Economic modelling in arterial vascular diseases; studying the cost-effectiveness of various strategies for screening, diagnosis and treatment
The research presented in this thesis was conducted at the School for Public Health and Primary Care (CAPHRI), Cardiovascular Research Institute Maastricht (CARIM), and Department of Health Services Research and department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University. CAPHRI participates in the Netherlands School of Primary Care Research (CaRe), acknowledged by the Royal Dutch Academy of Science (KNAW). CAPHRI was classified as ‘excellent’ by the external evaluation committee of leading international experts that reviewed CAPHRI in December 2010. CARIM is one of the largest cardiovascular research institutes in Europe. Furthermore, the research presented in this thesis are part of the study group DUCODIS (DUtch COagulation Diagnostics Study) under the umbrella of the Innovative Coagulation Diagnostics (INCOAG) project. This research was performed within the framework of CTMM, the Centre for Translational Molecular Medicine (http://www.ctmm.nl), project INCOAG (grant 01C-201), and supported by the Nederlandse Hartstichting (Dutch Heart Foundation).

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Economic modelling in arterial vascular diseases; studying the cost-effectiveness of various strategies for screening, diagnosis and treatment

DISSERTATION

to obtain the degree of Doctor at Maastricht University, on the authority of the Rector Magnificus, Prof. Dr. Rianne Letschert in accordance with the decision of the Board of Deans, to be defended in public on Friday, 16 September 2016, at 12.00 hours

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CHAPTER 1

General introduction
Atherosclerosis and arterial vascular diseases

Atherosclerosis is a chronic systemic inflammatory disease which is the main cause of morbidity and mortality in the western world and is a substantial and growing problem in most of the developing regions of the world [1, 2].

Atherosclerosis is a complex multifocal arterial disease involving interactions of multiple genetic and environmental factors. It develops as a response to damage of the vessel wall and is induced by endothelial dysfunction and inflammation as a result of diabetes mellitus, hypercholesterolemia, dyslipidaemia, hypertension, obesity, cigarettesmoking, physical inactivity and/or stress [3, 4]. It is the usual cause of myocardial infarction, ischemic stroke and peripheral artery disease, together referred to as ‘arterial vascular diseases (AVDs)’.

AVDs have various manifestations depending upon the arterial location. Myocardial Infarction (MI) is due to ischemic damage of the heart caused by the atherosclerotic plaque rupture and thrombosis. Ruptured plaques in the major brain’s arteries can cause ischemic stroke with the potential of permanent brain damage. Atherosclerotic narrowing in the arteries of the legs causes Peripheral Artery Disease (PAD). PAD commonly shows symptoms of pain on walking, with limited walking distance as a result, as well as poor wound healing. Severe PAD may lead to irreversible ischemia and the need for amputations. Arterial vascular diseases (AVDs) take a huge toll on our society and are the number one cause of death globally, accounting for almost 17 million deaths annually. AVDs are projected to remain the single leading cause of death [5]. The World Health Organization has estimated that the number of people, who die from AVDs, mainly from ischemic heart disease and stroke, will increase to reach 23.3 million by 2030. As per the European cardiovascular disease statistics published by the European heart network, each year AVDs cause over 4 million deaths in Europe and over 1.9 million deaths in the European Union [6]. Finally, 38000 Dutch residents lost their lives in 2012 due to AVDs [7]. The very high clinical and economic burden of AVDs makes primary prevention and secondary prevention of AVDs public health priorities [8-10].

In PAD the atherosclerotic plaque builds up in the arteries that carry blood to the limbs, affecting the circulation in the legs, but it is also a feature of systemic atherosclerosis. It is a chronic, progressive disease that can remain asymptomatic for a long time. When the chronically expanding atherosclerotic lesion causes lumen stenosis, this can result in intermittent claudication (IC) and ultimately critical limb ischemia (CLI) [11]. In patients without overt AVDs, the presence of PAD predicts approximately a 30% risk of myocardial infarction, ischaemic stroke, and vascular death over 5 years. Patients with PAD show a 2 to 6 fold increase in death from cardiovascular causes and a greater risk of limb amputation than those without PAD [12-16]. As an indicator of multifocal atherosclerosis, PAD is emerging as an important aid in risk stratification of patients with CVDs [17].
Early patient identification and use of biomarkers

The challenge for physicians, researchers, and clinical chemists is to develop diagnostic strategies that safely, accurately, and cost-effectively identify individuals at risk for cardiovascular events well before symptoms appear. Preventive interventions are likely to be most effective in this period, because atherosclerosis can take decades to manifest. The measurement of biomarkers could be an important component of these strategies. A biomarker can be anything that reflects a biological process from genetic markers to imaging tests. The Biomarkers Definitions Working Group defines a biomarker as ‘A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ [18]. The overall expectation from a biomarker is to enhance the ability of the clinician to optimally manage the patient. Biomarkers hold the promise of earlier and more accurate cardiovascular risk stratification and could be used to better identify high-risk individuals, to diagnose disease conditions promptly and accurately, and to effectively prognosticate and treat patients with disease. The past decade has seen increasing interest in cardiovascular biomarkers due to advances in genetic and molecular research providing insight about early cardiovascular pathophysiology and platforms for biomarker discovery. An increasing number of studies have investigated the role of cardiovascular biomarkers [19]. Biomarkers provide a powerful approach to understanding the spectrum of AVDs with applications in at least 5 areas: screening, diagnosis, prognostication, prediction of disease recurrence, and therapeutic monitoring [20].

Biomarker based personalized health care with stratified and tailored treatment is the next echelon in health care [21, 22]. Although medicine is inherently personal to each patient, personalized medicine denotes the use of technology enabling a level of personalization, which was previously not feasible. The aim of personalized medicine is to give each patient an individually tailored therapy while minimizing the adverse effects. Personalized medicine will only be successful when accurate diagnostic tests identify the patients who can benefit from targeted therapies and eventually reach the desired goal of prevention and prediction.

Biomarker based personalized medicine can, at least theoretically, significantly improve the outcomes. For biomarker identified patients tailored treatment could be provided to increase their chance of a good outcome and identification of biomarker test negative patients would reduce the waste of resources. The healthcare system saves money in both scenarios. Therefore, use of biomarkers to guide the diagnosis and treatment can confer both clinical and economic benefits.

Biomarkers have become one of the most promising areas of investigation and the number of biomarkers available in medical practice has been increasing rapidly over the past decades and is likely to increase even further given the quest for stratified and personalized medicine. In spite of the gain in number, there are not many biomarkers that have yet delivered value for money. Consequently, there is growing concern about
the judicious utilization of biomarkers, the potential long term health consequences (both positive and negative), and the steeply rising costs of new health technologies [23]. To address these problems in-depth evaluation of the downstream consequences (long term costs and benefits) is required to improve the decision-making in terms of patient outcomes, financial impact and social consequences[24].

**Health Technology Assessment (HTA)**

HTA is the systematic evaluation of properties, effects, and/or impacts of health technology and as such HTAs involve evaluations of clinical effectiveness, cost-effectiveness, and the ethical, legal, and social implications of health technologies on patient health and the health care system. Its main purpose is to inform decision-making in health care, and thus improve the uptake of efficacious, safe, cost-effective, and acceptable new technologies and prevent the uptake of technologies that are of doubtful value for the health system [25, 26]. It is an interdisciplinary activity using explicit analytical frameworks, drawing from a variety of methods. One of the cornerstones of HTA is known as health economic evaluation. The preferred type of economic evaluation done under the heading of HTA is cost-utility analysis (CUA). Health outcomes are measured as “quality-adjusted life-years” (QALYs) in CUA and the expected lifespan resulting from an intervention is weighted by the quality of that life. The estimation of QALYs is increasingly based upon the health state utilities predicted from a multi-attribute utility instrument. Commonly used multi-attribute instruments are the Euroqol 5D (EQ-5D), Short form 36 health survey (SF-36), and Health utilities Index (HUI). Each of these instruments has two components: first, a descriptive system that consists of a set of items and response categories used to describe a person’s health. Secondly, a utility formula converts the item responses into an index of utility on a 0.00 (death)—1.00 (best health) scale. It has been shown that the utilities generated with these instruments differ, and can result in vastly different incremental QALY, and hence incremental cost-per-QALY ratios, estimates [27, 28].

However, QALYs are useful for making comparisons among alternative technologies as they are generic units that can reflect changes brought about by different health care interventions for the same or different health problems. With regulatory bodies recommending CUA as the preferred form of economic evaluation, QALY is increasingly used along with more traditional outcome measures to assess health care technologies [29-31].

Economic evaluations could be model-based or trial-based. Decision analytic modeling is a valuable alternative to lengthy and resource consuming clinical trials to quantify the effects of testing on long term outcomes and costs. Decision analytic modeling is used to represent the sequence of clinical decisions and its health and economic impacts. It uses available quantitative estimates to represent the sequences of alternative strategies (diagnosis and/or treatment) in terms of the probabilities that certain events and
outcomes will occur and the values of the outcomes that would result from each strategy [23, 24]. Models synthesize the evidence from various sources, including pre-clinical studies (e.g. evidence on risks), diagnostic test accuracy studies, therapeutic intervention studies (e.g. evidence on outcomes) [25], and observational studies. Subsequently, the life course of hypothetical individuals can be simulated while tracking risk factors, complications, quality of life, and costs, to assess the incremental cost-effectiveness of a new diagnostic strategy [26].

Due to competing health interventions and limited resources, model-based economic evaluations are used to assist in setting priorities, making resource allocation decisions and designing services. Economic evaluations can be used to inform decisions about incorporating new health technologies or treatments into existing health service delivery systems. Economic evaluations can also be used to support policy making to increase coverage of a service or to scale up projects from pilots to national programs by providing decision makers with information on the tradeoffs in resource costs and health benefits involved in choosing an intervention over another.

