corby, Northamptonshire (both areas of high smoking prevalence), to test the value of easy access for a chest X-Ray and associated publicity campaign for those with possible symptoms and at high risk (Campbell, Pyer & Rogers, 2012). The chest X-Ray was chosen for its low radiation dose (around 400 times less than chest CT), and its local availability, and is currently considered to be the first test when patients present by the National Institute for Health and Care Excellence. Both trials had positive outcomes.

Mapping of radon potential and smoking prevalence across Europe should continue, as this will indicate where health interventions would be most cost-effective. In addition, it may identify areas where both radon levels and smoking prevalence are high, and therefore have the highest risk of lung cancer incidence.

As noted above, a major challenge of radon remediation programmes is public involvement, and in this regard, the output and conclusions of the Framework 7 EAGLE project may be very informative, and could suggest methodologies for radon remediation programmes which could be evaluated to judge the extent of public involvement and cost-effectiveness.

Matthew Jones Faculty of Medicine & Health Sciences University of Nottingham UK	Smoking during pregnancy is a major public health issue. While smoking can impact on the health of the mother and infant during pregnancy [e.g. increased risk of delivery complications such as placenta abruption and previa (Castles et al., 1999), miscarriage (DiFranza & Lew, 1995), premature birth (Shah & Bracken, 2000), and low birth weight (DiFranza & Lew, 1995)], it can also have a lasting impact on the health of the infant after birth, being associated with an increased risk of respiratory illness (Burke et al., 2012), in addition to any effects from exposure to passive smoking (RCP, 2010). Despite these risks, many countries report that between 16% and 27% of mothers report smoking at some point during their pregnancy (NHS, 2011; WHO, 2011; Bloom, Cohen & Freeman, 2011; AIHW, 2011). Although there are studies which have investigated the cost-effectiveness of cessation interventions during pregnancy, the evidence remains limited (Ruger & Emmons, 2008; Ruger et al., 2008; Taylor, 2009; NICE, 2013). Current literature tends to focus on limited time horizons (usually within pregnancy), rarely controls for uncertainty in the parameters robustly, and on either the mother or infant, rarely both. However, the current evidence suggests that cessation interventions during pregnancy are potentially cost-effective. Future research should focus on prospectively modelling both the short and long term health effects of smoking during pregnancy, use comparable measures such as health related quality of life rather than cost per quitter outcomes, and incorporate robust statistical methods to control for uncertainty.

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Health Economic Evidence Analysis: Prevention of Ischemic Heart Disease

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14 Prevention of Ischemic Heart Disease

14.1 Bibliometrics

The main focus of this report is on primary prevention of Ischaemic Heart Diseases (IHD). That is reducing and treating risk factors in order to reduce the incidence of IHD. A total of 50 studies were mapped to the various interventions outlined in Table 14.1. Five reviews identified were all published before the cutoff date in the present review (2009 – 2014) and are excluded from the analysis (Brown & Garber 1998; Jönsson 1994; Jacobson 1996; Tsevat 1992; Martens & Guibert 1994).

Table 14.1 Bibibliometric data for Prevention of IHD

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Myocardial Ischemia"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	24
Reviews	5
Excluded	1,789
Total	1,818
Additional studies suggested by reviewers	
Total	1

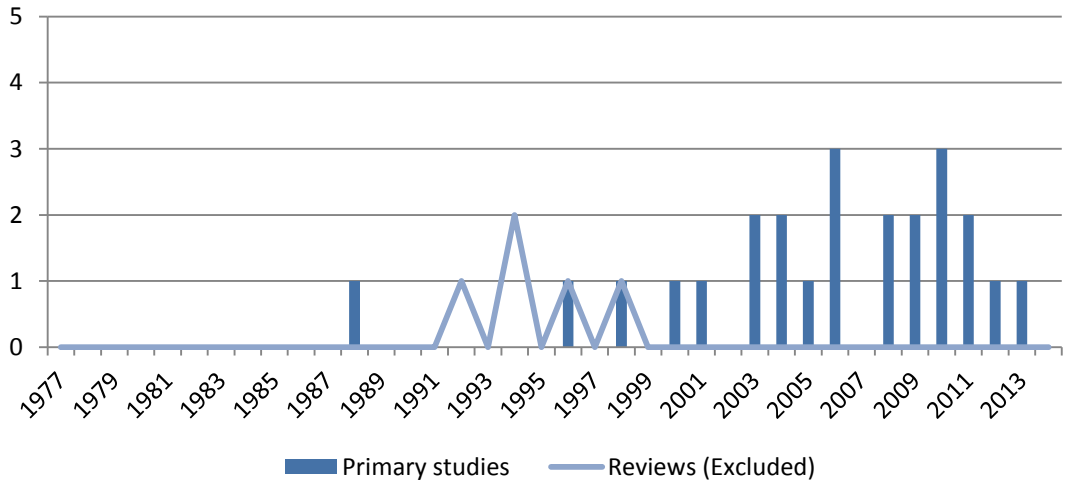

Figure 14.1 Bibliometric data for prevention of ischemic heart disease by year

14.2 Evidence Analysis

The following section presents information gathered from primary studies. Table 14.2 summarizes the volume of health economic studies identified according to each method of prevention.

Table 14.2 Health economic evidence for the prevention of ischemic heart disease

Prevention of Ischemic Heart Disease	Studies	Reviews
Primary Prevention		
Hypertension treatment: Pharmacotherapy, sodium reduction,	6	0
Lipid control: Pharmacotherapy, non pharmacological therapy	4	0
Aspirin	2	0
Physical exercise and dietary measures	7	0
Smoking cessation	1	0
Management of Obesity	2	0
Secondary Prevention		
Hypertension treatment	0	0
Lipid control	2	0
Diabetes treatment	0	0
Anticoagulant therapy	1	0
Smoking cessation	0	0
Diet and physical activity	0	0

14.2.1 Primary Prevention

The evidence on primary prevention of IHD was found in 22 primary studies addressed in the following sub-sections.

A single study assessed the cost-effectiveness of primary prevention across several interventions. Smoking cessation, anti-hypertensive treatment, lipid control and dietary modification were evaluated in patients with cardiovascular risk factors in Spain (Plans-Rubió 1998). The cost analysis was undertaken using direct costs but the perspective or comparators used were not stated. The results showed the ICER for smoking cessation ranged from USD 2,608 – 8,058/Life Year Gained (LYG), lipid control treatment from USD 33,850 – 302,088/LYG, hypertension (HT) treatment from USD 7,061 – 126,990/LYG, and for dietary modification USD 12,742 – 149,246/LYG. The authors concluded that smoking cessation

Main finding:

- Smoking cessation was found to be significantly more cost-effective than other interventions in the prevention of IHD, although this conclusion from 1998 may change following patent expiry of eg. statins.

14.2.1.1 Hypertension Control

Pharmacotherapy

Three studies assessed different pharmacotherapy options for the treatment of HT while one study assessed the cost-effectiveness of different adherence levels to anti-hypertensive treatment.

The Hypertension in the Very Elderly Trial (HYVET) was a Randomized Controlled Trial (RCT) conducted in 13 countries in Western and Eastern Europe, Australasia, China and North Africa. It assessed the effectiveness of a stepped care approach; starting with Indapamide SR 1.5 mg (sustained release diuretic) and then adding Perindoprol 2 – 4 mg (angiotensin converting enzyme inhibitor) if needed to achieve the target blood pressure of <150/80 mmHg compared with a placebo in reducing the incidence of cardio-vascular events (CVEs). The efficacy data from this trial was applied to the context of Switzerland by Szucs et al. 2010 to assess the cost-effectiveness of anti-hypertensive treatment for an elderly population (80+). From a third party payer's perspective treatment of HT with the stepped care approach was cost saving compared with placebo. The additional cost of treatment was outweighed by the costs saved from prevention of CVEs. The treatment group showed an additional gain of 0.045 life years.

The data of ASCOT-BPLA (Anglo Scandenavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) was applied to a Markov model in the context of the UK and Sweden to predict the long term cost-effectiveness in treating HT with an Amlodipine (Calcium Channel Blocker) based regimen compared to an Atenolol (Beta Blocker) based regimen (Lindgren et al. 2008). Patients attending a primary care setting with moderate HT and three or more CV risk factors were modelled. For the duration of the six year trial period, the cost-effectiveness of the Amlodipine based regimen compared to the Atenolol based regimen was EUR 18,965/CVE avoided and EUR 21,875/QALY gained in UK and EUR 13,210/CVE avoided and EUR 16,856/QALY gained in Sweden. When the price of generic amolodipine was added to the model the cost-effectiveness improved to EUR 7,257/QALY in UK and EUR 8,372/QALY gained in Sweden. It was concluded that an Amlodipine based regimen was cost-effective compared with an Atenolol based regimen in moderately hypertensive patients with additional CV risk factors in accordance with the willingness to pay (WTP) thresholds applied by both countries.

Another analysis was undertaken using data from the ALLHAT (Anti-hypertensives and Lipid Lowering to prevent Heart Attack Trial) to assess three pharmacological options in treating patients above 55 years with HT and one other CV risk factor (Heidenreich et al. 2008). The three options evaluated were Chlorthiolidone (Diuretic), Amlodipine and Lisinopril (ACE inhibitor). The cost-effectiveness of life time treatment from a single payer perspective was assessed. The comparison was conducted between the lowest cost strategy with the strategy that has the next lowest cost. The study showed patients receiving Chlorthiolidone had the least cost of care over the lifetime. Amlodipine showed a non-significantly higher survival benefit over the other two drugs. However the quality of life value was not different in the three groups. The cost-effectiveness of Amlodipine compared to Chlorthiolidone was USD 48,400/LYG. At a WTP threshold of USD 50,000/LYG, Amlodipine was preferred 50% of the time, Chlorthiolidone 40% and lisinopril only 10% of the time according to bootstrap analysis. At a WTP threshold of USD 20,000/LYG Chlorthiolidone was preferred 74% of the time.

A cohort study conducted in Italy (Scotti et al. 2013) assessed the cost-effectiveness of increasing adherence to anti-hypertensive treatment in patients between the ages of 40 – 79. The cost-effectiveness of different adherence rates were compared with baseline adherence of 52%. The study showed with 52%, 60% and 80% adherence the rates of CVE events were 85, 83 and 77 respectively per 10,000 person years. The cost-effectiveness improved from EUR 76,000 at 60% adherence to EUR

74,000 at 80% adherence per CVE avoided when compared with the baseline of 52%. The study concluded that an increased adherence to anti-hypertensive treatment would reduce the incidence of future CVEs, but at a relatively high cost.

Main findings:

- Patents expired for Amlodipine in 2007 and Lisinopril in 2001. Cost-effectiveness studies using the on-patent price published around or prior to these years were not considered relevant for the analysis.
- For hypertensive patients above 80 years - Treatment with Indapamide SR 1.5 mg (sustained release diuretic) and then adding Perindoprol 2 – 4 mg (angiotensin converting enzyme inhibitor) is cost saving in reducing future CVEs compared to a placebo. (1 study)
- For moderately hypertensive patients with three or more CV risk factors - An Amlodipine based regimen (Calcium Channel Blockers) is cost-effective compared to an Atenolol based regimen (Beta blocker) according to WTP thresholds of UK and Sweden. (1 study)
- For hypertensive patients with only one CV risk factor, initial treatment with Chlorthiolidone is less expensive than Amlodipine or Lisinopril. Amlodipine showed a non-significantly higher survival benefit, but the quality of life value in the 3 treatment groups were not different. The most cost-effective option of the three is unclear (1 study)
- Enhancing adherence of anti hypertensive treatment from the usual baseline level would reduce the incidence of future CVEs but at a considerably higher cost (1 study)

Sodium content

The cost-effectiveness of two population strategies to reduce the sodium content in food was evaluated in the US in a single study (Smith-Spangler et al. 2010). One strategy was government coordination with food manufacturers to promote voluntary reduction of sodium content in food production. The other strategy was implementation of a sodium tax. A Markov model was used with a life time horizon and the analysis was undertaken from a societal perspective. The results showed voluntary reduction of sodium content by the food manufacturers would lead to a mean reduction of sodium by 9.5%, reducing 513,885 strokes in the population aged 40 – 85 years and saving USD 32.1 billion on medical costs. With a sodium tax, a 6% reduction in the mean sodium intake would occur with USD22.4 billion savings in medical costs. The authors concluded a reduction of sodium intake in food would substantially reduce the incidence of strokes and produce substantial savings in direct healthcare costs.

Main findings:

- Reducing sodium in food would save USD 32 billion in healthcare costs if a voluntary reduction of sodium content by food manufacturers is achieved or USD22.4 billion if a sodium tax is implemented (1 study).

14.2.1.2 Lipid Control

The evidence discussed in this section is for pharmacological lipid management. Results of 22 primary studies on cost-effectiveness of drugs belonging to the classes of statins, bile acid sequestrans (Cholestyramine) and fibrates (Gemfibrosil) were found. Many of the studies that were conducted using the patented price of the drug were excluded from the present review as they are now available in generic form.

Statins

The cost-effectiveness of six drugs that fall under the class of statins; Atorvastatin, Simvastatin, Rosuvastatin, Fluvastatin, Levostatin and Pravastatin were analyzed. Patents for five of these drugs (except Rosuvastatin due in 2016) have expired: Lovastatin in 2001, Simvastatin and Pravastatin in 2006, Atorvastatin and Fluvastatin in 2011. Out of the 13 studies identified in this section, 8 were excluded due to patent expiry (Lindgren et al. 2005; Martens et al. 1990; Hjalte et al. 1992; Chrisp et al. 1992; Nagata-Kobayashi et al. 2005; Pinto et al. 2008; Palmer et al. 2003; Hay et al. 1991;Plans-Rubió 2006).

Four studies assessed the cost-effectiveness of different prescribing conditions for statins. Of these, one study conducted in the US using a Markov model compared Adult Treatment Panel III (ATP III) guidelines with alternative strategies based on risks and age to identify the most cost-effective strategy to initiate treatment with statins (Pletcher et al. 2009). A population of 35 – 85 year olds were modeled and the analysis was conducted from a health care provider's perspective. The statin therapy costs were calculated by considering the average cost value of different dosages of different statins that is required to achieve a target LDL reduction of 27%. The study showed full adherence to ATP III guidelines for the US population of 11.1 million eligible adults would prevent 20,000 myocardial infarctions and 10,000 deaths due to coronary heart disease (CHD). The ICER for the intervention would be USD 42,000/QALY gained if the cost per statin pill is USD 2.11 which is cost-effective at a WTP threshold of USD 50,000/QALY gained. In addition, they estimated that with a lower cost pill (<USD 0.11) treating all individuals with a LDL value higher than 3.4 mmol/L would be cost-saving. Therefore, if ATP III is fully implemented with lower cost statins, it is cost saving and will yield large public health benefits. But if the cost of statins are higher (> USD 2.11/pill), ATP III would not be likely to be cost-effective.

Another primary study assessed the cost-effectiveness of lipid control in patients with diabetes mellitus (DM) in reducing the incidence of CVD (Sorensen et al. 2009). The ATP III guidelines which promoted monotherapy were assessed against usual care practice which promoted combination therapy of statins and fibrates. A simulation model with two time horizons (1 and 20 years) was implemented with a US healthcare provider perspective. With the one year time horizon the ICER was USD 1,020/QALY gained for ATP III guidelines over usual care. Over 20 years, it was estimated that 176 CVEs would be prevented in a sample of 1,000 patients and 0.18 QALYs would be gained but with an increased ICER of USD 50,315/QALY gained. The authors concluded that treatment according to the ATP III guidelines would be cost-effective compared to usual care when treating patients with DM and dyslipideamia.

The cost-effectiveness of two different prescribing criteria for statins in Australia was assessed in a study by Lim et al. 2001 using an economic model. According to the Pharmaceutical Benefits Scheme (PBS)

treatment is initiated based on the level of blood cholesterol with the cut off value for initiation of therapy varying with presence or absence of CV risk factors. The PBS criteria were compared with initiation of treatment depending on a 15 year CV risk assessment. Pravastatin 40mg daily was modeled for eligible patients between the ages of 25 – 85 years. Direct costs of treatment and cost savings from prevention of deaths were considered as cost data. Compared with the 15 year risk assessment, PBS did not accurately identify people at high risk of CVD. Only 61% of people with a higher than 10% risk of CHD for the next 15 years were identified and 11% with a lower than 2.5% risk were also identified as needing treatment according to the PBS criteria. The ICER for treatment according to PBS criteria compared to the 15 year risk assessment criteria was AUD 87,000 – 110,000/life years saved (LYS). It also showed that if the treatment initiation risk level was raised to 32.5% 15 year CV risk, the ICER would improve to AUD 31,000 – 39,000/LYS. Therefore, this study showed that treatment based on the PBS criteria is not likely to be cost-effective compared to the 15 year risk assessment criteria. However, initiating therapy in those at high risk of CVD can improve the cost-effectiveness of PBS.

Another study from the Netherlands showed similar results regarding cost-effectiveness of generic statins targeted at people with a high risk of CVD (Greving et al. 2011). A Markov model was used with a 10 year time horizon to analyze data of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial) to evaluate the cost-effectiveness of low dose statins in the prevention of vascular disease compared to no treatment. For men aged 55 years with a 10% 10 year CV risk, the ICER was EUR 35,000/QALY gained. When the risk level was increased to 25% the ICER value improved to EUR 5,000/QALY gained, demonstrating statin treatment is more cost-effective in patients with a higher risk of CVD.

Main findings:

- Primary prevention with statins is cost-effective compared with no treatment, particularly in patients with a 10 year CV risk of more than 10% (1 study)
- Lipid lowering therapy with statins for primary prevention is more cost-effective if treatment is better targeted at patients with higher risk of CHD, including patients with HT, diabetes mellitus, or smokers in addition to dyslipideamia (5 studies)
- Adherence to ATP III guidelines in the US would be cost-saving if the cost per pill is less than USD 0.11 (1 study). ATP III guidelines promoting monotherapy were more cost-effective when treating patients with diabetes mellitus and dyslipideamia than the usual care involving combination therapy of statins and fibrates (1 study)

14.2.1.3 Aspirin

Two studies assessed the cost-effectiveness of aspirin in primary prevention. An economic model with a lifetime horizon was used to compare the cost-effectiveness of 4 strategies in reducing the incidence of CVEs (Pignone et al. 2006): Aspirin alone, statins alone, combination therapy with aspirin and statins and no therapy. A population of middle-aged men without CVD at 6 levels of 10-year risk for CHD (2.5%, 5%, 7.5%, 10%, 15% and 25%) was modelled. The results showed, for men with a higher than 7.5% 10 year risk, aspirin is more effective and less costly than no treatment. However, the ICER of combination

therapy with statins was USD 56,200/QALY gained compared to treatment with aspirin alone, however this study applied 2003 prices of branded simvastatin and lovastatin rather than the generic equivalents, and consequently the present day cost-effectiveness is likely to be much improved.

The final study assessed the cost-effectiveness of adding asprin to the treatment of HT with felodipine (calcium channel blocker) in patients with a diastolic blood pressure (DBP) of more than 100 mmHg (Jönsson et al. 2003). The data from the HOT (Hypertension Optimal Treatment) study, which was conducted in 15 countries, was applied to the Swedish context. The cost-effectiveness of different target levels for DBP (80, 85, 90 mmHg) was assessed for felodipine with or without aspirin. For the subgroup of patients with diabetes it was cost saving in the base case (ICER of SEK -10,360 per major CVE avoided, 95% confidence interval SEK -78,195 to 75,630) to target a DBP value of 80 mmHg compared with 90mmHg. When aspirin was added to felodipine the cost of avoiding a major CVE was estimated at SEK 162,018, with a 95% confidence interval of SEK 43,220 to SEK 3,260,000.

Main findings:

1. Aspirin was cost-effective in treating patients with more than 7.5% 10 year CV risk compared to no treatment. Combination therapy with statins was studied using on-patent prices, and was consequently inconclusive at current generic prices (1 study)
2. Relatively wide confidence intervals were reported in a study addressing addition of aspirin to felodipine anti-hypertension treatment, as well as different diastolic blood pressure targets (1 study)

14.2.1.4 Obesity Management

Two primary studies assessed the cost-effectiveness of weight reduction in obese individuals. One study by Trueman et al. 2010, assessed the long term cost-effectiveness of a primary care weight management programme "Counterweight" (prescribed eating plan, goal setting, targeted calorie intake, group interventions and if necessary medication) compared with a base case scenario (untreated). Outcome was measured by the improvement in quality of life relative to diabetes, CVD and colon cancer. It showed the mean weight loss of participants in the counterweight programme was 3 kg at 12 months follow up and 2.3kg at 24 months follow up. Participants in the control group gained weight at a rate of 1kg/year. Following the 12 month intervention and a 2 year follow up period (in which the counterweight programme participants are also assumed to gain weight at a background rate of 1kg/year) the counterweight programme was cost saving even with a 55% drop out rate. Consequently weight management using the counterweight programme principles was highly cost-effective at primary care level even when considering the effect on only three diseases.

The second study assessed the cost-effectiveness of delivering nutritional counseling to obese patients at risk of IHD through GPs and dieticians in Denmark (Olsen et al. 2005). The results showed GP counseling was the most cost-effective with an ICER of DKK 8,213/LYG compared with no counseling. The ICER of dietician counseling was DKK 59,987/QALY gained compared with no counseling.

Main findings:

- A weight loss programme in a primary care setting was cost saving in the long term compared to no intervention (1 study)
- Nutritional counseling delivered by GPs is more cost-effective than delivered by dieticians. (1 study)

14.2.1.5 Physical Activity and Dietary Advice

Seven studies in total have assessed the cost-effectiveness of non-pharmacological interventions in primary prevention of CVD including physical activity, dietary measures, counseling techniques and population wide approaches through media.

Two of these studies compared non-pharmacological interventions with statin therapy for primary prevention of CVEs. In Sweden, a RCT was conducted for 18 months to assess the cost-effectiveness of two types of advice; usual and intensive advice given with or without pharmacological treatment (Johannesson et al. 1996). Pharmacological treatment was with Pravastatin. The participants were between 35 – 59 years and had at least one CV risk factor and moderate hyperlipideamia. The target was to achieve a 15% reduction in the total cholesterol level. Usual advice alone had no effect on risk factors, and intensive advice plus drug had no additional effect over usual advice plus drug. Usual advice with pharmacological treatment showed an ICER of USD 61,000/LYG against no treatment. Drug costs in this study were based on the patented price. Although the relative effects of intensive vs. usual advice are independent of this, the overall conclusions regarding advice plus pharmacological treatment may be different at generic prices.

The second study (Prosser et al. 2000) modelled the cost-effectiveness of "Step 1 diet"[1] and statin therapy for primary and secondary prevention of CVEs in patients with different risk profiles according to the age, sex, smoking status, blood pressure, LDL and HDL levels of patients. A societal perspective and a 30 year time horizon was modelled. The ICER for dietary primary prevention compared to no intervention varied between USD 1,900 – 500,000/QALY gained depending on risk sub group characteristics. Statin therapy for primary prevention compared with dietary measures resulted in an ICER of between USD 54,000 – 1,400,000/QALY gained. When considering secondary prevention, statin therapy was always associated with an ICER of less than USD 50,000/QALY gained across all risk groups compared with the both step 1 diet and no intervention. The study found for primary prevention of CVD the "step 1 diet" to be a cost-effective intervention for most risk groups, except for otherwise healthy young women, and statin therapy was not cost effective for young individuals with a low risk. For secondary prevention, statins were cost effective across all subgroups and cost saving in high risk groups compared with the two options. The cost-effectiveness profile of statin therapy requires an update following patent expiry.

One RCT was conducted in Wales to assess the cost-effectiveness of the Wales National Exercise Referral Scheme (NERS) compared to usual care (Murphy et al. 2012). The NERS is a 16-week tailored

[1] The "Step 1 diet" recommends a total calorie intake of less than 500 – 1000 kcal/day to lose 1-2lbs/week, fats to be no more than 30% of the total calorie intake, complex carbohydrates to be 55%, lean proteins 15% and no more than 6g of sodium chloride per day.

programme of exercise including motivational interviewing, goal setting and relapse prevention. The enrolled participants were referred to the programme due to increased CV risk, depression, stress or both CV risk and mental distress. Patients were followed up for 1 year and the intervention was costed from the public payer perspective. The level of physical activity increased in all participants in the intervention group compared with usual care, but the increase was only significant among participants referred due to increased CV risk. The ICER of the NERS group was GBP 12,111/QALY gained compared with usual care. It was further shown if the participants were willing to pay GBP 2 per session the ICER would improve to GBP 9,741/QALY gained. The NERS programme was considered cost-effective in increasing the level of physical activity in patients with an increased CV risk.