**Economic evaluation of biomarkers**

Regardless of the purpose for its use (whether for screening, diagnosis, treatment or prognosis) a new biomarker will be of clinical and societal value only if it is accurate, it is acceptable to the patient and it is cost-effective to be introduced in a health system. Use of biomarkers in disease identification, prevention and management could change treatment decisions and as a result improve patient health. At the same time, the use of biomarkers impacts on the costs of diagnosis and treatment. Thus, the economic aspect of the use of biomarkers has become increasingly subject to scrutiny by reimbursement and regulatory authorities worldwide.

While there is growing appreciation of the need to demonstrate the clinical impact of biomarkers for altered decision making [32], research into the effectiveness and cost effectiveness of different strategies using biomarkers has been lacking. Research that identifies cardiovascular biomarkers and measures their performance is plentiful, but evidence of biomarker utility in terms of health and economic impact is harder to find [29, 33].

It is paramount that these models reflect not only the initial testing aspects, but also any follow-up testing, treatment and monitoring of patients. Thus, it is important to accurately reflect the test–treatment strategies and associated clinical pathways. Cost-effectiveness modelling of biomarkers can rapidly provide insights into the value of the use or introduction of a new biomarker in terms of improved patient outcomes. Cost-effectiveness models can also be readily updated when new evidence e.g. on new treatment becomes available.
Moreover, the cost-effectiveness model could be used for ‘biomarkers under development’. It is suggested to use HTA tools and methods to inform biomedical product development and to anticipate further development and market access [34]. McAteer described an early HTA method called “headroom analysis” [35]. A headroom analysis determines the societal value of innovations in health care by using a threshold approach. Headroom analysis estimates the maximum costs required to bring a perfect biomarker to the market, while still being considered cost-effective. It is a quick and useful way to consider the investment opportunity at a very early stage and to reduce the risk of investing in a new technology that once developed is unlikely to be reimbursed by the healthcare providers. Therefore, headroom analysis could help in research and development-investment decisions, pricing decisions, market access and reimbursement decisions.

**Thesis objectives and scope**

This dissertation is mainly related to DUCODIS (DUtch COagulation Diagnostics Study), a program under the umbrella of the INnovative COAGulation diagnostics (INCOAG) consortium. This dissertation focuses on health technology assessment and related aspects of peripheral atherosclerosis and coronary artery thrombosis (PAD and MI).

The general aim of the research presented in this thesis was to assess the value of strategies for screening, diagnosing and/or treating PAD or MI by performing economic modelling. This general aim was achieved by exploration into three objectives. First, to provide a general overview of the methodological quality of economic evaluations published in the field of PAD; second, to perform economic evaluations of biomarkers associated with PAD and MI; third, to assess the health related quality of life (HRQoL) in the PAD patients using two most widely used instruments.

**Chapter 2** deals with systematically reviewing model-based full economic evaluations performed in the field of PAD in order to assess their general characteristics, model structure, and methodological quality. In **Chapter 3**, available evidence was synthesized to populate a decision analytic model in order to determine the cost effectiveness of PAD screening. Chapter 4 considers the role of risk assessment biomarker and tailored treatment for PAD patients. **Chapter 5** is based upon a multi-center cross sectional study to measure the HRQoL in PAD patients. **Chapter 6**, a model based economic evaluation assesses the cost effectiveness of high-sensitivity Troponin in MI. Finally, in the general discussion, **Chapter 7**, methodological and theoretical considerations are presented followed by clinical and policy implications as well as suggestions for future research are addressed.
REFERENCES


CHAPTER 2

A systematic review of model-based economic evaluations of diagnostic and therapeutic strategies for lower extremity artery disease
A systematic review of model-based economic evaluations of diagnostic and therapeutic strategies for lower extremity artery disease

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Summary
Lower extremity artery disease (LEAD) is a sign of widespread atherosclerosis affecting coronary, cerebral and renal arteries and is associated with increased risk of cardiovascular events. Many economic evaluations have been published for LEAD due to its clinical, social and economic importance. The aim of this systematic review was to assess modelling methods used in published economic evaluations in the field of LEAD. Our review appraised and compared the general characteristics, model structure and methodological quality of published models. Electronic databases MEDLINE and EMBASE were searched until February 2013 via OVID interface. Cochrane database of systematic reviews, Health Technology Assessment database hosted by National Institute for Health research and National Health Services Economic Evaluation Database (NHSEED) were also searched. The methodological quality of the included studies was assessed by using the Philips’ checklist. Sixteen model-based economic evaluations were identified and included. Eleven models compared therapeutic health technologies; three models compared diagnostic tests and two models compared a combination of diagnostic and therapeutic options for LEAD. Results of this systematic review revealed an acceptable to low methodological quality of the included studies. Methodological diversity and insufficient information posed a challenge for valid comparison of the included studies. In conclusion, there is a need for transparent, methodologically comparable and scientifically credible model-based economic evaluations in the field of LEAD. Future modelling studies should include clinically and economically important cardiovascular outcomes to reflect the wider impact of LEAD on individual patients and on the society.

Keywords
Lower extremity artery disease, economic evaluation, decision analytic model, systematic review

Introduction
Lower extremity artery disease (LEAD) is the manifestation of systemic atherosclerosis and is caused by the build-up of fatty deposits in the arteries leading to reduced blood flow to the legs and feet. The most common symptom of LEAD is intermittent claudication (IC), which is calf pain triggered by exercise and relieved by rest. Advanced LEAD may present as rest pain, ulceration or gangrene progressing to occasional lower limb amputation (1). LEAD patients have a two- to six-fold higher risk of acute cardiovascular events, e.g. myocardial infarction, stroke, aortic aneurysm rupture and vascular death (2). LEAD patients experience a significant functional decline and reduction in their health-related quality of life (HRQoL), comparable to other forms of cardiovascular disease (3). The high economic burden of LEAD is reported to be comparable with the costs related to myocardial infarction (4). A previously published review focused on the economic analyses of open and endovascular treatment of lower extremity peripheral arterial disease and had included only three model-based economic evaluations (5). Another review included one cost utility analysis and two cost analyses for endoscopic saphenous vein harvest for coronary and lower extremity bypass compared with open harvesting (6). The aim of this study was to systematically review all model-based full economic evaluations performed in the field of LEAD in order to assess their general characteristics, model structure, and methodological quality.
Methods

Study design
A systematic literature review was performed to identify model-based economic evaluations performed in the field of LEAD. The following eligibility criteria were applied:
1. Model-based economic evaluation
2. Decision analytic models comparing two or more diagnostic or therapeutic strategies or a combination of both for LEAD
3. Studies meeting the criteria of full economic evaluation with explicit analysis of both costs and effects of an intervention and at least one comparator (7)
4. Model reflecting an adult population (18 year +)
5. Published in English
6. Original research

Search strategy
Several electronic databases were searched to identify all peer-reviewed publications of model-based economic evaluations for diagnostic and therapeutic strategies for LEAD until February 2013. Electronic databases MEDLINE and EMBASE were searched through OVID interface using Maastricht University library subscription. This search used the economic evaluations search filters developed by National Health Services (NHS) Quality Improvement Scotland filter 2005 for Ovid interface. Cochrane database of systematic reviews, Health Technology Assessment database hosted by National Institute for Health Research and National Health Services Economic Evaluation Database (NHS EED) were searched via Cochrane library. The detailed search strategy is shown in the Supplementary Appendix 1 (available online at www.thrombosis-online.com).

Study selection
Screening of the titles (all) and abstracts (selection based on title) retrieved from the electronic database search was done by three independent reviewers (AV, MJ & JS). The reasons for not fulfilling the inclusion criteria were registered, e.g. not full economic evaluation, not model-based economic evaluations, not in the field of LEAD. Complete details of excluded studies with reasons are shown in the study flow diagram (Figure 1).

Data extraction
After inclusion based on title and abstracts full papers were retrieved and read by two reviewers (AV & MJ). General characteristics of the included studies were tabulated under the headings as

Figure 1: Study flow diagram.
identification of first author, year of publication, country, population, study setting, perspective, type of economic evaluation, model approach and competing strategies, summary of results and conclusion. We followed the recommendations by Pignone et al. to identify important data from the reviewed economic analyses (8). The model structures used in the included articles were assessed. We identified the important clinical events and/or health states included in the model and tabulated the exact definitions used.

Methodological quality

Assessment of the methodological quality of the included studies was performed using a comprehensive 60 points checklist for quality assessment in decision analytic models published by Philipps et al. (9). This document is based upon and incorporates review of all existing guidelines and provides a best practice guideline in decision modelling for cost effectiveness analysis. This guideline provides a systematic approach to review a decision model and covers all the key attributes for critical assessment. The Philipps check-list includes a number of methodological areas that previously have not received attention in the literature on good practice. This checklist allows to appraise the methodological quality of economic models in three broad dimensions namely structure, data and consistency. The quality of included studies was appraised by two independent reviewers (AV and MJ) and disagreements were dealt with by consensus or through the third reviewer (JS), if necessary.

Results

Study selection

Eight hundred thirty eight publication hits were recorded using the search strategy. Inspection of the titles led to the exclusion of many articles and only 72 abstracts were selected for reading. Abstract reading led to the elimination of more articles and finally full copies of 17 articles were retrieved. Reading these articles excluded five more articles and 12 articles were selected for review. At this stage manual evaluation of references from selected articles and hand picking of key journals led to the addition of four more publications. All in all we selected 16 model-based economic evaluations for this systematic review (10-25). The study flow diagram shows the selection process (► Figure 1).