Two other economic modeling studies were conducted to assess the cost-effectiveness of jogging and walking. Hatziandreu et al. 1988 used a hypothetical sample of 1,000 35 year old males to predict the cost-effectiveness of jogging in preventing CVEs. Direct and indirect costs associated with exercise, injury and treating CHD were included. The study estimated regular exercise would prevent 78 CVEs and 1,138 QALYs would be gained over the 30 year time horizon. In the base case jogging was associated with an ICER of USD 11,313/QALY gained due in part to the value of time spent exercising. The second study conducted a cost benefit analysis of walking to prevent CHD among a hypothetical cohort of 35 – 74 year old sedentary individuals (Jones & Eaton 1994). They found if at least 10% of adults began regular walking, USD 5.6 billion would be saved annually due to the reduction in relative risk of CHD. If the entire population took up regular walking it would save USD 4.3 billion annually with the cost of time accounted for in those who dislike walking. The economic benefit is more pronounced specially in males of 35 – 64 and in females 55 – 64 years old. If only the volunteers take up regular walking even at a threshold relative risk of 1.15 for CVD it was shown to be economically beneficial. The value of time was an important factor in the cost-effectiveness of physical activity in preventing CHD.

An economic model conducted in Stockholm, Sweden assessed the cost-effectiveness of dietary advice, exercise or a combination of both in reducing CV risk factors (Lindgren et al. 2003). The analysis was performed from a health care provider's and a societal perspective. Dietary advice showed the longest predicted survival. From a societal perspective, the cost-effectiveness of dietary advice remained almost the same even if a declining benefit was shown over time with ICER only varying between SEK 127,065 and 141,555/LYS compared to no intervention. This is due to increased survival being balanced by additional costs of life. But when a health care provider's perspective was considered the ICER of dietary advice compared with no intervention was considerably lower if the intervention effect remained constant (SEK 11,642/LYG) compared with a decline in effect over time (SEK 98,725/LYG). The authors concluded dietary advice is the most cost-effective out of the three options in reducing CV risks. But exercise with an ICER of SEK 180,470/LYG compared with no intervention can be promoted as an alternative cost-effective option in the absence of dietary advice.

The final study assessed the cost-effectiveness of population wide programmes in reducing serum cholesterol levels in the adult population free of CVD in the US (Tosteson et al. 1997). Three community programmes (Stanford five City project, Stanford three community study and North Karelia project) were assessed which included education through media campaigns, direct community programmes and face to face instructions. At a cholesterol lowering benefit of 2% the Stanford five city project with a cost

of USD 4.5 per person showed an ICER of USD 3,200/LYG and the North Karelia project with a cost of USD 16.5 in the first year and USD 8 thereafter showed an ICER of USD 6,100/LYG compared with no intervention. At a higher cholesterol lowering benefit (>2%) programmes costing USD 4.5 per person were estimated to be cost saving. Across the whole population, assuming an intervention even at a cost of USD 16.55 per year per person, if the programme achieves a cholesterol reduction of 2% the interventions would be more cost-effective than medical interventions.

Main findings:

- Intensive advice is not a cost-effective option for primary prevention of IHD when compared with usual advice plus pharmacological treatment. The cost-effectiveness of advice given in combination with pharmacological treatment requires updated analysis following the availability of generic statins (1 study)
- For primary prevention, the “step 1 diet” is a cost-effective intervention for most risk categories except for otherwise healthy young women. Statins were not found to be cost-effective in primary prevention in young low-risk individuals, however these conclusions may change if current generic prices are incorporated.
- Dietary advice was the most cost-effective in reducing CV risks compared to exercise or combination of exercise and diet, however the ICER was almost 10-fold higher if benefits from the dietary intervention were not sustained over time (1 study)
- The 16 week National Exercise Referral Scheme was cost-effective in increasing the level of physical activity compared to usual care in patients with an increased CV risk (1study). Jogging or walking are also cost-effective interventions, but significant costs are accounted for by the opportunity cost of time, which is considered to be lower if individuals undertake these activities voluntarily (2 studies)
- If population based programmes can achieve a cholesterol level reduction of more than 2% they will be cost-effective compared with many medical interventions for CVD (1 study).

14.2.1.6 Smoking

An economic model in the context of Gujarat, India assessed the cost-effectiveness of the “prohibition of smoking in public places rule” compared with a complete ban of smoking in all public areas (Donaldson et al. 2011). The Prohibition rule includes only a partial ban of smoking in public places, allowing separate smoking areas in restaurants and airports and excluding some public places from the smoking ban altogether. Outcomes assessed were gains in life years and reduction of acute myocardial infarctions (AMI), costs were assessed from a societal perspective. After 1 year of implementation a complete ban of smoking in all public places would be cost saving or highly cost-effective compared to the Prohibition rule. In the worst case scenario (with higher cost of implementation and lower effects) a complete ban would cost USD 262/AMI averted and USD 56/LYG.

Main findings:

- In Gujarat, India, a complete smoking ban in all public places would be cost saving or highly cost-effective in preventing CVEs compared with a partial ban of smoking in public places (1 study)

14.2.2 Secondary Prevention

Secondary prevention of CHD is only studied under lipid control and anticoagulation. Evidence on hypertension management comparing Ramipril with placebo was published prior to the Ramipril patent expiry in 2007 and was excluded from the present review (Lamy et al. 2003). No evidence was identified for diabetes management, increasing physical activity, dietary measures, smoking cessation or weight management.

14.2.2.1 Lipid control

Two studies assessed the cost-effectiveness of Simvastatin compared to a placebo in secondary prevention of IHD. One additional study was published prior to the Simvastatin patent expiry and was excluded from the present review (Jönsson et al. 1999).

A Markov model was developed using data from a RCT conducted in 69 hospitals in the UK to assess the cost-effectiveness of Simvastatin 40 mg daily given for the life time compared to a placebo in patients with existing CHD, cerebrovascular diseases, diabetes or HT (Mihaylova et al. 2006). These patients had vascular risks of 12 – 42%. Costs taken into consideration were direct costs due to hospitalization and costs of Simvastatin. When the analysis was conducted for a study population with a CV risk between 12 – 42%, it showed lifetime treatment with generic simvastatin is cost saving compared with placebo in all age and risk categories except in one (>70 year olds with a 12% CV risk which showed an ICER of GBP 80/LYG). When the data was extrapolated beyond the study population to include patients with a lower CV risk and wider age group, treatment with generic simvastatin was cost-effective with an ICER of GBP 450 – 2500/LYG and ICER less than GBP 4,000/QALY gained.

A decision model was used to assess the cost-effectiveness of adding N-3 Poly unsaturated fatty acids (N-3 PUFA) to the usual secondary prevention care of myocardial infarctions (Lamotte et al. 2006). The data was taken from a RCT conducted in 5 countries (Australia, Belgium, Canada, Germany and Poland) for 3.5 years with participation of 59 year olds who recently had a myocardial infarction. The analysis was conducted from a health care provider perspective. The results showed that adding N-3 PUFA to the usual treatment yielded between 0.261 (Poland) and 0.284 (Australia) life years more than the usual regimen at an ICER of between EUR 2,788 (Canada) and EUR 5,097 (Belgium). Addition of N-3 PUFA was cost-effective more than 98% of the time in the 4 countries except Poland where it was 93%.

Main findings:

- Generic Simavastatin given to patients with existing CHD or DM is cost saving if given for a lifetime or highly cost effective or cost saving even in the short term (5 years follow up) when compared with a placebo (1 study)
- Adding N-3 PUFAs to usual secondary prevention is cost effective at approx.. EUR 5,000/LYG or less (1 study)

14.2.2.2 Anticoagulation

A single study was identified addressing anticoagulation therapy with clopidogrel plus aspirin (C+A) vs aspirin alone (A) in patients with established cardiovascular disease, a sub-population of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial. This trial did not find any benefit of clopidogrel in the overall study cohort, consisting of high-risk patients already receiving aspirin monotherapy, but for patients with established cardiovascular (CV) disease, addition of clopidogrel was found to be associated with a 12.5% reduction in CV deaths, myocardial infarction or stroke over 28 months follow-up, although adverse outcomes (severe or moderate bleeding) were also more common in the C+A group. The ICER was estimated at USD 36,343/LYG in an economic analysis performed alongside the trial (Chen et al. 2009)

Main findings:

- In patients with established cardiovascular disease, one economic analysis based on the CHARISMA trial found clopidogrel to be cost-effective when added to aspirin monotherapy, compared with aspirin monotherapy alone, with an ICER of USD 36,343/LYG.

14.3 Evidence gaps in preventive interventions for Ischemic Heart Disease

Observations from published studies

- Studies assessing pharmacological interventions in primary and secondary prevention are diverse in terms of age groups and risk factors included and in terms of comparators, with some studies using placebo/no treatment and others using alternative pharmaceuticals. Consequently no two studies replicated each other's results.
- The availability of up to date cost-effectiveness analysis was further limited by the patent expiry of most statins between 2001 and 2011. Despite currently lower generic costs of statins, new data on real-world effectiveness of these drugs may significantly alter the conclusions of prior cost-effectiveness analyses.
- The comparison of multiple interventions (more than two) in the same study was not common, making it difficult to judge the relative cost-effectiveness of unrelated interventions according to the same standards and methodologies. One study found smoking cessation was more cost-effective than anti-hypertensive treatment, lipid control and dietary modifications (prior to patent expiry of the study drug).
- Sodium reduction was only studied on an aggregate population level, and not as an intervention targeted at individuals.
- Only one study incorporated co-morbidity, studying the cost-effectiveness of lipid management in diabetics.
- Aspirin alone was found to be cost-effective in prevention of cardiovascular events above a certain risk according to a single study, however results from two studies addressing combination of aspirin with a statin or an anti-hypertensive were inconclusive.
- Limited evidence suggests nutrition and weight loss councelling delivered in primary care can be cost-effective or even cost saving. The most extensive study estimated health benefits based on

diabetes, cardiovascular disease and colon cancer, although obesity is likely to have an impact on many other conditions.

- Several positive results are reported from studies assessing cost-effectiveness physical activity and diet interventions. Only one study compared both interventions and found dietary advice was more cost-effective than exercise or a combination. There is some uncertainty regarding the long-term effects of such programs, including adherence to diet and exercise regimens, which can have a significant impact on cost-effectiveness.
- Very limited evidence was identified on smoking cessation interventions in the context of ischemic heart disease.
- The use of aspirin and clopidogrel in secondary prevention was only addressed by a single study, which found addition of clopidogrel to be cost-effective.

Contributor	Comment
Janette Greenhalgh Institute of Psychology Health and Society University of Liverpool UK	Studies using pre-generic treatment costs were excluded. The use of pre-generic costs can be remedied by simple arithmetic if the studies were properly reported (i.e. giving unit costs for each medication). Excluding whole studies risks throwing away large quantities of useful evidence, and possibly biasing findings as a result.

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Health Economic Evidence Analysis: Prevention of Stroke

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15 Prevention of Stroke

15.1 Bibliometrics

The focus of this section is primary prevention of ischemic stroke through the reduction of risk factors. A total of 21 economic studies were identified in the search, of which 9 were excluded from the review as they modelled pharmaceuticals which are now off-patent. All studies were published after 2003. Of the nine reviews identified which were published after 2009, six addressed stroke prevention in atrial fibrillation, and one addressed secondary prevention with antiplatelet therapy. These interventions were discussed in section 4 of this report.

Table 15.1 Bibiliometric data for Prevention of stroke

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Stroke"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Number of studies	
Included in model	12
Reviews	9
Excluded	440
Total	461

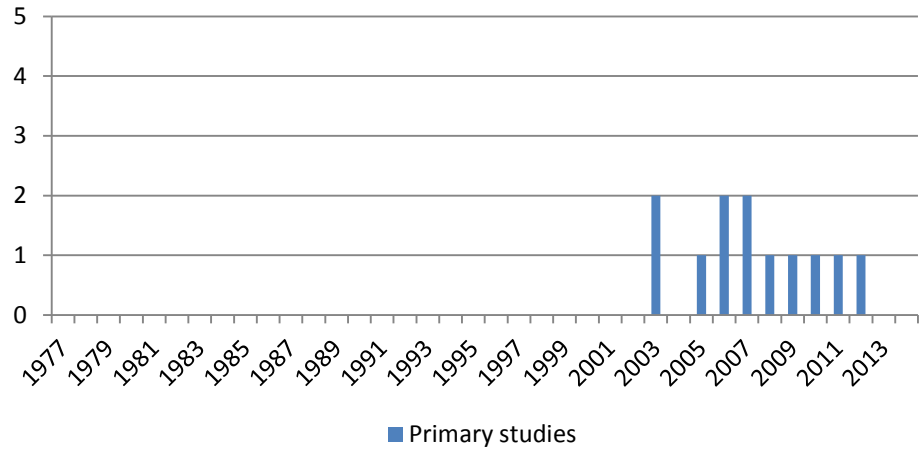

Figure 15.1 Bibliometric data for prevention of stroke by year

15.2 Evidence Analysis

The following section present information gathered from primary evidence. Table 15.2 summarizes the volume of health economic evidence identified according to each prevention strategy.

Table 15.2 Primary health economic evidence for prevention of strokes

Prevention of Stroke	Studies	Reviews
Primary Prevention		
Smoking cessation: Behavioural counseling, pharmacology (bupropion or varenicline), financial incentives	2	0
Hypertension treatment: Sodium reduction, pharmacology, intensive multidisciplinary BP control programmes	4	0
Lipid control: Statin therapy	3	0
Glycemic control: Pharmacology	1	0
Aspirin	2	0

15.2.1 Primary Prevention

15.2.1.1 Smoking Cessation

Two primary studies were identified discussing cost-effectiveness of smoking cessation on reducing the incidence of stroke. Bolin et al., 2009, assessed the cost-effectiveness of Varenicline (a nicotine receptor partial agonist) compared to Nicotine Replacement Therapy (NRT) in four European countries (UK, France, Sweden and Belgium). Analysis was conducted with a national healthcare provider's perspective using a Markov model over a lifetime time horizon. The incidence of four smoking related diseases were assessed: lung cancer, chronic obstructive pulmonary disorder, coronary heart disease and stroke. The number of prevented morbidities per 1,000 smokers attempting to quit ranged from 6.5 to 9.7. Varenicline was cost saving in all countries except in France where an ICER of EUR 2,800/QALY gained was reported.

Another study in Sweden evaluated the cost-effectiveness of smoking cessation using Bupropion (an antidepressant) compared to NRT (Bolin, Lindgren & Willers, 2006). The effect of smoking cessation was assessed for five diseases: chronic obstructive pulmonary disorder, asthma, coronary heart disease, stroke, lung cancer. Bupropion was cost-saving compared with two NRT comparators (nicotine patches and gum) when indirect costs were included, but cost-saving only when compared with gum when only direct costs were considered, in which case the ICER over nicotine patches was EUR 725/QALY.

Main findings:

- Varenicline and bupropion are reported to be cost-saving or very cost-effective interventions for smoking cessation compared with nicotine replacement therapy, considering effects on stroke, lung cancer, chronic obstructive pulmonary disease, coronary heart disease and asthma (two studies)

15.2.1.2 Treatment of Hypertension

The cost-effectiveness of reduction of hypertension (HT) to reduce the incidence of stroke is discussed under the subheadings of sodium reduction in food and pharmacological management.

Sodium reduction in food

The cost-effectiveness of two population strategies to reduce sodium content in food was evaluated in the US (Smith-Spangler et al., 2010): government coordination with food manufacturers to promote voluntary reduction of sodium content in products, and implementation of a sodium tax. A Markov model was implemented with a lifetime horizon and from a societal perspective. Voluntary reduction of sodium content by food manufacturers would lead to a mean reduction of sodium intake by 9.5%, averting 513,885 strokes and 480,350 myocardial infarctions in the population aged 40 – 85 years, resulting in a gain of 2.1 million QALY's and savings of USD 32.1 billion in medical costs. With a sodium tax, a 6% reduction in sodium intake would occur saving USD22.4 billion in medical costs.

Pharmacotherapy

Seven studies assessed the cost-effectiveness of various pharmacotherapy options in controlling HT to reduce cardiovascular events (CVE) including stroke. Four of these seven studies are now outdated due to patent expiry of the study drug and will not be discussed in detail, although central points from these papers will be included for completeness.

Data from the RCT ASCOT-BPLA (Anglo Scandenavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) was applied to a Markov model in the context of the UK and Sweden to estimate the long term cost-effectiveness of treating HT with an Amlodipine (calcium channel blocker) based regimen compared to an Atenolol (beta blocker) based regimen (Lindgren et al., 2008). Patients attending a primary care setting with moderate HT and three or more CV risk factors were modelled. The cost-effectiveness of the Amlodipine based regimen compared to the Atenolol based regimen was EUR 18,965/CVE avoided and EUR 21,875/QALY gained in UK, and EUR 13,210/CVE avoided and EUR 16,856/QALY gained in Sweden. When the price of generic amolodipine was used in the model the cost-effectiveness improved to EUR 7,257/QALY in the UK and EUR 8,372/QALY gained in Sweden. It was concluded that an Amlodipine based regimen was cost-effective compared with an Atenolol based regimen in moderately hypertensive patients with additional CV risk factors in accordance with the willingness to pay (WTP) thresholds applied by both countries.

Two other studies assessed the cost-effectiveness of implementing intensive programmes to control blood pressure (BP) compared with the usual practice. A modelling study from Israel (Yosefy et al., 2003) estimated the cost-effectiveness of scaling up the Israeli BP Control (IBPC) programme. The IBPC programme implemented in primary care achieved BP control in 46.4% of patients compared to 29% in usual care, and improvements were also seen in cholesterol and fasting plasma glucose. Extrapolated to 100 clinics with a total of 14,800 patients IBPC was estimated to save USD 977,993 and add 602 QALYs compared to the usual practice.

The second study conducted in Australia (Cadilhac et al., 2012) assessed the cost-effectiveness of organized BP control programs for the prevention of stroke compared with usual care. Both primary and secondary prevention strategies were assessed in this study. A micro simulation model with a lifetime horizon was run using data derived from two RCTs and costs from a societal perspective were included. In primary prevention, the intervention was most cost-effective when targeted at >75 year olds with an ICER of AUD 11,764/QALY gained compared with usual care. If targeted at patients with a CV risk level of >15% in 55 – 84 year olds the ICER was AUD 18,201/QALY gained. Secondary prevention was more cost-effective with ICER's of AUD 1,811 for any anti-hypertensives and AUD 4,704/QALY for ACE inhibitor plus diuretic.

Cost-effectiveness of four drugs, Ramipril (ACE inhibitor), Candestran (Angiotensin Receptor Blocker), Nebovolol (vasodilating beta 1-adrenoceptor antagonist) and Felodipine (long lasting Calcium Channel Blocker), was assessed in several studies conducted before patent expiry of these drugs. Briefly, Ramipril given to high CV risk patients without heart failure was shown to be cost-effective compared with a placebo (McQueen et al., 2005; Lamy et al., 2003), Candestran given to elderly hypertensive patients was cost-effective compared with usual care (Lundkvist et al., 2005), and a post marketing surveillance study in Germany found Nebivolol to be cost-saving compared with usual care (Kaltwasser, 2005). The cost-effectiveness evidence on combination of Felodipine and aspirin was inconclusive due to wide confidence intervals reported by Jönsson et al. 2003.

Main findings:

- Reducing sodium content in food would save USD 32 billion in healthcare costs if a voluntary reduction of sodium by food manufacturers is achieved or USD 22.4 billion would be saved if a sodium tax is implemented (1 study).
- For moderately hypertensive patients with three or more CV risk factors – An Amlodipine (Calcium Channel Blocker) based regimen is more cost-effective than an Atenolol (Beta blocker) based regimen according to WTP thresholds in UK and Sweden (1 study)
- An Israeli blood pressure control programme was estimated to generate monetary savings and increase QALY's if rolled out on a larger scale (1 study). Organized BP monitoring for the prevention of stroke in Australia was most cost-effective in secondary prevention of stroke but was also considered cost-effective (ICER's of AUD 11,764 – 18,201) in primary prevention for particular patient groups, ie. higher age and with relatively high risk of stroke (1 study)
- Earlier studies prior to patent expiry showed Ramipril (ACE inhibitor), Candestran (Angiotensin Receptor Blocker) and Nebovolol (vasodilating beta 1-adrenoceptor antagonist) to be cost-effective or cost-saving. Although these drugs are now available at generic prices, new effectiveness and safety data may also impact cost-effectiveness evaluations and consequently updated analysis is warranted.

15.2.1.3 Lipid control

Four studies addressed the cost-effectiveness of statin treatment for the prevention of CVEs including stroke. One study was excluded from the present review due to patent expiry of the study drug Atorvastatin in 2011 (Lindgren et al., 2005).

Two studies were conducted in primary care settings in Netherlands. The first study modelled the cost-effectiveness of implementing new guidelines for a reduced threshold of statin prescription compared to the old Dutch guidelines (Kok et al., 2009). The new guidelines were based on assessment of a 10 year CV risk using an adopted version of the Systematic Coronary Risk Evaluation (SCORE)[1], feature a lower threshold of blood cholesterol (4.5 mmol/l) and no maximum age limit for initiating statin therapy. Over a 20 year period the cumulative incidence of stroke was expected to drop by 3.9%, acute myocardial infarction by 3.0% and all-cause mortality by 0.9%. The new guidelines were most cost-effective in the age group 30–69 years with an ICER of EUR 15,000/QALY gained compared with the old guidelines. The highest ICER was seen in the oldest age group (80+) at EUR 32,300/QALY.

The second study from the Netherlands assessed the cost-effectiveness of generic statins targeted at people with a high risk of CVD (Greving et al., 2011). A Markov model was used with a 10 year time horizon to analyze data of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial) to evaluate the cost-effectiveness of low dose statins in the primary prevention of vascular disease compared to no treatment. For men aged 55 years with a 10% 10 year CV risk, the ICER was EUR 35,000/QALY gained. When the risk level was increased to 25% the ICER value improved to EUR 5,000/QALY gained, and at a 5% risk the ICER was EUR 125,000/QALY, demonstrating statin treatment is more cost-effective in patients with a higher risk of CVD.

The final study assessed the cost-effectiveness of statin therapy in secondary prevention of stroke. A high dose (Atorvastatin 80 mg daily) strategy was compared with the usual low dose (Simvastatin 20mg daily) strategy in patients with previous Acute Coronary Syndrome (ACS) or stable Coronary Heart Disease (CHD) (Chan et al., 2007). Evidence from 4 RCTs was incorporated in a Markov model and analyzed over a lifetime horizon from a societal perspective. In ACS patients, the high-dose regimen was estimated to be more effective (QALY gain of 0.35 per patient) than low dose, at an ICER of less than USD 30,000/QALY under a range of model assumptions. In stable CAD patients, the added effectiveness of high dose statins was estimated to be lower (QALY gain of 0.10 per patient), the ICER was more sensitive to model assumptions on statin efficacy and the daily additional cost of the high dose regiment would have to be less than USD 1.70 for the treatment to be cost-effective at a WTP of USD 50,000/QALY.

One other study assessing cost-effectiveness of combination therapy of statins with aspirin (Pignone et al., 2006) is discussed in section 15.2.1.5 below.

Main findings:

[1] Systematic Coronary Risk Evaluation (SCORE): the risk functions depends on sex, age, smoking behavior, blood cholesterol levels and BP level.

- The new Dutch guidelines implemented for primary prevention of CVEs are less cost-effective in older populations, in the worst case EUR 32,300/QALY compared with the old guidelines (1 study).
- In the Netherlands, primary prevention of CVE's with generic statins incurs ICER's of EUR 35,000/QALY for men aged 55 with a 10% 10-year risk, and EUR 5,000 to 125,000/QALY if the 10-year risk is 25% to 5% (1 study).
- Secondary prevention with high dose compared with conventional dose statin is more cost-effective in patients with previous acute coronary syndrome than in patients with stable coronary heart disease (1 study)

15.2.1.4 Glycemic control

One study was identified assessing the cost-effectiveness of glycemic control in diabetics for reducing the incidence of CVEs (Lowey et al., 2007), a prospective observational study in one pharmacy led hospital clinic in Yorkshire, England. Patients with type 2 diabetes mellitus, HT and with or without hyperlipidaemia were recruited, and 4-weekly adjustments were made to antihypertensive treatment as well as hyperlipidaemia treatment if needed. Before and after analysis showed the 10-year risk of coronary heart disease and cerebrovascular accidents was reduced by 11.9% and 9.6% respectively, and the cost per event avoided was GBP 34,708/coronary heart disease avoided and GBP 63,320/cerebrovascular accident avoided.

Main findings:

- Pharmacists led clinics to monitor anti-hypertensive treatment incur costs of GBP 34,708 per coronary heart disease avoided and GBP 63,320 per cerebrovascular event avoided, comparing pre- and post-intervention risks (1 study).