General characteristics

All studies identified for this review were published between January 1995 and December 2011. Fourteen studies had a patient population with symptoms of intermittent claudication while one study had patients with asymptomatic LEAD (19) and one study had peripheral arterial occlusion (18). Seven studies were performed in the United States (10, 13, 16, 17, 21, 24, 25), four in the Netherlands (11, 12, 22, 23), three in the UK (14, 18, 20) and one study each in Germany (15), and in Sweden (19). Half of the studies were done from a societal perspective (10, 11, 13, 21-25) and the remaining half used a payer’s perspective. Thirteen studies were cost utility analyses (CUA). The remaining three studies were cost-effectiveness analyses (CEA) expressing outcomes in natural units; ‘incremental walking distance’ (14, 21) and ‘extra correctly identified case’ (12). Three articles described models for the radiological diagnosis of peripheral vascular occlusion (12, 23, 25). Twelve articles modelled surgical (10, 11, 13, 15-18, 21, 22, 24) or pharmacological (14, 20) therapeutic interventions to improve circulation in the limb. One study compared the systemic effects of four treatment strategies in reduction of cardiovascular events in LEAD patients (19). The majority of the studies declared their source of funding; except two studies (12, 25).

The general characteristics of the reviewed studies are listed in Table 1. Results of included studies are summarised and conclusions are presented in Table 2.

Model structure and outcomes

Three articles published by Visser et al. (22-24) used the model developed and published by de Vries et al. (13). Similarly two studies by Bosch et al. (10, 11) and one article by Bharad et al. (17) referred to the model from Hunink et al. (16). One study did not describe any model structure (Treesak) (21). As a result, in total nine distinct model structures were used in the 16 published articles of economic evaluations for LEAD.

Two diagnostic models and one therapeutic model were based on a decision tree approach (12, 14, 25). The decision tree in the article by Yin et al. (25) compared magnetic resonance angiography (MRA) with conventional angiography (CA) to identify the presence or absence of a target run-off vessel during the pre-operative work up of a LEAD patient. The events modelled in this tree were positive lesion, negative lesion and non-diagnostic test. Non diagnostic cases were subjected to re-evaluation by MRA or CA. This study showed that MR angiography is cost-effective, particularly those with limb-threatening LEAD (25).

Similarly, Coffi et al. (12) compared duplex scanning and Digital Subtraction Angiography combinations for detection of occlusion or stenosis in the aortoiliac or femoropopliteal arteries in LEAD patients, to plan a surgical intervention. The tree distinguished between significant lesion and insignificant lesion and later between true positive and false positive. They reported that the Digital Subtraction Angiography is a cost-effective strategy only in case of high prevalence of obstructive lesions (12). Time horizons were not stated in these two studies by Yin et al. (25) and Coffi et al. (12).

The therapeutic decision tree used by Guest et al. (14) considered the decision by a vascular surgeon to treat an intermittent claudicant patient with cilostazol, naftidrofuryl or pentoxifylline. Percentage increase in the maximal walking distance at 24 weeks was calculated as the measure of clinical effectiveness in this model. The authors justified the time horizon of 24 weeks by stating that absence of robust data for longer treatment effects may lead to substantial uncertainties. In this model the patient continued the initial treatment, discontinued or switched to another drug. This study concluded that from the perspective of National Health
Table 1: General characteristics of the included model-based economic evaluations.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Time horizon</th>
<th>Setting</th>
<th>Population</th>
<th>Type of analysis/Unit of outcome</th>
<th>Perspective</th>
<th>Model type</th>
<th>Diagnostic/Therapeutic</th>
<th>Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yin (29)</td>
<td>1995</td>
<td>Not stated</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Decision tree</td>
<td>D</td>
<td>MRA, Angiography</td>
</tr>
<tr>
<td>Hunink (16)</td>
<td>1995</td>
<td>Life time</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Markov model</td>
<td>T</td>
<td>PTA-No treatment, PTA-PTA, PTA-BS, BS-No treatment, BS-graft revision</td>
</tr>
<tr>
<td>Sculpher (18)</td>
<td>1996</td>
<td>25 years</td>
<td>UK</td>
<td>Peripheral arterial occlusion</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Decision tree + Markov model</td>
<td>T</td>
<td>Laser assisted angioplasty / conventional angioplasty</td>
</tr>
<tr>
<td>Bosch (11)</td>
<td>1998</td>
<td>Not stated</td>
<td>NL</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>T</td>
<td>PTA, selective stent placement, repeated PTA, PTA with selective stent placement, Primary stent placement, No revascularization (in several combinations)</td>
</tr>
<tr>
<td>Bosch (10)</td>
<td>2000</td>
<td>Not stated</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>T</td>
<td>PTA, selective stent placement, repeated PTA, PTA with selective stent placement, No revascularization (in several combinations)</td>
</tr>
<tr>
<td>Muradin (17)</td>
<td>2001</td>
<td>Life time</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Markov model</td>
<td>T</td>
<td>Bypass surgery, PTA, hypothetical endovascular device</td>
</tr>
<tr>
<td>De Vries (13)</td>
<td>2002</td>
<td>Life time</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>T</td>
<td>Ex ± PTA, Ex ± PTA / BS, PTA / Ex, PTA / BS / Ex</td>
</tr>
<tr>
<td>Visser (22)</td>
<td>2003</td>
<td>Life time</td>
<td>NL</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>D + T</td>
<td>DUS + PTA / Ex, MRA + PTA / Ex, DSA + PTA / Ex, DUS + PTA / BS / Ex, MRA + PTA / BS / Ex, DSA + PTA / BS / Ex / Ex + No test</td>
</tr>
<tr>
<td>Visser (24)</td>
<td>2003</td>
<td>Life time</td>
<td>US</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>D + T</td>
<td>DUS, MRA, DSA, no diagnostic work up</td>
</tr>
<tr>
<td>Visser (23)</td>
<td>2003</td>
<td>Life time</td>
<td>NL</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Societal</td>
<td>Markov model</td>
<td>D</td>
<td>CTA Gadolinium enhanced MRA</td>
</tr>
<tr>
<td>Treesak (21)</td>
<td>2004</td>
<td>6 months</td>
<td>US</td>
<td>IC</td>
<td>CEA/Initial claudication distance and absolute claudication distance</td>
<td>Societal</td>
<td>Not specified</td>
<td>T</td>
<td>Exercise rehabilitation PTA, Cilostazol, Naftidrofuryl, Pentoxifylline</td>
</tr>
<tr>
<td>Guest (14)</td>
<td>2005</td>
<td>24 weeks</td>
<td>UK</td>
<td>IC</td>
<td>CEA/% increase in maximum walking distance</td>
<td>Payer's</td>
<td>Decision tree</td>
<td>T</td>
<td>Cilostazol, Naftidrofuryl, Pentoxifylline, PGE1, PTA, BS, no treatment</td>
</tr>
<tr>
<td>Höller (15)</td>
<td>2006</td>
<td>5 years</td>
<td>Ger</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Markov model</td>
<td>T</td>
<td>PGE1, PTA, BS, no treatment</td>
</tr>
<tr>
<td>Goffi (12)</td>
<td>2008</td>
<td>Not stated</td>
<td>NL</td>
<td>IC</td>
<td>CEA/Per extra correctly identified case</td>
<td>Payer's</td>
<td>Decision tree</td>
<td>D</td>
<td>DS + Supplementary Angiography, DS + Confirmative Angiography, Angiography</td>
</tr>
<tr>
<td>Sigmund (19)</td>
<td>2011</td>
<td>Life time</td>
<td>Sweden</td>
<td>Asymptomatic LEAD</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Markov model</td>
<td>T</td>
<td>Low dose Aspion, ACE inhibition, non-aspirin anti-platelet therapy, Lipid lowering therapy with Statins, no active treatment</td>
</tr>
<tr>
<td>Squires (20)</td>
<td>2011</td>
<td>100 years</td>
<td>UK</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>Payer's</td>
<td>Markov model</td>
<td>T</td>
<td>Cilostazol, Naftidrofuryl oxalate, Pentoxifylline, Inositol nicotinate, No vaso-active drug</td>
</tr>
</tbody>
</table>

US = United States of America, NL = The Netherlands, UK = United Kingdom, IC = Intermittent Claudication, D = Diagnostic, T = Therapeutic, DUS = Duplex Ultrasoundography, MRA = Magnetic Resonance Angiography, DSA = Digital Subtraction Angiography, PTA = Percutaneous Transluminal Angioplasty, PGE1 = Prostaglandin E1 infusion, BS = Bypass Surgery, EX = Supervised exercise program, CUA = Cost Utility Analysis, CEA = Cost Effectiveness Analysis, QALY = Quality Adjusted Life Years, ICER = Incremental Cost Effectiveness Ratio, ACE-I = Angiotensin Converting Enzyme 1, LEAD = Lower Extremity Artery Disease.
Table 2: Summary of results and conclusions of the included model-based economic evaluations.

<table>
<thead>
<tr>
<th>First author</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yin (25)</td>
<td>Repeated infusion of PGE1 is cost-effective strategy compared to Repeated infusion of PGE1 is cost-effective with €4944.19/QALY.</td>
<td></td>
</tr>
<tr>
<td>Hunink (16)</td>
<td>For a 65 years old patient with disabling claudication or chronic critical ischaemia and a femoropopliteal stenosis initial angioplasty increased QALE by 2–13 months and resulted in decreased life time expenditure. For patients with occlusion initial bypass surgery increased QALE by 1 to 4 months.</td>
<td>Angioplasty is the preferred initial treatment in patients with disabling claudication and a femoropopliteal stenosis or occlusion and in those with chronic critical ischaemia and a stenosis. Bypass surgery is the preferred initial treatment in patients with chronic critical ischaemia and a femoropopliteal occlusion.</td>
</tr>
<tr>
<td>Visser (23)</td>
<td>MRA in combination with angioplasty had an ICER of €20,000/QALY.</td>
<td>The ICER for laser assisted angioplasty in claudicants was 3040 pounds and in patients with rest pain/ulceration was 1810 pounds per QALY.</td>
</tr>
<tr>
<td>Visser (22)</td>
<td>If the treatment were limited to angioplasty, a new imaging modality would be cost-effective if the costs were $300 and the sensitivity was 85%, even if 35% of patients needed additional work-up. When both angioplasty and bypass surgery were considered as treatment options, a new imaging modality was cost-effective if the costs were $300, the sensitivity was higher than 94%, and 20% of patients required additional work-up.</td>
<td>On average the expected gain in effectiveness achieved with bypass surgery for intermittent claudication is small compared with the costs. Angioplasty performed whenever feasible was more effective than exercise therapy which is cost-effective with a 12% increase in maximal walking distance at 24 weeks compared with primary stent placement or PTA alone in the treatment of intermittent claudication caused by an iliac arterial stenosis.</td>
</tr>
<tr>
<td>Visser (11)</td>
<td>PTA with selective stent placement yielded equal complication rates, better patency results and higher quality of life. ICER for PTA with selective stent placement followed by no revascularisation was $4073/QALY.</td>
<td>PTA with selective stent placement is a cost-effective treatment strategy compared with primary stent placement or PTA alone in the treatment of intermittent claudication.</td>
</tr>
<tr>
<td>Vischer (18)</td>
<td>The ICER for laser assisted angioplasty in claudicants was 3040 pounds and in patients with rest pain/ulceration was 1810 pounds per QALY. Secondary use of laser assisted angioplasty is worth funding in the UK.</td>
<td>The program of supervised exercise provides clinical efficacy, cost-effectiveness, and probable cost-savings for improvement of claudication in individuals with claudication.</td>
</tr>
<tr>
<td>Bosch (10)</td>
<td>Treatment strategies using angioplasty with selective stent placement dominated treatment strategies using angioplasty alone. ICER for PTA with selective stent placement followed by no revascularisation was $7624/QALY.</td>
<td>Multi-detector row CT angiography has the potential to be cost-effective in the evaluation of patients with intermittent claudication as compared with currently used imaging modalities such as MR angiography.</td>
</tr>
<tr>
<td>Muradin (17)</td>
<td>CEA of a device with different costs and patency rates was performed. Use of a device that costs $3000 would be cost effective compared with angioplasty for critical ischaemia if the 5-year patency rate is 29%-46%. Use of the same device would be cost-effective compared with angioplasty for disabling claudication and stenosis if the 5-year patency rate is 69%-86%.</td>
<td>Target values of primary patency rates and costs for a endovascular device were estimated.</td>
</tr>
<tr>
<td>De Vries (13)</td>
<td>Revascularisation improved effectiveness by 33–61 quality-adjusted life days among patients with no history of coronary artery disease when compared with an exercise program. The ICER was $38,000 per QALY when angioplasty was performed whenever feasible.</td>
<td>On average the expected gain in effectiveness achieved with bypass surgery for intermittent claudication was small compared with the costs. Angioplasty performed whenever feasible was more effective than exercise alone, and the cost-effectiveness ratio was within the generally accepted range.</td>
</tr>
<tr>
<td>Visser (24)</td>
<td>The ICER for MR angiography yielded $35,000/QALY compared with no diagnostic work-up.</td>
<td>MR angiography or duplex US can replace DSA without substantial loss in effectiveness and with a slight cost reduction.</td>
</tr>
<tr>
<td>Visser (23)</td>
<td>MRA in combination with angioplasty had an ICER of $20,000/QALY relative to the conservative strategy.</td>
<td>Non-invasive imaging modalities can replace DSA without important loss in effectiveness and a minimal cost-reduction.</td>
</tr>
<tr>
<td>Treesak (21)</td>
<td>PTA is the more effective treatment at 3 months and costs an additional $123 per additional meter walked before the onset of claudication, compared with exercise therapy. However, at six months, exercise therapy is cost-effective.</td>
<td>The program of supervised exercise provides clinical efficacy, cost-effectiveness, and probable cost-savings for improvement of claudication in individuals with claudication.</td>
</tr>
<tr>
<td>Guest (14)</td>
<td>Starting treatment with Cilostazol instead of Naftidrofuryl is expected to increase the percentage improvement in maximal walking distance by 32% for a 12% increase in NHS costs.</td>
<td>Starting treatment with Cilostazol is expected to be clinically more effective strategy for improving maximal walking distance at 24 weeks than starting treatment with Naftidrofuryl or Pentoxifylline and potentially the most cost-effective strategy in the UK.</td>
</tr>
<tr>
<td>Holler (15)</td>
<td>Repeated infusion of PGE1 is cost-effective with $4944.19/QALY.</td>
<td>Repeated infusion of PGE1 is cost-effective strategy compared to various combinations of PTA, BS and no treatment.</td>
</tr>
</tbody>
</table>
Table 2: Continued

<table>
<thead>
<tr>
<th>First author</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffi (12)</td>
<td>Duplex scan plus Digital Subtraction Angiography is the most cost effective strategy if the prevalence of significant obstructive lesions in the aortoiliac and femoropopliteal tract exceeds 70%, or if the sensitivity of duplex scanning is lower than 83%. The ICER was reported to be 210 Euros per extra correctly identified case.</td>
<td></td>
</tr>
<tr>
<td>Sigwart (19)</td>
<td>Statin, aspirin, anti-platelet therapy and ACE-i treatment yielded a 28%, 13%, 28% and 33% reduction in composite endpoints respectively. Of the four therapies, ACE-i treatment resulted in the highest mean QALYs (7.44 and 8.45 for men and women respectively), and was associated with the lowest mean cost compared to other four treatment options.</td>
<td>ACE-I treatment was associated with the largest reduction in CV events leading to the highest quality – adjusted survival compared to the other drugs.</td>
</tr>
<tr>
<td>Squares (20)</td>
<td>Pentoxifylline and Cilostazol are dominated by Naftidrofuryl oxalate and Naftidrofuryl oxalate is the most cost effective compared with other vasoactive drug and no vasoactive drug.</td>
<td></td>
</tr>
</tbody>
</table>

DUS = Duplex UltraSonography, MRA = Magnetic Resonance Angiography, DSA = Digital Subtraction Angiography, PTA = Percutaneous Transluminal Angioplasty, PGE1 = Prostaglandin E1 infusion, BS = Bypass Surgery, EX = Supervised exercise program, CUA = Cost Utility Analysis, CEA = Cost Effectiveness Analysis, QALY = Quality Adjusted Life Years, ICER = Incremental Cost Effectiveness Ratio, ACE-I = Angiotensin Converting Enzyme 1, LEAD=Lower extremity Artery Disease. 

A SYSTeMAtIC reVIeW of ModeL-BASed eConoMIC eVALuAtIonS of dIAGnoStIC And tHERAPeutIC StrAteGIeS for LoWer extreMIty Artery dISeASe

Three articles (22-24) used the Markov model developed by de Vries et al. (13) with health states based on symptom severity in the limb namely; asymptomatic or mild claudication, severe claudication, critical limb ischaemia, below knee amputation, above knee amputation and death. In this model patients were followed over their lifetime. de Vries et al. assessed the cost-effectiveness of various combinations of exercise, angioplasty and bypass surgery for the treatment of intermittent claudication. This study found that angioplasty is more effective and cost-effective than exercise alone while bypass surgery is not a cost-effective option in these patients (13). Visser et al. determined the target values for dialysis accuracy of multi-detector row CT angiography to be cost-effective in comparison of gadolinium-enhanced MR angiography. This study reported the potential of CT angiography to be cost-effective at the cost of $300 and at sensitivity of 85% (23). Another study using the Markov model by de Vries et al. compared various combinations of diagnostic imaging modalities (no imaging, duplex ultrasound, magnetic resonance angiography and digital subtraction angiography) and management options (exercise, angioplasty and bypass surgery). This study suggests that non-invasive imaging modalities can replace digital subtraction angiography and angioplasty is a cost-effective management strategy for intermittent claudication in the Netherlands (22). Visser et al. also used the same Markov model (13) to determine the optimal imaging strategy in pre-treatment workup of patients with intermittent claudication. A non-diagnostic workup, duplex ultrasound, MR angiography and digital subtraction angiography were compared in this analysis. This study found only slight differences in the costs and effectiveness of different imaging modalities and inferred that MR angiography or duplex ultrasound replace digital subtraction angiography without substantial loss in effectiveness and with a slight cost reduction (24). Sculpher et al. (18) built a model comparing effectiveness of conventional angioplasty and a laser-assisted angioplasty in re-canalising arterial occlusions. An initial decision tree (reflecting the diagnostic phase) combined with an eight state Markov model estimates the costs and benefits of the initial re-canalsation process over 25-year period. The Markov health states were: asymptomatic, claudication, rest pain, ulceration, un-operated, operated, post amputation and death. This study found use of laser cost-effective but cautioned about the uncertainty due to limited patient data and suggested further research before widespread diffusion of the laser (18).

Holler et al. (15) compared various combinations of no treatment, angioplasty, bypass surgery and infusion of prostaglandin E1 in a Markov model. The Markov health states reflected lower
limb symptoms (Fontaine II, Fontaine III/IV, amputation), and death. Prostaglandin E1 infusion was found to be the most cost-effective strategy in this study using a time horizon of five years (15).