15.2.1.5 Aspirin

Two studies addressed treatment with aspirin in the primary prevention of CVEs. An economic model with a lifetime horizon was used to compare the cost-effectiveness of 4 strategies: aspirin alone, statins alone, combination therapy with aspirin and statins and no therapy for the reduction of CVE incidence (Pignone et al., 2006). For non-smoking, non-hypertensive men aged 45 with a higher than 7.5% 10 year risk, aspirin is more effective and less costly than no treatment, and addition of a statin cost USD 56,200/QALY gained compared with aspirin alone. The results were sensitive to the risk level of CHD, level of adherence to treatment and gastrointestinal bleeding. The statin costs applied (simvastatin, lovastatin) were 2003 originator prices (annual cost of USD 922 for simvastatin and USD 503 for lovastatin) in the base case. Statin costs accounted for more than 70% of the total costs in the combination therapy, and significantly lower ICER's were estimated in the sensitivity analysis when lower statin costs were used. At USD 200/year the ICER would be less than USD 20,000/QALY.

The second study assessed the cost-effectiveness of different targets for blood pressure reduction, and of adding aspirin to the treatment of HT with felodipine (calcium channel blocker) in patients with a diastolic blood pressure (DBP) of more than 100 mmHg (Jönsson, Hansson & Stålhammar, 2003). The data from the HOT (Hypertension Optimal Treatment) study, which was conducted in 15 countries, was

applied to the Swedish context. The cost-effectiveness of target levels 80, 85, 90 mmHg was assessed with or without aspirin. For the subgroup of patients with diabetes it was cost saving in the base case (ICER of SEK -10,360 per major CVE avoided, 95% confidence interval SEK -78,195 to 75,630) to target a DBP value of 80 mmHg compared with 90mmHg. When aspirin was added to felodipine the cost of avoiding a major CVE was estimated at SEK 162,018, with a 95% confidence interval of SEK 43,220 to SEK 3,260,000.

Main findings:

- Aspirin for the primary prevention of CVE's is cost-saving for certain risk profiles, and addition of a generic statin is likely to be cost-effective at <USD20,000/QALY gained, although on-patent statins were not found to be cost-effective in combination therapy (1 study).
- Cost-effectiveness of combination therapy with aspirin and felodipine is unclear due to wide confidence intervals reported.

15.3 Evidence gaps for the prevention of stroke

- Pharmaceutical alternatives to nicotine replacement therapy (including antidepressants and nicotine receptor partial agonists) appear to be cost-saving or very cost-effective when considering the impact on major smoking-related morbidities (stroke, lung cancer, chronic obstructive pulmonary disease, coronary heart disease and asthma)
- Sodium reduction on a population level could avert a significant number of strokes and result in significant savings to healthcare systems, according to a single US study
- The cost-effectiveness of organized blood pressure screening and management may be cost-saving or cost-effective depending on the setting, and whether primary or secondary prevention is considered. Of the limited studies available,
- Earlier studies prior to patent expiry showed Ramipril (ACE inhibitor), Candestran (Angiotensin Receptor Blocker) and Nebovolol (vasodilating beta 1-adrenoceptor antagonist) to be cost-effective or cost-saving in primary prevention of stroke. Although these drugs are now available at generic prices, new effectiveness and safety data may also impact cost-effectiveness evaluations and consequently updated analysis is warranted.
- The cost-effectiveness of primary prevention with statins depends significantly on the target group, ie. age and other risk factors for stroke (2 studies). In secondary prevention, the cost-effectiveness varies according to type of previous/existing illness (1 study)
- Limited evidence was identified for the management of hypertension and lipids in diabetics. One study suggested costs of averting coronary heart disease and cerebrovascular events in this patient group were GBP 34,708-63,320 per event (1 study)
- Aspirin for the primary prevention of cerebrovascular events appears to be cost-saving for certain risk profiles, and adding a generic statin may also be a cost-effective strategy (1 study)

15.4 References:

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Health Economic Evidence Analysis: Prevention of Diabetes

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16 Prevention of Diabetes

16.1 Bibliometrics

A total of 52 studies were mapped to the Diabetes Prevention model (Table 16.1 and Figure 16.1) with majority of studies (83%) published since 2004. Only one literature review was identified which was published in 2011.

Table 16.1 Bibliometric data for Prevention of Diabetes

PubMed/MEDLINE	
Search terms	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Diabetes Mellitus"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt]) NOT ("Diabetes Mellitus, Experimental"[MeSH Terms] NOT "Diabetes, Gestational"[MeSH Terms] NOT "Donohue Syndrome"[MeSH Terms] NOT "Prediabetic State" [MeSH Terms] NOT "Diabetes Complications"[MeSH Terms])
Number of studies	
Included in model	52
Reviews	1
Excluded	1,155
Total	1,208

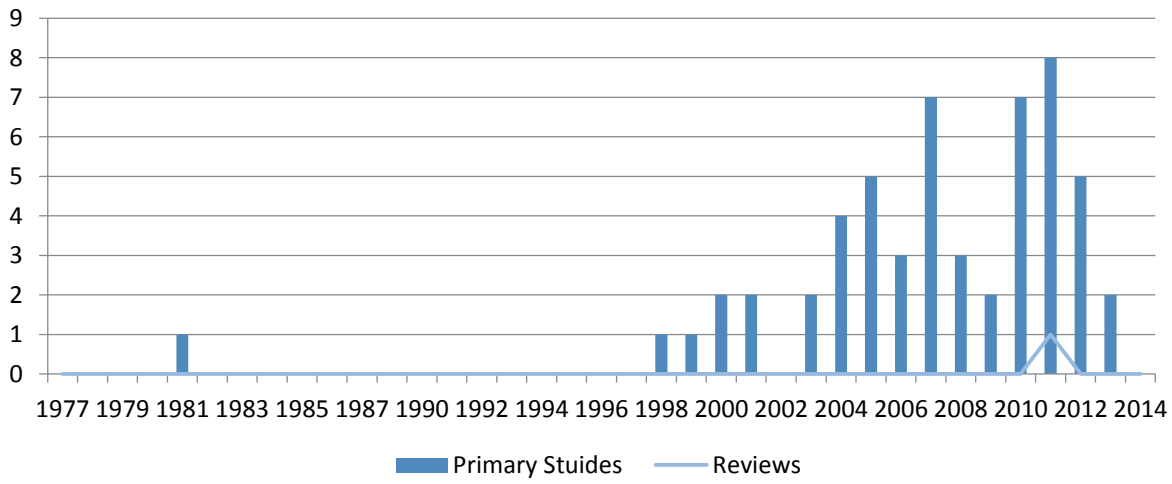

Figure 16.1 Bibliometric data for prevention of diabetes

16.2 Review Coverage

One literature review was identified addressing clinical effectiveness of screening for T2DM and dysglycemia (Echouffo-Tcheugui et al., 2011). The authors also included a sub-heading on cost-effectiveness of diabetes prevention which included an analysis of 32 primary studies. Out of the 32 studies, the present search identified 23. Another five of the studies were included in the section on treatment of diabetes elsewhere in this report.

Table 16.2 Table of reviews for prevention of diabetes and associated treatments

Title and reference	Year	Treatments covered
"Screening for Type 2 Diabetes and Dysglycemia" (Echouffo-Tcheugui et al., 2011)	2011	Primary Prevention: Screening for the detection of dysglycemia followed by LSI or Metformin or both. Screening; Optimal age and the frequency in healthy adults Secondary prevention: Screening to detect hyperglycemia followed by treatment with pharmacotherapy with or without LSI.

16.3 Evidence Analysis

The following sections present information gathered from primary studies. Table 16.3 summarizes the volume of health economic studies and reviews identified according to the level of prevention of Diabetes.

Table 16.3 primary health economic evidence and reviews for the treatment of prevention of diabetes

Prevention of Diabetes	Studies	Reviews
Life Style Interventions LSI vs usual care, LSI vs Phamacotherapy	20	1
Pharmocotherapy	3	0
Screening	27	1

16.3.1 Life style interventions

16.3.1.1 Life Style Interventions vs Usual care

Community based programmes

Four community based programmes have been assessed in four different country settings. A Markov model was used to analyze the effects of '10,000 steps Ghent' programme in Belgium (De Smedt et al., 2012) which promoted walking to reduce sedentary time by the use of pedometers, local media campaigns and physical activity projects. A population of 25 – 75 year olds in good health was modelled over 20 years, only direct costs were included from the payer perspective. The '10,000 steps Ghent' programme increased QALYs by 0.11 and 0.16 per participating female and male, respectively, and reduced total healthcare costs by EUR 427 and 576 compared with no intervention. The programme was consequently considered a dominant intervention.

A model by Smith et al. 2010 was conducted to assess the cost-effectiveness of a modified Diabetes Prevention Programme (mDPP)[1] in USA, Pennsylvania. A Markov model with a 3 year time horizon was used with cost data from a "modified societal perspective" which did not include cost of patient's time. The mDPP reduced the relative risk of developing DM and CVD by 16.2% with an ICER of USD 3,420/QALY gained compared with usual care. At a WTP threshold of USD 20,000/QALY gained mDPP was cost-effective with 78% probability.

The third study (Johansson et al., 2009) assessed a community based programme implemented in three municipalities in Stockholm, Sweden, promoting LSI. Data from a cohort study which followed up the intervention group 10 years following implementation was modelled using a Markov model. The ICER was calculated from a societal perspective comparing the intervention with no intervention. In all three areas, risk factor levels increased during follow-up leading to increased societal costs and QALY losses, although for females the increase was less than in a control group in two of the three municipalities. Among women, the program was thus estimated to lead to net cost-savings including the program costs, while for men worse outcomes were observed at higher costs.

Finally, a Randomized Controlled Trial (RCT) has been established to assess the effect of a DM prevention programme in China (Qiao et al., 2010) including cost-effectiveness outcomes. The planned interventions were health promotion and life style counseling. No results have been reported to date.

LSI targeted at high-risk individuals

Six studies assessed the cost-effectiveness of targeting LSI to high risk individuals. An economic model was conducted in Australia (Colagiuri & Walker 2008) to assess the cost-effectiveness of LSI targeted at individuals newly diagnosed with IGT. The cost per Disability Adjusted Life Year (DALY) saved was calculated using outcome data derived from two other DPP from Finland and US. The cost per DALY saved was AUD 49,713 compared with no intervention. It further showed if the participation rate was increased from 50% to 100% (with additional resources added), the cost/DALY saved would drop to AUD 44,699.

Another study (Lindgren et al., 2007) used a simulation model to predict the cost-effectiveness of an intensive LSI directed at 60+ year olds in Stockholm, Sweden, with IGT compared with no intervention. From a healthcare payer perspective the intervention was cost saving, and from a societal perspective, taking into account increased consumption due to longer survival, it was highly cost-effective with an ICER of EUR 2,363/QALY gained.

In the UK, an economic analysis (Irvine et al., 2011) was performed alongside a clinical trial assessing the effectiveness of a group based education, physiotherapy and peer support intervention to modify the behavior of newly diagnosed IGT and T2DM patients. Mean follow-up was 7 months. Cost-effectiveness of the intervention compared with usual care was GBP 67,184/QALY gained. It was more cost-effective for patients with IGT (GBP 20,620/QALY) and with longer (>4 months) follow up (GBP 17,075/QALY). The authors note significant uncertainty of the estimates resulting from this relatively small trial of 177 participants.

[1] Modified Diabetes Prevention Programme (mDPP) : mDPP differs from DPP by delivering the interventions as group based sessions as opposed to individual based sessions in DPP and 12 sessions in mDPP as opposed to 16 sessions in DPP.

Gagnon et al. (2011) conducted a clinical trial to compare two LSI programmes delivered individually or as a group intervention for participants at high risk of developing T2DM (high BMI plus IGT). In the individually delivered group none of 22 participants developed DM but in the group sessions three out of 26 developed DM. Costs of the interventions were USD 733/year/participant for individual sessions and USD 83/year/participant for group sessions.

A study protocol (Costa et al., 2011) was published for a cohort study conducted in Spain aiming to evaluate the effect of the intensive diabetes prevention programme DE-PLAN (Diabetes in Europe - Prevention using Lifestyle, physical Activity and Nutritional) compared with usual practice in a real life setting. The trial is conducted in 18 primary care settings with the participation of individuals at high risk of developing diabetes according to the Finnish Diabetes Risk Score (FINDRISC) and glucose tolerance. Cost-effectiveness of the intervention is the primary study outcome, and will include direct and indirect costs in cost-effectiveness and –utility estimates.