To model the effects of vasoactive drugs cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate on intermittent claudication a Markov model was developed by Squires et al. (20). This model had a time horizon of 100 years and included three health states: vasoactive drug treatment, no vasoactive drug treatment and death. The 100-year time horizon closely resembled a lifetime time horizon.

This study suggested that naftidrofuryl oxalate was the most cost-effective vasoactive pharmacological agent for LEAD (20).

One study compared the systemic effects of four pharmacological treatment strategies in reduction of cardiovascular events in LEAD patients for their lifetime. Four active drug treatments compared in this Markov model were low-dose aspirin, angiotensin converting enzyme inhibitors, non-aspirin platelet therapy and lipid-lowering therapy with statins. This study included health states of asymptomatic LEAD, symptomatic LEAD, angina pectoris, post myocardial infarction, post stroke, cardiovascular death and non-cardiovascular death in the model. Angiotensin converting enzyme inhibitors were found to be the most cost-effective in reducing the cardiovascular events in LEAD patients (19).

Methodological quality of the included studies

Very limited comparability between the studies was observed due to use of different model structures, model assumptions and input parameter estimates. Most of the studies did not perform consistently well on the items from the Philips’ checklist. Details of individual study performance against the 60 item Philips checklist is shown in the Figure 2. A summary of the studies’ performance clustered in the three dimensions (structure, data and consistency) of the checklist is presented below.
Structure

All studies stated a clear decision problem and objective, but no study specified the primary decision maker. Three studies stating a societal perspective did not take productivity loss into account (15, 22, 23). All studies defined the scope of the model but none of them provided a justification. None of the included studies specified sources of data used to develop the model structure. There is no clear statement and justification of the structural assumptions in 12 out of the 16 studies (10-15, 17, 19, 21-24). One study did not specify the model type (21) used in analysis while the other studies used appropriate model types for the given decision problems. Only eight studies used a lifetime horizon (13, 16, 18-20, 22-24), and only two out of the remaining eight studies justified the use of a shorter time horizon (14, 15). In six studies disease states or pathways were not stated because the authors referred to previous publications of the same, or a similar, model (10, 11, 17, 22-24). Referral to pre-existing models in these six articles made it difficult to understand the model structures.

Data

Assessment of the quality of data was not performed in any of the included studies. Modelling methodologies were clear and transparent in all the studies except one (21). Calculation of transition probabilities was not transparent in five studies (13, 14, 17, 21, 25). Only five studies showed a transparent data incorporation process (12, 14, 18, 20, 22). In one study different sources of utility values for different health states were used (19). At least three studies were not transparent in showing the derivation of utility weights (15, 24, 25). None of the studies have addressed structural and methodological uncertainties, three studies performed probabilistic sensitivity analysis (14, 19, 20). Seven studies did not address heterogeneity by running the model separately for different subgroups (11, 12, 14, 15, 21, 22, 25).

Consistency

Mathematical logic of the model was not tested before use, and therefore internal consistency was not validated in any of the included studies. One study obtained and explained counterintuitive results of the analysis (19). None of the studies provided evidence that their model was calibrated against independent data. All studies compared their results with those of previous studies; except four (11, 17, 18, 21).

Complete details of methodological assessment of included model-based economic evaluations are available in Suppl. Appendix 2 (available online at www.thrombosis-online.com).

Discussion

We conducted a systematic review of the literature to identify model-based economic evaluations in the field of LEAD. Sixteen studies from five different countries were included. To the best of our knowledge this is the first systematic review featuring all available evidence pertaining to the ‘model-based economic evaluation’ of therapeutic and/or diagnostic technologies for LEAD. This review brings together all applied modelling methods for the disease progression of LEAD that could be used in future model-based economic evaluations in this field. The aim of this systematic review was to summarise and compare the findings of ‘model-based economic evaluations’ performed in the field of LEAD and to assess the general and methodological qualities of included studies.

It was found that the diversity of the studies did not allow a valid comparison of the exact outcomes on cost-effectiveness. Different researchers chose to structure their models based on different assumptions and used various estimates for key input parameters. Also, a variety of diagnostic and therapeutic options were assessed, and performed for a number of different settings. Furthermore, several methodological differences were observed between the studies, including model type, outcome measure, time horizon and perspective. These aspects could have a major impact on the cost-effectiveness estimate of the results. Using the quality checklist, the overall assessment of the studies revealed important methodological flaws in the included model-based economic evaluations. This finding is consistent with another systemic review of economic analyses (5). The checklist is a very detailed instrument to judge the methodological quality of model-based economic evaluations, which came in existence in the year 2004. Eleven out of the 16 included studies in our review were published earlier than 2004 and hence were not designed and reported with the criteria set out by Philips et al. (9) in mind. Moreover, several items of the checklist could be interpreted in different ways, and judgments remain subjective. This had to be solved by consensus among three reviewers. Overall reviewers experienced that an insufficient degree of information was available to assess all items of the framework for decision-analytic models, thus increasing uncertainty on the interpretation and generalisability of the results. Sometimes practical reasons could limit the scope of reporting finer details of the model in the assigned journal space (word limits).

There is an urgent need to address the problem of transparency in the economic modelling studies. Scientific rationale for modelling method and assumption used to develop the model structure should be clearly reported. Data identification, statistical methods used to incorporate data and synthesis of evidence should be transparent and accessible to the readers. Parameter uncertainty should be addressed by performing rigorous sensitivity analyses and preferably probabilistic sensitivity analysis. There are structured guidelines available to improve the transparency and quality of the economic models. To make methods more accessible to readers and to bring uniformity in reporting the results, researchers and modellers may follow the ISPOR task force guidelines for decision analytic modelling (26). A practical solution nowadays to provide more detailed information is to include an online appendix.

In some of the studies included in our systematic review the structure of the model used could only be assumed and some input parameters were only traceable by sifting the referenced
articles (10, 11, 17, 22-24). Lack of a clear description of the model structure creates confusion to the reader. LEAD signifies a widespread atherosclerosis in the circulatory system. Functional decline in LEAD patients ranging from intermittent claudication to the amputation of the limb are local and uncommon manifestations of the arterial narrowing. Considering the fact that LEAD poses a high economic burden largely because of the high rate of cardiovascular events like myocardial infarction and stroke hospitalisations, it is advisable to model all the important cardiovascular events likely to happen in the lifetime of LEAD patients.

More transparent depiction of model structure with precise description of disease states/pathways and calculation of transition probabilities is advised.

Another area that needs attention is utility values used in the decision model. As utility values used in an economic evaluation have a strong impact on the results of cost utility analysis. Therefore very careful and consistent use of utility values is warranted to obtain valid results. Discrepancy was noticed in utility weights used for similar health conditions in different studies posing a challenge to compare the economic evaluations.

Societal perspective for economic studies is preferred in order to estimate the societal costs and societal gains from an intervention in question. Half of the included decision analytic models had societal perspective. Three studies reported to have been done from societal perspective have failed to address certain costs, such as productivity loss (15, 22, 23).

Brief time horizons are clearly inconsistent with the chronic nature of LEAD, but were used in half of the included studies. To correctly assess the impact of any therapeutic intervention in a chronic health condition a lifetime horizon of the study would be preferable. Also in case of evaluating a diagnostic test that has therapeutic implications, we recommend using a lifetime time horizon.

Our systematic literature search also identified 11 trials based on economic evaluations conducted in the field of LEAD (27-37). Seven out of the 11 trials had patient populations with chronic intermittent claudication while four trials had patients with acute arterial occlusion (29, 30, 33, 36). These trials were conducted between the years 1991 and 2011 and had time horizons ranging from two days to two years. Clinical trials usually have a limited time frame with short-term clinical endpoints. Health care resources allocation decisions should be based on assessment of long-term economic and health impact on the whole society. Economic modelling provides a framework to incorporate data and to synthesise evidence across trials comparing different interventions and extrapolating long-term outcomes from short-term effects. Therefore, we only included model-based economic evaluations for LEAD in this systematic review.

This systematic review has some limitations as none of the non-English language articles were included. In addition, publication bias cannot be excluded as almost all the economic evaluations demonstrated cost-effectiveness. Only articles published in the peer reviewed journals were included in this review while grey literature (such as unpublished reports and conference proceedings) were not included. It is possible that more economic evaluation were done in the field of LEAD which were not included due to the specific inclusion and exclusion criteria.

Conclusion

This review has looked at modelling approaches applied to model the progression of LEAD. The process of evidence synthesis in the reviewed LEAD models is inconsistent, and there is considerable room for improvement. Explicit description of the model structure showing clear health states/pathways is required to make the reader understand the natural progression of the LEAD. Increased risk of clinically and economically important cardiovascular events in LEAD patients warrants the inclusion of these events in the model structure in order to capture the true costs and consequences of LEAD. Accounting for all relevant costs and transparent data incorporation is recommended for future LEAD models. Clearly stated assumptions, and probabilistic sensitivity analysis to test them, will improve the validity of the model outcomes. Researchers could address the issue of methodological quality and comparability by adhering to best practices to conduct economic evaluations of new interventions to inform the allocation of resources.

Acknowledgements

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Conflict of interest

None declared.

References

A SYSTEMATIC REVIEW OF MODEL-BASED ECONOMIC EVALUATIONS OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES FOR LOWER EXTREMITY ARTERY DISEASE


CHAPTER 3

Screen or not to screen for peripheral arterial disease:
guidance from a decision model
Screen or not to screen for peripheral arterial disease: guidance from a decision model

Anil Vaidya1,2*, Manuela A Joore1,2, Arina J ten Cate-Hoek3, Hugo ten Cate3 and Johan L Severens4

Abstract

Background: Asymptomatic Peripheral Arterial Disease (PAD) is associated with greater risk of acute cardiovascular events. This study aims to determine the cost-effectiveness of one time only PAD screening using Ankle Brachial Index (ABI) test and subsequent antiplatelet preventive treatment (low dose aspirin or clopidogrel) in individuals at high risk for acute cardiovascular events compared to no screening and no treatment using decision analytic modelling.

Methods: A probabilistic Markov model was developed to evaluate the life time cost-effectiveness of the strategy of selective PAD screening and consequent preventive treatment compared to no screening and no preventive treatment. The analysis was conducted from the Dutch societal perspective and to address decision uncertainty, probabilistic sensitivity analysis was performed. Results were based on average values of 1000 Monte Carlo simulations and using discount rates of 1.5% and 4% for effects and costs respectively. One way sensitivity analyses were performed to identify the two most influential model parameters affecting model outputs. Then, a two way sensitivity analysis was conducted for combinations of values tested for these two most influential parameters.

Results: For the PAD screening strategy, life years and quality adjusted life years gained were 21.79 and 15.66 respectively at a lifetime cost of 26,548 Euros. Compared to no screening and treatment (20.69 life years, 15.58 Quality Adjusted Life Years, 28,052 Euros), these results indicate that PAD screening and treatment is a dominant strategy. The cost effectiveness acceptability curves show 88% probability of PAD screening being cost effective at the Willingness To Pay (WTP) threshold of 40000 Euros. In a scenario analysis using clopidogrel as an alternative anti-platelet drug, PAD screening strategy remained dominant.

Conclusion: This decision analysis suggests that targeted ABI screening and consequent secondary prevention of cardiovascular events using low dose aspirin or clopidogrel in the identified patients is a cost-effective strategy. Implementation of targeted PAD screening and subsequent treatment in primary care practices and in public health programs is likely to improve the societal health and to save health care costs by reducing catastrophic cardiovascular events.

Keywords: Cost-effectiveness, Peripheral arterial disease, Ankle brachial index, Decision model

Background

Peripheral Arterial Disease (PAD) is a common disorder with a prevalence estimated at 16% in those aged over 55 years and 29% in high-risk groups [1,2]. PAD is a sign of widespread atherosclerosis also affecting coronary, cerebral and renal arteries. PAD is associated with a significant reduction in Quality of Life (QoL) and greater risk of acute cardiovascular events [3,4]. The increased risk for cardiovascular morbidity, such as myocardial infarction and stroke, and increased risk for mortality is also observed in asymptomatic patients [5]. The Cardiovascular consequences of PAD, are known to be expensive and contribute substantially to national health care costs [6].

European Society of Cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC) clinical practice guidelines recommend low dose...
aspirin to reduce the cardiovascular events and mortality in symptomatic PAD patients [7,8]. Clopidogrel is recommended as an effective alternative anti-platelet therapy to aspirin for secondary prevention in PAD [8]. Ankle Brachial Index (ABI) is used for detection of PAD. The ABI is calculated by measuring both arm and leg blood pressure (at ankle level). This reliable and inexpensive test is highly sensitive and specific for PAD. However, ABI screening in asymptomatic patients is a controversial topic among the health professionals. United States preventive services task force (USPSTF) assigned a “D” recommendation to the routine screening of PAD [9]. This recommendation is intensely debated and a routine targeted screening for PAD is recommended to increase the frequency of diagnosis, improve the use of recommended medical therapies, and consequently reduce cardiovascular morbidity and mortality rates [10]. Researchers have voiced that it’s not just about legs and ABI measurement in asymptomatic individuals should be regarded as the biomarker of cardiovascular disease risk [11]. While expansion of the evidence base for PAD screening is recommended in the year 2011 focussed update of the guidelines [12], targeted ABI screening is recommended by all professional vascular societies including the ACC [8].

The Rotterdam study has identified risk factors that are most strongly associated with PAD such as older age, cigarette smoking, diabetes mellitus, hypercholesterolemia and hypertension [13]. These risk factors can be used to guide targeted ABI screening in a general population over 55 years of age. In current health care practice, asymptomatic PAD often remains undiagnosed and opportunities for secondary prevention are missed [2]. Therefore, there is a clinical need of early detection of asymptomatic PAD and for the initiation the appropriate preventive treatment in a high risk population. Although, prevention and subsequent treatment comes at a certain cost the secondary prevention of cardio-vascular consequences in PAD patients may at the same time improve prognosis and save healthcare resources. This study aims to determine the cost-effectiveness of PAD screening using ABI and subsequent preventive treatment in high risk individuals at high risk for acute cardiovascular events with low dose aspirin or clopidogrel compared to no screening and treatment.

Methods
A model-based economic evaluation of targeted ABI screening in high-risk group was performed taking lifetime costs and health effects in account for a Dutch health care setting. Microsoft Excel 2010© software was used for this modelling work. Future costs and outcomes were discounted at the rates of 4% and 1.5% respectively, as per the Dutch guidelines for pharmaco-economic research [14]. This study was conducted from the societal perspective and indirect costs (productivity loss) were taken into account.

Model approach
The hypothetical population consists of asymptomatic males and females aged 55 years with at least one of the vascular risk factors identified in the Rotterdam study [13]. The intervention is one time screening in a high risk population at the age of 55 years using ABI, the current standard test to detect PAD in primary care. Screening in principle is intended to take place in the general practitioner’s office, in a similar manner as ‘The prevention visit’ for the cardiovascular risk assessment, defined in the Dutch College of General Practitioners’ practice guideline [15]. We modelled that all ABI test positive patients will receive preventive treatment with low dose aspirin in the base case analysis. In a scenario analysis low dose aspirin is replaced with clopidogrel as preventive treatment in patients with a positive test.

ABI screening is compared to no screening of the high risk population and preventive treatment is only given to the incidentally diagnosed or incidentally symptomatic patients. Model Outcomes were life years (LYs), quality adjusted life years (QALYs) and costs. The model has a time horizon of a life time as the hypothetical patient cohort was followed until death. The model cycle duration was one year.

Model structure
Based on a systematic review of modelling approaches for PAD, we used a combination of two modelling approaches: a decision tree and a Markov state transition model shown in the Figure 1 and Figure 2 [16]. The decision tree was used to determine the number of screened individuals falling into the categories of test positive or test negative on the basis of test accuracy and prevalence of PAD. A Markov model was subsequently used to model the on-going risk of cardiovascular events over a lifetime.

The model assumes that the patient is always in one of a finite number of states of health referred to as Markov states. The time horizon of the analysis is divided into equal increments of time, referred to as Markov cycles, in this case one year. During each cycle, the cohort of patients is redistributed over the Markov states, thus theoretically a patient may make a transition from one state to another. Each state is assigned a utility and a cost. Total costs and utility for screening versus no-screening are calculated depending upon the distribution of the cohort over the Markov states and the length of time spent in each state [17].
Chapter 3  Research Article

Positive test
Negative test
True True
False False

High risk population

ABI Screening

Figure 1 Decision tree.

Preventive treatment to symptomatic patients only.

Figure 2 Markov model.

Preventive Rx
Preventive Rx
Preventive Rx
Preventive Rx
Preventive Rx
We included all the relevant cardiovascular health states in the Markov model (no PAD, asymptomatic PAD, and symptomatic PAD, post myocardial infarction, post stroke, post bleed-in treated patients and the absorbing state of death). Risk reductions of cardiovascular events and mortality as well as increased bleeding risk caused by the preventive anti-platelet treatment were modelled accordingly in our model. All the model parameters are shown in Table 1.

**Transition probabilities**
Transition probabilities for PAD patients were calculated from the REACH (Reduction of Athero-thrombosis for Continued Health) registry. This multinational database contains 68,375 consecutive outpatients from 5587 physician practices in 44 countries and was enrolled between December 2003 and June 2004 [24]. Patients on anti-platelet preventive treatment have reduced cardiovascular morbidity and mortality but on the other hand this treatment increases the risk of bleeding in the recipients. Transition probabilities for cardiovascular events in patients receiving Aspirin were calculated from a meta-analysis of randomised trials ‘Aspirin for the Prevention of Cardiovascular Events in Patients With Peripheral Artery Disease’ [26]. Probabilities for Clopidogrel were calculated from a Cochrane review of anti-platelet agents for intermittent claudication [28]. Bleeding risks in patients receiving low dose aspirin or clopidogrel were assigned from a randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) [27].

**Costs**
The acute phase costs and subsequent costs of cardiovascular events were taken from Thurston et al. [21] and the costs of amputation and of cardiovascular death are from Oostenbrink et al. [20]. The annual costs for an average PAD patient were published by van Asselt et al. [18] Dutch costs of anti-platelet medications aspirin and clopidogrel were obtained from the medicine cost website in the Netherlands [19]. Travel costs for attending the PAD screening were calculated based on the average distance to a primary practice. The average distance to a Dutch primary practice is 1.1 KM [32]. Cost of a session at a primary care physician and productivity loss for a 55 years old individual in the Netherlands are published in the Dutch manual for costing in economic evaluations [33]. All costs used in the model were converted to Year 2012 Dutch costs using harmonized index of consumer prices data from the Dutch bureau of statistics [34].

**Utilities**
Since Dutch utility scores for the health states defined in our model were not found in the literature, we used Sullivan et al. to estimate utilities for all the health states except amputation [30]. The utility of an amputee using standard gamble method was taken from Berry et al. [31].