Another RCT conducted in the Netherlands assessed the effectiveness of implementing a multidisciplinary programme for obese adolescents (Go4it), including cognitive behavioural therapy, education on healthy diet and physical activity, to prevent future development of DM and CVD. A cost-effectiveness analysis from a societal perspective was planned (Hofsteenge et al., 2008). To date only the clinical results are reported (Hofsteenge et al., 2013), showing small beneficial effects of the intervention on health-related quality of life.

Main findings:

- The '10,000 steps Ghent' programme which promoted walking among healthy individuals was cost saving compared to no intervention (1 study), however in other community-based programmes there was an additional cost per QALY gained in preventing diabetes and cardiovascular disease (USD 3,420/QALY, 1 study) or the interventions under study were not particularly effective in reducing risk factors (1 study). Cost-effectiveness of preventive interventions in healthy individuals thus appears to rely on the context and the details of the intervention.
- LSI programmes targeted at individuals with impaired glucose tolerance (high risk of developing DM) ranged from cost-saving to GBP 67,184/QALY. Four studies described interventions targeted at different groups, ie. elderly with IGT, high BMI with IGT, newly diagnosed IGT, and different types of interventions.
- Two clinical trials assessing diabetes prevention in high risk individuals have yet to report economic results. One trial has reported relatively modest clinical outcomes in terms of weight loss.

16.3.1.2 Life Style Interventions vs Pharmacotherapy

Two studies of the same trial (Herman et al., 2012; Diabetes Prevention Programme (DPP) Research Group, 2003) followed up for 3 and 10 years assessed the cost-effectiveness of intensive LSI and Metformin in 3,234 individuals with IGT. The Diabetes Economic data was included from a healthcare provider and a societal perspective. At 10-year follow-up, the ICER for LSI vs placebo from a healthcare (societal) perspective was USD 10,037/QALY (USD 14,365/QALY), and for metformin vs placebo it was cost-saving from both perspectives. LSI vs metformin yielded slightly higher QALY gains at USD 13,420/QALY (USD 42,753/QALY).

Following publication of the 3-year follow-up, a Markov model was used to predict the life time benefits of the DPP (Herman et al., 2005). Healthcare and societal perspectives were used for the analysis. Compared with placebo LSI delayed development of DM by 11 years, while Metformin delayed only by three. The survival of LSI group increased by 0.5 years and by 0.2 in the Metformin group. The ICER of LSI vs placebo intervention from a healthcare provider perspective was USD 1,100/QALY, and for metformin vs placebo was USD 31,300/QALY. From a societal perspective the ICER's were USD 8,800/QALY (LSI) and USD 29,000/QALY (metformin). The authors concluded when considering long term outcomes, intensive LSI would be more cost-effective than Metformin in all age groups. Further, Metformin did not prove cost-effective for people aged over 65.

A study using the Archimedes model assessed the cost-effectiveness of three strategies; the DPP for pre-diabetics, LSI after development of DM, and metformin after the development of DM (Eddy, Schlessinger & Kahn, 2005). These two groups were compared with a high risk group receiving no intervention. The results showed DPP reduced the risk of developing DM in the next 30 years by 72 – 61%, reduced the risk of developing serious complications by 38 – 30% and reduced the risk of dying of a diabetes complication by 13.5 – 11.2%. Metformin only achieved 1/3 of the long term outcomes achieved by LSI. The ICER of LSI compared with no intervention was USD 143,000/QALY gained from a health care providers perspective and USD 62,600/QALY gained from a societal perspective. Delaying implementation of LSI until after the development of DM showed the best value of ICER (USD 24,500/QALY gained). The authors concluded that LSI should be more recommended for high risk patients as it has a bigger effect on reducing morbidity. However, less expensive ways of delivering would be needed to make it more cost-effective or even cost saving over 30 years.

Another three primary studies have been conducted to assess the applicability of the DPP and similar programmes in other country settings. Palmer et al. 2004 used a Markov model to predict the cost-effectiveness of the DPP applied to Australia, France, Germany, Switzerland and the UK. A life time horizon was used and the economic analysis was undertaken from a third party payer perspective using only the direct medical costs of each country. The results showed LSI increased the non-discounted life expectancy by 0.22 years and Metformin by 0.11 years compared with control. Both interventions were associated with cost savings in all countries except the UK. The ICER of LSI was EUR 6,381/life year gained (LYG) and of Metformin EUR 5,400/LYG compared with control. A sub group analysis further showed Metformin to be more cost-effective than LSI in younger and more obese patients.

A decision analytical model was used by Icks et al. 2007 with a 3 year time horizon to assess the real world cost-effectiveness of the DPP in the context of routine healthcare setting in Germany using population based data. People aged 60 – 74 with high BMI and IGT were modelled, and cost data was analyzed both from a statutory health insurance (SHI) perspective and a societal perspective. Out of the 72,435 participants modelled, without an intervention 14,908 would develop DM within the following three years. With LSI, 184 cases and with Metformin 42 cases would be prevented. The ICER of LSI compared with no intervention was EUR 4,664 (EUR 27,015) per case prevented from the health insurance (societal) perspective. LSI was more cost-effective than metformin.

A three year RCT conducted in India assessed the cost-effectiveness of an Indian DPP (Ramachandran et al., 2007). Interventions were LSI and Metformin given to participants with IGT. The cost analysis was performed from a healthcare provider perspective and included only direct costs. They found the number of participants needed to be treated to prevent one case of diabetes

was 6.4 with LSI, 6.9 with Metformin and 6.5 with LSI and Metformin combined. The cost to prevent one case was USD 1,052, 1,095 and 1,359 respectively for LSI, Metformin and LSI and Metformin combined.

One RCT protocol was published for an Indian study assessing the effectiveness and cost-effectiveness of a community LSI programme (Weber et al., 2012) for patients with IGT. The interventions include LSI group classes conducted by trained professional and treatment with Metformin if needed. A cost effective analysis is planned to be conducted alongside the trial.

LSI compared with alternative pharmaceutical interventions

Two studies (Caro et al., 2004; Bertram et al., 2010) assessed the cost-effectiveness of LSI compared with pharmacotherapy options other than metformin in different country settings. Caro et al. used an economic model to assess the cost-effectiveness of Acarbose, Metformin and LSI compared with each other and with no treatment in patients with IGT in the Canadian context. A health care provider's perspective was taken. Out of the 1,000 patients, with no intervention 542 would develop DM. With LSI, Metformin and Acarbose treatments 117, 52 and 74 cases would be prevented. Implementation costs of LSI were higher than acarbose or metformin. Compared with no treatment, both metformin and acarbose were dominant, while LSI incurred USD 749/LYG. The highest ICER reported was for LSI compared with acarbose, which was USD 9,988/LYG, followed by LSI compared with metformin at USD 7,252/LYG. While pharmaceutical interventions appeared most cost-effective, the authors noted that lifestyle changes, if maintained, led to the greatest health benefit at reasonable incremental cost.

Bertram et al. (2010) used a micro simulation model to assess cost-effectiveness of a screening programme followed by LSI, Metformin, Acarbose or Orlistat compared with no intervention offered to pre-diabetics in Australia. A life time horizon was applied and cost data were analyzed from a healthcare provider perspective. The study showed LSI and Metformin to be the most cost-effective interventions with ICERs of AUD 22,500/DALY averted and AUD 21,500/DALY averted, respectively, although combining the two options was not found to be cost-effective.

Main findings:

- LSI and Metformin were both cost-effective interventions in prevention of DM compared with controls (7 studies). Relative to LSI, metformin (and acarbose) tended to be more cost-effective or dominant, while LSI tended to yield higher overall health benefits but at additional cost. In one study looking at real-world cost-effectiveness, LSI was found to be more cost-effective than metformin.
- LSI and metformin were more cost-effective interventions than acarbose or orlistat (1 study)

16.3.2 Pharmacotherapy

Studies discussing the cost-effectiveness of metformin compared with lifestyle interventions (LSI) were discussed in the previous section. Another two studies discussing the cost-effectiveness of two other drugs in preventing DM compared with a placebo are discussed here: One study assessed the cost-effectiveness of Acarbose (Quilici et al. 2005) while one study assessed cost-effectiveness of Sibutramine (Ara & Brennan, 2007).

Quilici et al. 2005 assessed the cost-effectiveness of Acarbose compared with placebo in the treatment of impaired glucose tolerance (IGT) using data from the STOP-NIDDM (The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial in Sweden. The analysis was undertaken for the duration of the trial period (3.3 years) using only direct healthcare costs. The cost per patient free of DM over the 40 months of the study was SEK 28,009 for the total study population, but only SEK 7,662 for patients at high risk of DM. For patients at high risk of coronary heart disease (CHD) or combined risk of CHD and DM, acarbose was dominant.

Sibutramine plus diet and lifestyle advice was compared with diet and lifestyle advice given in primary care for weight loss in obese patients across four countries: Finland, Germany, Switzerland and UK (Ara & Brennan, 2007). The model quantifies benefit as weight loss and reduced incidence of coronary heart disease and diabetes. A healthcare provider perspective was adopted using direct costs only. When including all benefits, the ICER's ranged from EUR 10,700/QALY in Switzerland to EUR 13,700/QALY in Germany. However, due to increased adverse effects the drug was withdrawn from the market in October 2010 (Kang & Park, 2012).

Main findings:

- Acarbose was a cost-effective treatment compared with placebo in patients with IGT (1 study).

16.3.3 Screening

Screening followed by interventions

Four studies assessed the cost-effectiveness of screening when followed by an intervention.

Gillies et al. (2008) assessed three screening strategies: one time screening for Type 2 diabetes mellitus (T2DM); screening for impaired glucose tolerance (IGT) and T2DM followed by lifestyle intervention (LSI) in those with IGT; and screening followed by metformin for those with IGT. All scenarios were compared with no screening. A population of 45 year olds with above average risk of DM was modeled over a 50-year time horizon. Screening for IGT and T2DM followed by LSI was the most cost-effective option with an ICER of GBP 6,242/QALY gained, while screening for T2DM alone was the least cost-effective option with an ICER of GBP 14,150/QALY gained compared with no screening. At a WTP threshold of GBP 20,000 the possibility of interventions being cost-effective was 49% for screening alone, 93% for screening followed by LSI, and 85% for screening followed by Metformin. The authors conclude that screening for T2DM or IGT is more cost-effective than screening for T2DM alone in high risk populations.

Similarly, Schaufler and Wolff (2010) used a Markov Monte Carlo microsimulation model to compare screening plus either LSI or treatment with metformin, to current BSC (i.e. diagnosis of T2DM in routine clinical care or after the occurrence of the first clinical symptoms) from the perspective of the German SHI. Both follow up interventions were found to be highly cost-effective with an ICER of EUR 562/QALY gained in the LSI group and EUR 325/QALY gained in the metformin group compared with BSC. Schaufler and Wolff (2010) conclude that early detection and disease prevention may be cost-effective in the long term, however, additional political measures are necessary to support implementation, as the German SHI lacks the necessary long-term incentives to support preventive screening programmes.

Hoerger et al.(2007) aimed to estimate the cost-effectiveness of two pre-diabetes screening overweight and obese individuals for pre-diabetes and then modifying their lifestyle based on the Diabetes Prevention Program (DPP). A Markov simulation model was used to estimate disease progression, costs, and quality of life, and cost-effectiveness was evaluated from a health care system perspective. The first strategy offered LSI to confirmed cases following positive results in both IGT and impaired fasting glucose (IFT). The second strategy offered LSI to those who tested positive with either IGT, IFT or both Both strategies were then compared with a program of no screening. The results showed an ICER of USD 8,181/QALY gained with strategy 1 and USD 9,511/QALY gained with strategy two when compared with no screening. It also showed strategy 1 would be cost-saving if LSI is offered as a group intervention as opposed to an individual intervention. Hoerger et al. (2007 concluded that screening for pre-diabetes in the overweight and obese U.S. population followed by the DPP lifestyle intervention has a relatively attractive cost-effectiveness ratio

The ADDITION (The Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care) study, a RCT conducted in the UK, Denmark and the Netherlands evaluated the effectiveness of a stepwise population screening programme to detect T2DM in reducing all-cause mortality. A high risk group was selected and screened using three strategies; screening followed by routine care, screening followed by intensive multifactorial treatment and no screening. Though the trial protocol (Echouffo-Tcheugui et al., 2009) included a cost-effectiveness evaluation the economic analysis has not yet been reported (Simmons et al., 2012). The clinical outcome data reported that screening is not associated with all cause or diabetes related mortality within the 10-year follow up period. One RCT protocol (Lauritzen et al., 2000) with a five year follow up in three European countries had planned to assess the effect of screening for T2DM followed by two treatment strategies; the conventional treatment and an intense multifactorial treatment. The outcomes to be assessed were level of mortality, macro vascular and micro vascular complications and a cost-effective analysis. The result of the study is not yet published.