**Analysis**
Discounted and undiscounted expected life years and QALYs (1.5% discount rate), and costs (discount rate 4%) for each strategy were calculated. Based on the discounted expected values, the Incremental Cost Effectiveness Ratios (ICERs) of the screening and treatment strategy were calculated over the standard existing practice of no screening and preventive treatment with low dose aspirin for incidentally diagnosed or symptomatic patients only.

The results of cost-effectiveness analysis were based on Probabilistic Sensitivity Analysis (PSA). Results of 1000 Monte Carlo simulations were graphically displayed in the form of cost-effectiveness planes (CE planes) and the subsequent probability of being cost-effective at different values of willingness to pay (WTP) thresholds was shown as cost-effectiveness acceptability curves (CEACs).

One way sensitivity analyses were performed to identify the two most influential model parameters affecting model outputs. For this purpose, upper and lower limits of 95% confidence interval of model parameters were used. Then, a two way sensitivity analysis was conducted for combinations of values tested for these two most influential parameters.

**Scenario analysis**
We performed a scenario analysis by replacing routinely prescribed low dose aspirin with a relatively new anti-platelet drug clopidogrel for the secondary prevention of cardiovascular events in identified PAD patients.

**Results**

**Cost-effectiveness analysis**
The expected model outcomes show that the targeted ABI screening and treatment with low dose aspirin produce 21.79 mean LYS and 15.66 mean QALYs for a cost of 26,548 Euros. The cost of PAD screening and treatment followed by low dose aspirin was 1503 Euros lower compared to ‘no screening’ and 0.07 QALYs were gained (Table 2). Therefore, ABI screening followed by preventive treatment with low dose aspirin is a dominant strategy. The relationship between costs and effects and the uncertainty surrounding these estimates are shown in the cost effectiveness planes in the Figure 3. Monte Carlo simulation shows that the 88% of ICER dots are in the right lower quadrant indicating that the strategy ‘PAD screening’ tended to have favourable health outcomes against lower costs in comparison with a strategy of ‘no screening’. The probability of being cost effective at different values of willingness to pay (WTP) thresholds...
Table 1 Model parameters and distribution used in the probabilistic sensitivity analyses

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Value</th>
<th>Probability distribution</th>
<th>Moments of the probability distribution $\alpha/\min, \beta/\max$</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discount rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost discount rate</td>
<td>4%</td>
<td>Fixed</td>
<td>-</td>
<td>[14]</td>
</tr>
<tr>
<td>Outcome discount rate</td>
<td>1.5%</td>
<td>Fixed</td>
<td>-</td>
<td>[14]</td>
</tr>
<tr>
<td><strong>Costs (Euros)</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of ankle brachial index test</td>
<td>74†</td>
<td>BETA Pert</td>
<td>55.7;92.8</td>
<td>MUMC4</td>
</tr>
<tr>
<td>Annual cost of PAD treatment</td>
<td>2369</td>
<td>GAMMA</td>
<td>325;972.20</td>
<td>[18]</td>
</tr>
<tr>
<td>Annual cost of Aspirin</td>
<td>10</td>
<td>Fixed</td>
<td>-</td>
<td>[19]</td>
</tr>
<tr>
<td>Annual cost of Clopidogrel</td>
<td>19</td>
<td>Fixed</td>
<td>-</td>
<td>[19]</td>
</tr>
<tr>
<td>Costs of Amputation</td>
<td>14343†</td>
<td>BETA Pert</td>
<td>10683;17804</td>
<td></td>
</tr>
<tr>
<td>Cost of AMI in first year</td>
<td>25328</td>
<td>GAMMA</td>
<td>100;253.27</td>
<td>[21]</td>
</tr>
<tr>
<td>Annual costs of MI treatment in subsequent years</td>
<td>3584</td>
<td>GAMMA</td>
<td>999;235.86</td>
<td>[21]</td>
</tr>
<tr>
<td>Cost of stroke in first year</td>
<td>27964</td>
<td>GAMMA</td>
<td>999;95;279.66</td>
<td>[21]</td>
</tr>
<tr>
<td>Annual costs of treatment of stroke in subsequent years</td>
<td>10646</td>
<td>GAMMA</td>
<td>999;99;106.47</td>
<td>[21]</td>
</tr>
<tr>
<td>Costs of bleeding</td>
<td>3457</td>
<td>GAMMA</td>
<td>999;87;346.1</td>
<td>[21]</td>
</tr>
<tr>
<td><strong>ABI test accuracy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.90†</td>
<td>BETA Pert</td>
<td>0.681</td>
<td>[22]</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.95†</td>
<td>BETA Pert</td>
<td>0.711</td>
<td>[22]</td>
</tr>
<tr>
<td><strong>Incidence/prevalence of PAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of PAD</td>
<td>0.184</td>
<td>BETA</td>
<td>1372;6082</td>
<td>[6]</td>
</tr>
<tr>
<td>Annual incidence of PAD in 55–64 years aged</td>
<td>0.005</td>
<td>BETA</td>
<td>See Additional file 1</td>
<td>[23]</td>
</tr>
<tr>
<td>Annual incidence of PAD in 65–74 years aged</td>
<td>0.007</td>
<td>BETA</td>
<td>See Additional file 1</td>
<td>[23]</td>
</tr>
<tr>
<td>Annual incidence of PAD in 75–84 years aged</td>
<td>0.008</td>
<td>BETA</td>
<td>See Additional file 1</td>
<td>[23]</td>
</tr>
<tr>
<td>Annual incidence of PAD in &gt;85 years aged</td>
<td>0.010</td>
<td>BETA</td>
<td>See Additional file 1</td>
<td>[23]</td>
</tr>
<tr>
<td><strong>Event probabilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of amputation in patients with no PAD</td>
<td>0.003</td>
<td>BETA</td>
<td>32;11734</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of AMI in patients with no PAD</td>
<td>0.008</td>
<td>BETA</td>
<td>89;11677</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of stroke in patients with no PAD</td>
<td>0.008</td>
<td>BETA</td>
<td>94;11672</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of amputation in PAD patients</td>
<td>0.016</td>
<td>BETA</td>
<td>140;9441</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of AMI in PAD patients</td>
<td>0.013</td>
<td>BETA</td>
<td>111;9470</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of stroke in PAD patients</td>
<td>0.019</td>
<td>BETA</td>
<td>165;8416</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of symptomatic PAD</td>
<td>0.3</td>
<td>BETA</td>
<td>138;320</td>
<td>[25]</td>
</tr>
<tr>
<td>Relative risk in PAD patients on low dose aspirin</td>
<td>0.78</td>
<td>BETA</td>
<td>25;5;72</td>
<td>[26]</td>
</tr>
<tr>
<td>Probability of bleeding in PAD patients on aspirin</td>
<td>0.026</td>
<td>BETA</td>
<td>255;9311</td>
<td>[27]</td>
</tr>
<tr>
<td>Relative risk in PAD patients on Clopidogrel</td>
<td>0.016</td>
<td>BETA</td>
<td>See Additional file 1</td>
<td>[28]</td>
</tr>
<tr>
<td>Probability of bleeding in PAD patients on Clopidogrel</td>
<td>0.020</td>
<td>BETA</td>
<td>191;9386</td>
<td>[27]</td>
</tr>
<tr>
<td><strong>Mortality in ‘untreated’ patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual probability of death in PAD patients</td>
<td>0.037</td>
<td>BETA</td>
<td>323;8258</td>
<td>[24]</td>
</tr>
<tr>
<td>Probability of death in post Amputation</td>
<td>0.155</td>
<td>BETA</td>
<td>429;72;1281</td>
<td>[29]</td>
</tr>
<tr>
<td>annual probability of death in post MI alive patients</td>
<td>0.028</td>
<td>BETA</td>
<td>521;17492</td>
<td>[24]</td>
</tr>
<tr>
<td>annual probability of death in post stroke alive patients</td>
<td>0.031</td>
<td>BETA</td>
<td>121;2370</td>
<td>[24]</td>
</tr>
<tr>
<td><strong>Utility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>0.652</td>
<td>BETA</td>
<td>0.804</td>
<td>[30]</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.45</td>
<td>BETA</td>
<td>210;8257.7</td>
<td>[31]</td>
</tr>
</tbody>
</table>
was shown as cost effectiveness acceptability curves (CEACs) in the Figure 4. The curves show the probability of PAD screening being cost effective at a range of Willingness To Pay thresholds. There is 88% probability of PAD screening being cost effective at the WTP of 40000 Euros.

Scenario analysis with the use of clopidogrel as an alternative anti-platelet therapy produced similar results indicating dominance over ‘no screening’ (Table 2).

The one way sensitivity analysis identified PAD prevalence and relative risk reduction by low dose aspirin in the treated PAD patients, as the two most influential model parameters. Although the ICER for ABI screening remained dominant for all the variations in parameter values, two way sensitivity analysis varying PAD prevalence and relative risk reduction by aspirin showed a consistent QALY gain by either increasing the prevalence of PAD or relative risk reduction by low dose aspirin.

Discussion

Our cost-effectiveness model output suggests that targeted screening of high risk individuals and consequent secondary prevention of cardiovascular events by anti-platelet medication is cost effective and results in significant health gain by reducing cardiovascular events in PAD patients.

The analysis has been performed from societal perspective and all direct and indirect costs are incorporated for all the health states in the model. Our analysis interprets that PAD screening and anti-platelet preventive treatment is a highly cost-effective intervention. Changing the analysis perspective to health care payer’s, would further strengthen this interpretation. This is the case in countries like the United Kingdom where health care is financed by general taxation, a health care provider’s (National Health Services) perspective is used in pharmaco-economic analyses and only direct costs are covered.