Main findings:

1. Screening followed by LSI or metformin for positive cases is more cost-effective than no screening. LSI was the most cost-effective option out of the two interventions (2 studies).
2. Following up with LSI in pre-diabetics among obese individuals is more cost-effective than no screening. Identifying positive cases either with two positive results from both IGT and IFT (strategy 1) or with one positive result from either IGT or IFT or both (strategy 2) is cost-effective.

Types of screening tests

Six studies were identified that assessed the cost effectiveness of different screening tests and screening strategies, three of which aimed to find the most cost-effective test.

Shirasaya et al.(1999) assessed the most cost-effectiveness of screening tests for DM and IGT without fasting. The objectives of this study were (1) to elucidate the efficacy of 1,5-anhydroglucitol (1,5-AG), glycosylated hemoglobin, and fructosamine (FRA) as screening tests for non-insulin-dependent diabetes mellitus (NIDDM) or for impaired glucose tolerance (IGT) and (2) to perform an economic evaluation for each indicator using only the cost of tests from a healthcare perspective. They found that 1,5 AG detected the most number of cases, though FRA was the most cost-effective.

Zhang et al. (2003) conducted an analysis in the US using survey data to identify the most cost-effective strategy among oral glucose tolerance test (OGTT), a fasting plasma glucose (FPG) test, an HbA(1c) test, a capillary blood glucose (CBG) test, and a risk assessment questionnaire to detect pre-diabetes. A health care provider's and societal perspective were used. OGTT was found to be the most cost-effective test, followed by the FPG test, while HbA1C was the most expensive test. The cost per case for screening in general ranged from USD 176 – 236 from a health care providers perspective and USD 247 – 332 from a societal perspective.

Three studies assessed the cost-effectiveness of stratifying individuals before offering confirmatory investigations. A study conducted by Sullivan et al. (2011) in the US used a Markov model to compare the costs and benefits of two approaches for identifying those at high risk of developing type 2 diabetes for entry into a DPP. The two methods tested were; IFG alone and IFG+ pre Diabetic Risk Score (pDRS). pDRS was used to further stratify individuals who recieved a positive result following IFG. The markov model integrated direct medical costs over a 10-year time horizon and was analyzed from a US payer's perspective. Considering the number needed to treat to prevent one case of DM, IFG detected more cases (39) than the IFG+ pDRS (15) method. At 5 years, the number needed to treat (NNT) in the IFG-only approach was 39 patients to prevent one case of diabetes compared to an NNT of 15 in the IFG + DRS approach. When compared to IFG alone, the IFG + DRS approach results in an ICER of $17,100/QALY gained at 5 years and would become cost saving in 10 years. In contrast and as compared to no stratification, the IFG-only approach would produce an ICER of $235,500/QALY gained at 5 years and $94,600/QALY gained at 10 years. The authors concluded that the cost-effectiveness of diabetes prevention can be improved by better identification of patients at highest risk for diabetes using the DRS.

The second study that stratified individuals before offering confirmatory investigations was conducted in Australia by Chen et al. (2011). This study tested four strategies to screen for DM that incorporated various combinations of cut-points of fasting plasma glucose, the non-invasive Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK1) and a modified version of the tool incorporating fasting plasma glucose (AUSDRISK2). Sensitivity, specificity, positive predictive value, screening costs per case of incident or prevalent undiagnosed diabetes identified and intervention costs per case of diabetes prevented or reverted were compared. Chen et al. (2011) used a healthcare provider's perspective, and found that use of the non-invasive AUSDRISK1, followed by AUSDRISK2 in those found to be at increased risk on AUSDRISK1, had the highest sensitivity (80.3%; 95% confidence interval 76.6-84.1%), specificity (78.1%; 95% confidence interval 76.9-79.2%) and positive predictive value (22.3%; 95% confidence interval 20.2-24.4%) for identifying people with either prevalent undiagnosed diabetes or future incident diabetes. It required the fewest people (24.1%; 95% confidence interval 23.0-25.2%) to enter lifestyle modification programmes, and also had the lowest intervention costs and combined costs of running screening and intervention programmes per case of diabetes prevented or reverted. The lowest cost per case prevented was with the AUSDRISK 2 strategy (AUD 1,050/case prevented) and the highest cost per case prevented was when all were screened with FPG without stratifying using AUSDRISK 1 (AUD 1,350/case prevented). The study concluded when risks are more stratified it maximizes the cost-effectiveness of screening.

The third study was conducted in Germany using data from a survey (Icks et al., 2004). Four strategies of screening (FPG only, OGTT only, IFT followed by OGTT and HbA1C followed by OGTT) were assed with and without risk stratification based on family history of DM, HT or high blood

triglyceride levels. A decision analytic model with a one-year time horizon was used, taking both a third party payer's and a societal perspective. Icks et al. (2004) found that OGTTs (EUR 4.90 per patient) yielded the lowest costs from the perspective of the statutory health insurance and fasting glucose + OGTT (EUR 10.85) from the societal perspective. HbA1c + OGTT was the most expensive (EUR 21.44 and EUR 31.77) but also the most effective (54% detected cases). ICERs, compared with the next less effective strategies, were EUR 771 from the statutory health insurance and EUR 831 from the societal perspective. The authors concluded that the most effective screening strategy was HbA1c + OGTT due to it's high level of participation. However, costs were lower when screening with fasting glucose tests + OGTT or OGTT alone, and therefore, the most favorable strategy depends on whether the goal is to identify a high number of cases or to incur lower costs at reasonable effectiveness.

Finally, Kahn et al. (2010) aimed to identify the optimal age to start screening and the frequency of screening in healthy adults. An Archimedes model was used to compare eight simulated screening strategies for type 2 diabetes with a no-screening control strategy using a 50-year time horizon. The study showed all the screening strategies reduced DM related micro vascular complications. Five of the eight strategies showed an ICER less than USD 10,500/QALY gained. Screening for DM during the clinic visit for HT management in hypertensive patients was the most cost-effective (ICER USD 6,287/QALY gained for yearly screening and USD 6,490/QALY gained for 5 yearly screening). Screening strategies that started between 30 – 45 years and repeated every 3-5 years were all cost-effective. The maximum screening strategy which starts screening at 30 years and repeated every 6 months was the least cost-effective (ICER USD 40,778/QALY gained).

Main findings:

- In selecting tests, HbA1C was the least cost-effective for screening purposes.
    - Considering tests without fasting: Fructoseamine (FRA) was the most cost-effective to detect IGT and DM in Japan (1 study) and 50 g oral glucose challenge test followed by a 1 hour plasma glucose test to be the most cost-effective to screen for IGT in US (1 study).
    - Considering tests requiring fasting: OGTT was found to be the most cost-effective to detect IGT in US (1 study).
- Having better stratification methods to identify high risk patients to screen for pre-diabetes makes a screening programme more cost-effective than screening only with a plasma glucose tests (2 studies).
- When screening with an FPG test, screening individuals aged 30 – 45 years with a frequency of 3 – 5 years is more cost-effective than no screening (1 study).

Targeted screening strategies

Two studies were conducted in the US to assess the effectiveness of targeted screening for T2DM in high risk patients. Hoerger et al., 2004 used a Markov model to analyze the cost-effectiveness of two screening strategies: universal screening or targeted to people with hypertension. Both strategies were compared with no screening. Targeted screening of hypertensive patients was more cost-effective than universal screening at all ages when compared with no screening. At age 55 the ICER was USD 34,375/QALY for targeted compared to no screening. The ICER for universal screening compared to targeted screening was USD 360,966/QALY gained. Screening was also more cost-effective in older than in younger populations.

The second study, a trial conducted in the US, Minnesota, assessed screening of high risk patients with evidence of dyslipidemia and hypertension (O'Connor et al. 2001). Out of the 469 patients who were eligible for screening only 44% initiated diabetic screening and 38% (176) completed it. Five new patients were identified as having T2DM resulting in a rate of 1 new case per 40 high risk patients screened. The cost of screening was USD 4,064/case identified. The authors noted that costs were high and uptake of screening was low but could possibly be improved with one step screening methods.

Main findings:

- Screening targeted to patients with hypertension or dyslipidemia is more cost-effective than universal screening (two studies). The marginal benefit of universal screening is relatively low and may cost as much as USD 360,966/QALY (1 study).

Screening for diabetes in healthy individuals

Four studies were found that assessed the cost-effectiveness of different screening strategies for non-targeted populations.

Johnson, Tabaei, & Herman, 2005 conducted an analysis in the US to determine optimum parameters for screening. Economic modeling was performed with a 15 year time horizon to assess the cost-effectiveness of different thresholds for Random Plasma Glucose (RPG), and RPG combined with a multivariate equation including age, sex, BMI, etc.. The study found screening with RPG at three year intervals using a cut off value of 130mg/dl was the most cost effective. The cost was USD 275/true positive case which increased to USD 1,745/true positive with population screening.

In the US, a Monte Carlo simulation was performed over a lifetime time horizon to assess the cost-effectiveness of one time opportunistic screening compared to usual practice (The CDC Diabetes Cost-effectiveness Group, 1998). A single payer perspective was adopted. An ICER of USD 56,649/QALY gained for all persons over 25 years was estimated, though screening was more cost-effective in younger people and African-American populations.

A Taiwan study (Chen, Yen & Tung, 2001) described a strategy for mass screening with 2 and 5 year intervals compared with the routine practice (testing when symptomatic). The 5 yearly screening was slightly more cost-effective (USD17,113/QALY) than with 2 yearly screening (USD 17,833/QALY gained) compared with usual screening practice in Taiwan. The cost-effectiveness of screening deteriorated with increasing age. When considering screening every 5 years ICER was USD 9,193/QALY gained in 30 – 39 age group and USD 36,467/QALY gained in the 70+ age group.

The cost-effectiveness of community screening among Medicare beneficiaries was estimated with a Monte Carlo simulation model (Lee et al., 2000). Out of 826 screened 32 new cases were diagnosed. The cost of screening per diabetic identified (USD 4,850) was more than the cost saved from preventing complications (USD 378). This resulted in an average cost of USD 4,471/diabetic case identified.

Main findings:

- Adopting appropriate parameters for diabetes screening may improve the cost-effectiveness significantly compared with universal screening. In general, cost-effectiveness ratios vary significantly according to the target population screened – eg. there was a large difference reported for screening in the 30-39 age group (USD 9,193/QALY) compared with the 70+ age group (USD 36,467/QALY) in one study.
- Two studies addressing the question of age found screening to be more cost-effective in younger age groups.

Screening for complications

Two studies assessed the cost-effectiveness of screening for complications in patients with DM.

The cost-effectiveness of a health check strategy to detect and manage vascular disease across six European countries was studied using the Archimedes model (Schuetz et al., 2013). Healthy individuals aged 40-75 were modelled. Seven health check strategies consisting of assessments for diabetes, hypertension, lipids and smoking were compared for each country. The effects of each strategy on incidence of T2DM, major adverse cardiovascular events (MACE), microvascular complications, quality of life and costs were estimated and compared with usual care. Compared with usual care, the incidence of MACE and diabetes related microvascular complications was reduced (6-17 events and 5-11 events per 1,000 screened, respectively) and discounted QALY's were increased by 31-59 over 30 years in all countries. The ICER ranged from EUR 14,903 (France) to cost-saving (Poland). Cost-effectiveness was further improved by offering checks only to high-risk individuals.

Diamond, Kaul, & Shah, (2007) compared cost-effectiveness of Myocardial Perfusion Scintigraphy (MPS) to screen for atherosclerotic events in asymptomatic T2DM patients. They compared two strategies: test and treat positive cases with statins; or unconditional statin treatment without testing for all. Both strategies were compared with no treatment. The test+treat strategy cost USD 15,224/LYG compared with no treatment, whereas universal treatment cost USD 9,249/LYG. These ratios were based on statin prices of USD2 per day in 2006.

Main findings:

- A comprehensive health check strategy for healthy individuals with assessments for diabetes, hypertension, lipids and smoking status was cost-effective across seven countries, ranging from cost-saving to EUR 14,903. Cost-effectiveness was further improved by targeting high-risk populations.
- Universal statin treatment may be more cost-effective than screening followed by treatment for atherosclerotic events in asymptomatic T2DM patients.

16.4 Priorities for research

Contributor	Comment
Richard Glassock Emeritus professor of medicine, University of California at Los Angeles	There is limited economic evidence of favorable cost-benefit for identification of pre-diabetes in otherwise healthy community living adults

16.5 References

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I. APPENDIX: LIST OF CONDITIONS INCLUDED IN "OTHER MUSCULOSKELETAL DISORDER" CATEGORY

ICD10	Description	Category
M00	Pyogenic arthritis	Arthropathies
M01	Direct infections of joint in infectious and parasitic diseases classified elsewhere	Arthropathies
M02	Reactive arthropathies	Arthropathies
M08	Juvenile arthritis	Arthropathies
M11	Other crystal arthropathies	Arthropathies
M12	Other specific arthropathies	Arthropathies
M13	Other arthritis	Arthropathies
M20	Acquired deformities of fingers and toes	Arthropathies
M21	Other acquired deformities of limbs	Arthropathies
M22	Disorders of patella	Arthropathies
M23	Internal derangement of knee	Arthropathies
M24	Other specific joint derangements	Arthropathies
M25	Other joint disorders, not elsewhere classified	Arthropathies
M30	Polyarteritis nodosa and related conditions	Systemic connective tissue disorders
M31	Other necrotizing vasculopathies	Systemic connective tissue disorders
M32	Systemic lupus erythematosus	Systemic connective tissue disorders
M33	Dermatopolymyositis	Systemic connective tissue disorders
M34	Systemic sclerosis	Systemic connective tissue disorders
M35	Other systemic involvement of connective tissue	Systemic connective tissue disorders
M40	Kyphosis and lordosis	Dorsopathies
M41	Scoliosis	Dorsopathies
M42	Spinal osteochondrosis	Dorsopathies
M43	Other deforming dorsopathies	Dorsopathies
M44	n/a	Dorsopathies
M45	Ankylosing spondylitis	Dorsopathies
M46	Other inflammatory spondylopathies	Dorsopathies
M48	Other spondylopathies	Dorsopathies
M60	Myositis	Soft tissue disorders
M61	Calcification and ossification of muscle	Soft tissue disorders
M62	Other disorders of muscle	Soft tissue disorders
M65	Synovitis and tenosynovitis	Soft tissue disorders

M66	Spontaneous rupture of synovium and tendon	Soft tissue disorders
M67	Other disorders of synovium and tendon	Soft tissue disorders
M68	Disorders of synovium and tendon in diseases classified elsewhere	Soft tissue disorders
M69	n/a	Soft tissue disorders
M70	Soft tissue disorders related to use, overuse and pressure	Soft tissue disorders
M71	Other bursopathies	Soft tissue disorders
M72	Fibroblastic disorders	Soft tissue disorders
M75	Shoulder lesions	Soft tissue disorders
M76	Enthesopathies of lower limb, excluding foot	Soft tissue disorders
M77	Other enthesopathies	Soft tissue disorders
M78	n/a	Soft tissue disorders
M79	Other soft tissue disorders, not elsewhere classified	Soft tissue disorders
M80	Osteoporosis with pathological fracture	Osteopathies and chondropathies
M81	Osteoporosis without pathological fracture	Osteopathies and chondropathies
M82	Osteoporosis in diseases classified elsewhere	Osteopathies and chondropathies
M83	Adult osteomalacia	Osteopathies and chondropathies
M84	Disorders of continuity of bone	Osteopathies and chondropathies
M85	Other disorders of bone density and structure	Osteopathies and chondropathies
M87	Osteonecrosis	Osteopathies and chondropathies
M88	Paget disease of bone [osteitis deformans]	Osteopathies and chondropathies
M89	Other disorders of bone	Osteopathies and chondropathies
M90	Osteopathies in diseases classified elsewhere	Osteopathies and chondropathies
M91	Juvenile osteochondrosis of hip and pelvis	Osteopathies and chondropathies
M92	Other juvenile osteochondrosis	Osteopathies and chondropathies
M93	Other osteochondropathies	Osteopathies and chondropathies
M94	Other disorders of cartilage	Osteopathies and chondropathies
M95	Other acquired deformities of musculoskeletal system and connective tissue	Other disorders of the musculoskeletal system and connective tissue
M96	Postprocedural musculoskeletal disorders, not elsewhere classified	Other disorders of the musculoskeletal system and connective tissue

M97	n/a	Other disorders of the musculoskeletal system and connective tissue
M98	n/a	Other disorders of the musculoskeletal system and connective tissue
M99	Biomechanical lesions, not elsewhere classified	Other disorders of the musculoskeletal system and connective tissue

Source: (Lozano et al., 2012) web appendix table 3
http://download.thelancet.com/mmcs/journals/lancet/PIIS0140673612617280/mmc1.pdf?id=iaa6E6LvL6SPW8rI26sNu

II. APPENDIX: CLINICAL MANAGEMENT MODELS

Clinical management models for the present review were based on clinical guidance and expert opinion from UpToDate (Wolters Kluwer). Relevant references for each clinical model are given below.

A. ISCHEMIC HEART DISEASE

Donald Cutlip, MD. (2014). Management of left main coronary artery disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
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Judith S Hochman, MD, Alex Reyentovich, MD. (2014). Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA..
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B. LOW BACK PAIN

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Gwendolyn Sowa, MD, PhD, Anthony Delitto, PhD, PT, FAPTA. (2014). Exercise-based therapy for low back pain. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
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C. STROKE

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Brett L Cucchiara, MD. (2014). Intraventricular hemorrhage. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Guy Rordorf, MD, Colin McDonald, MD (2014). Spontaneous intracerebral hemorrhage: Treatment and prognosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Helen Hoenig, MD, MPH, Patrick M Kortebein, MD. (2014). Overview of geriatric rehabilitation: Program components and settings for rehabilitation. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
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D. MAJOR DEPRESSIVE DISORDER

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E. LUNG CANCER

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David E Midthun, MD. (2014). Overview of the initial evaluation, treatment and prognosis of lung cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Elizabeth H Baldini, MD, MPH, Gregory P Kalemkerian, MD. (2014). Limited stage small cell lung cancer: Initial management. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Elizabeth H Baldini, MD, MPH. (2014). Prophylactic cranial irradiation for patients with small cell lung cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Howard J West, MD, Steven E Schild, MD, Eric Vallières, MD, FRCSC. (2014). Management of stage I and stage II non-small cell lung cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
Karen Kelly, MD. (2014). Extensive stage small cell lung cancer: Initial management. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
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F. FALLS

Anne C Gill, DrPH, RN, MS, Nancy R Kelly, MD, MPH. (2014).
Douglas P Kiel, MD, MPH. (2014). Falls in older persons: Risk factors and patient evaluation. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.

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Sarah Berry, MD, Douglas P Kiel, MD, MPH. (2014). Falls: Prevention in nursing care facilities and the hospital setting. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.

G. CHRONIC OBSTRUCTIVE PULMONARY DISORDER

James K Stoller, MD, MS. (2014). Management of exacerbations of chronic obstructive pulmonary disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
John G Bartlett, MD, Sanjay Sethi, MD (2014). Management of infection in exacerbations of chronic obstructive pulmonary disease. In D.S. Basow (Ed.), UpToDate, Waltham, MA.
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J. NECK PAIN

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III. APPENDIX: SEARCH TERMS

Disease	MeSH	MeSH sub-tree (*excluded terms*)	Related or excluded terms	Full term

Ischemic heart disease	"Myocardial Ischemia"[MeSH Terms]	Myocardial Ischemia [C14.280.647]
		- Acute Coronary Syndrome [C14.280.647.124]
		- Angina Pectoris [C14.280.647.187]
		  ○ Acute Coronary Syndrome [C14.280.647.187.074]
		  ○ Angina, Unstable [C14.280.647.187.150]+
		  ○ Angina, Stable [C14.280.647.187.362]
		  ○ Microvascular Angina [C14.280.647.187.575]
		- Coronary Disease [C14.280.647.250]+
		- Myocardial Infarction [C14.280.647.500] +
		- Myocardial Reperfusion Injury [C14.280.647.625]
		- Myocardial Stunning [C14.280.647.750]
			n/a	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Myocardial Ischemia"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])

Low back pain	"Low Back Pain"[MeSH Terms]	Low Back Pain [C10.597.617.232.400]	n/a	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Low Back Pain"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Stroke	"Stroke"[MeSH Terms]	Stroke [C10.228.140.300.775] - Brain Infarction	n/a	("cost-benefit analysis"[MeSH Terms] OR "Economics,

Disease	MeSH	MeSH sub-tree (*excluded terms*)	Related or excluded terms	Full term
		[C10.228.140.300.775.200] + - Stroke, Lacunar [C10.228.140.300.775.600]		Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Stroke"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Major depressive disorder	"Depressive Disorder, Major"[MeSH Terms]	Depressive Disorder, Major [F03.600.300.375]	"Depressive Disorder, Treatment-Resistant"[MeSH Terms] [F03.600.300.387]	("Depressive Disorder, Major"[MeSH Terms] OR "Depressive Disorder, Treatment-Resistant"[MeSH Terms]) ("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Lung cancer	"Lung Neoplasms"[MeSH Terms]	Lung Neoplasms [C04.588.894.797.520] - Bronchial Neoplasms [C04.588.894.797.520.109] o Carcinoma, Bronchogenic [C04.588.894.797.520.109.220] ▪ Carcinoma, Non-Small-Cell Lung [C04.588.894.797.520.109.220.249] ▪ Small Cell Lung Carcinoma [C04.588.894.797.520.109.220.624]	n/a	

Disease	MeSH	MeSH sub-tree (*excluded terms*)	Related or excluded terms	Full term
		- Multiple Pulmonary Nodules [C04.588.894.797.520.237] - Pancoast Syndrome [C04.588.894.797.520.734] - Pulmonary Blastoma [C04.588.894.797.520.867] - Pulmonary Sclerosing Hemangioma [C04.588.894.797.520.933] - Solitary Pulmonary Nodule [C04.588.894.797.520.966]		
Falls	"Accidental falls"[MeSH Terms]	Accidental Falls [N06.850.135.122]	"Accident Prevention"[MeSH Terms:noexp]	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) ("Accidental falls"[MeSH Terms] OR "Accident Prevention"[MeSH Terms:noexp]) NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
COPD	"Pulmonary Disease, Chronic Obstructive"[MeSH Terms]	Pulmonary Disease, Chronic Obstructive [C08.381.495.389] - Bronchitis, Chronic [C08.381.495.389.500] - Pulmonary Emphysema [C08.381.495.389.750]	n/a	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Pulmonary Disease, Chronic Obstructive"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])
Diabetes	"Diabetes Mellitus"[MeSH	Diabetes Mellitus [C18.452.394.750]	NOT ("Diabetes Mellitus,	("cost-benefit analysis"[MeSH Terms] OR "Economics,

Disease	MeSH	MeSH sub-tree (*excluded terms*)	Related or excluded terms	Full term

	Terms]	- (*Diabetes Mellitus, Experimental [C18.452.394.750.074]*)
		- Diabetes Mellitus, Type 1 [C18.452.394.750.124]
		  o Wolfram Syndrome [C18.452.394.750.124.960]
		- Diabetes Mellitus, Type 2 [C18.452.394.750.149]
		  o Diabetes Mellitus, Lipoatrophic [C18.452.394.750.149.500]
		- *Diabetes, Gestational [C18.452.394.750.448]*
		- Diabetic Ketoacidosis [C18.452.394.750.535]
		- (*Donohue Syndrome [C18.452.394.750.654]*)
		- (*Prediabetic State [C18.452.394.750.774]*)
			Experimental"[MeSH Terms] NOT "Diabetes, Gestational"[MeSH Terms] NOT "Donohue Syndrome"[MeSH Terms] NOT "Prediabetic State" [MeSH Terms] NOT "Diabetes Complications"[MeSH Terms])	Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Diabetes Mellitus"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt]) NOT ("Diabetes Mellitus, Experimental"[MeSH Terms] NOT "Diabetes, Gestational"[MeSH Terms] NOT "Donohue Syndrome"[MeSH Terms] NOT "Prediabetic State" [MeSH Terms] NOT "Diabetes Complications"[MeSH Terms])

Other musculoskeletal				
Neck pain	"Neck Pain"[MeSH Terms]	Neck Pain [C10.597.617.576]	n/a	("cost-benefit analysis"[MeSH Terms] OR "Economics, Pharmaceutical"[MeSH Terms] OR "Technology Assessment, Biomedical"[MeSH Terms]) "Neck Pain"[MeSH Terms] NOT (Comment[pt] OR Editorial[pt] OR "English Abstract"[pt] OR Letter[pt])