A recent meta-analysis concluded that measurement of the ankle brachial index may improve the accuracy of cardiovascular risk prediction beyond the Framingham Risk Score [35]. After adjustment for the Framingham risk score, the ABI provided significant improvement in predicting cardiovascular risk independent of established risk factors in a broad population. There is unequivocal evidence establishing the importance of targeted ABI screening [36,37].

In our model costs and effects were modeled for aspirin and clopidogrel. The CAPRIE trial data show that clopidogrel is more effective than aspirin in reducing cardiovascular events in the subgroup of patients with

Table 1 Model parameters and distribution used in the probabilistic sensitivity analyses (Continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post MI</td>
<td>0.671</td>
<td>Beta 69.3;34</td>
</tr>
<tr>
<td>Post stroke</td>
<td>0.519</td>
<td>Beta 2.7;2.5</td>
</tr>
<tr>
<td>Post bleed</td>
<td>0.627</td>
<td>Beta 405.6;241.13</td>
</tr>
</tbody>
</table>

*All costs were converted to 2012 Dutch costs using harmonized index of consumer prices (HICP).
†This cost was obtained from the Financial department of Maastricht University Medical Centre.
‡Mode for Beta Pert distribution.

Table 2 Results – base case analysis and scenario analysis

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Treatment</th>
<th>Costs</th>
<th>LYs</th>
<th>QALYs</th>
<th>iCosts</th>
<th>iLY</th>
<th>iQALYs</th>
<th>iCERs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No screen</td>
<td>Low dose aspirin</td>
<td>28052</td>
<td>20.69</td>
<td>15.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI screening</td>
<td>Low dose aspirin</td>
<td>26548</td>
<td>21.79</td>
<td>15.66</td>
<td>−1503</td>
<td>1.10</td>
<td>0.007</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

Scenario analysis with Clopidogrel

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Treatment</th>
<th>Costs</th>
<th>LYs</th>
<th>QALYs</th>
<th>iCosts</th>
<th>iLY</th>
<th>iQALYs</th>
<th>iCERs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screen</td>
<td>Clopidogrel</td>
<td>29464</td>
<td>22.33</td>
<td>15.95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td>Clopidogrel</td>
<td>27681</td>
<td>22.57</td>
<td>16.17</td>
<td>−1783</td>
<td>0.24</td>
<td>0.22</td>
<td>Dominant</td>
</tr>
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</table>

PROBABILISTIC RESULTS (undiscounted)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Treatment</th>
<th>Costs</th>
<th>LYs</th>
<th>QALYs</th>
<th>iCosts</th>
<th>iLY</th>
<th>iQALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No screen</td>
<td>Low dose aspirin</td>
<td>63155</td>
<td>26.32</td>
<td>19.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI screening</td>
<td>Low dose aspirin</td>
<td>59544</td>
<td>27.47</td>
<td>19.50</td>
<td>−3611</td>
<td>1.15</td>
<td>0.11</td>
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</table>

Scenario analysis with Clopidogrel

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Treatment</th>
<th>Costs</th>
<th>LYs</th>
<th>QALYs</th>
<th>iCosts</th>
<th>iLY</th>
<th>iQALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screen</td>
<td>Clopidogrel</td>
<td>67799</td>
<td>28.30</td>
<td>19.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td>Clopidogrel</td>
<td>63759</td>
<td>28.66</td>
<td>20.27</td>
<td>−4039</td>
<td>0.36</td>
<td>0.31</td>
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</table>


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CHAPTER 4

Cost-effectiveness of risk assessment and tailored treatment for peripheral arterial disease patients
Research Article
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Biomarkers in Medicine

Cost-effectiveness of risk assessment and tailored treatment for peripheral arterial disease patients

Aim: The objective of this study was to explore the cost-effectiveness of D-dimer biomarker and the societal value (headroom) of a hypothetical perfect biomarker for risk assessment and subsequent treatment stratification of prophylactic treatments for peripheral arterial disease (PAD). Patients & methods: Decision analytic modeling. Results: Use of the D-dimer biomarker to prescribe oral anticoagulants in the high-risk subset of patients is a cost-effective healthcare intervention. The headroom (societal willingness to pay multiplied by incremental quality-adjusted life years) available for the hypothetical perfect biomarker amounted to €83,877. Conclusion: D-dimer-based PAD risk assessment and treatment tailoring is cost effective. Identification of high-risk PAD patients and prescription of oral anticoagulants could potentially save substantial costs and improve chances of survival for high-risk PAD patients. However, further research of risk stratifying biomarkers test accuracy is needed to support and strengthen the results of this modeling study.

Keywords: cost-effectiveness analysis • D-dimer • decision modeling • peripheral arterial disease • risk assessment

Background
Peripheral arterial disease (PAD) affects a large proportion of adult populations worldwide. The prevalence of PAD ranges between 3% and 10% and rises with age reaching to 15–20% in persons over 70 years [1]. Around 30 million people are affected by PAD in Europe and North America [2].

PAD is a marker of generalized atherosclerosis in coronary, cerebral and renal arteries. PAD patients are at higher risk of cardiovascular (CV) ischemic events due to atherothrombosis. Studies have shown a nearly two to sixfold increase in relative risk of CV events, for example, myocardial infarction (MI), stroke, aortic aneurysm rupture and vascular death in patients with PAD compared with those without [3]. Long-term acetyl salicylic acid (ASA) therapy is recommended and widely used for prophylaxis of CV events in PAD patients [3,4]. ASA is an affordable, safe and efficacious preventive treatment for most [4]. Although ASA remains the first line therapy for prevention of CV events in PAD patients, use of oral anticoagulants (OACs) is considered in high-risk patients [4]. Hackam and Eikelboom have conducted a systematic review and have recommended the use of other agents than ASA for thromboprophylaxis in some scenarios, for example, thromboembolic state or history of graft occlusion [4]. In another recent review a need for individualized anti-thrombotic regimen in patients with PAD is highlighted [5].

The investigators of the Dutch BOA study concluded that OACs are more effective than ASA in lowering the rate of ischemic events. Oral anticoagulation lowered the frequency of death, nonfatal MI, nonfatal stroke and amputation compared with the group assigned treatment with ASA. However, the risk of hemorrhage was found to be nearly double with the use of OACs in this study [6]. Routine use of OACs for the CV event prevention in PAD patients is...
therefore not recommended because of the unfavorable risk/benefit equation [5]. However, use of OACs instead of ASA in a selected patient population at high risk of ischemic events could have a more favorable risk/benefit ratio.

In a recently published meta-analysis, high D-dimer levels are shown to be associated with higher risk of CV events in PAD patients [11]. Development of other novel biomarkers for the risk assessment in PAD patients is underway. Thus, the spectrum of patients with PAD contains high and nonhigh-risk subgroups, which would necessitate different therapeutic strategies. Identification of individuals on greater risk of CV events among the established PAD patients and prescribing OACs may improve outcomes.

The objective of this study was to explore the cost–effectiveness (CE) of D-dimer and the headroom of a hypothetical perfect biomarker for risk assessment and subsequent treatment stratification of prophylactic treatment for PAD.

Patients & methods

Model approach

Decision analytic modeling was used to compare two strategies: the current practice of no risk assessment and uniform treatment (current practice), and D-dimer risk assessment and treatment stratification (D-dimer). In the current practice strategy, no risk assessment takes place, and all PAD patients are prescribed low-dose ASA for the prevention of CV events. In the D-dimer strategy, the high-risk subset of PAD patients is identified by elevated D-dimer in the blood. Subsequently, these high-risk patients receive preventive treatment using OAC. All the non-high-risk PAD patients are given preventive treatment using ASA.

Besides, to assess the CE of D-dimer versus usual care, the model was used to assess the value of a hypothetical perfect biomarker risk assessment and treatment stratification. This type of analysis has been called headroom analysis. A headroom analysis determines the societal value of innovations in healthcare by using a threshold approach. Headroom analysis estimates the maximum cost that a perfect biomarker can be brought to market and still be considered cost effective. The headroom analysis is a quick and useful way to consider the investment opportunity at a very early stage and helps industry to reduce the risk of investing in a new technology that once developed is unlikely to be reimbursed by the healthcare providers.

Based on a systematic review of modeling approaches for PAD and on recent European Society of Cardiology guidelines, a state transition Markov model was deemed appropriate to represent the natural history of PAD [12,13]. Markov model is the preferred modeling approach for chronic diseases such as PAD, where model parameters such as progression rates, utilities and costs may change overtime. Microsoft Excel 2010 software was used for this modeling work.

Health states used in our Markov model were PAD, post-lower-limb amputation (a local consequence of the PAD), post MI and poststroke (systemic consequences of generalized atherothrombosis), postbleed (adverse consequence of preventive treatment) and an absorbing state of death. To avoid complexity, and since we do not expect a significant impact of this simplification on the marginal difference between the decision options, we did not model secondary events in postamputation, post-MI, post-stroke or in post-bleed patients so these patients only moved to the absorbing state of death. A graphic representation of the model is shown in Figure 1. The outcomes were life years, quality-adjusted life years (QALYs) and costs. The time horizon was life time and the cycle duration was 1 year. This study was conducted using a societal perspective in the Dutch setting and future costs and outcomes were discounted as per the Dutch pharmacoeconomic guidelines at the rates of 4 and 1.5%, respectively [14]. The model input parameters are presented in Table 1.

Transition probabilities

CV event rates in a population with multiple risk factors and in PAD patients were published by Steg et al. (REduction of Atherothrombosis for Continued Health [REACH] registry). This database containing 68,375 consecutive outpatients from 5587 physician practices in 44 countries, including the Netherlands, and were enrolled between December 2003 and June 2004 [18].

Following the consultation with Dutch clinical experts in this field, the overall proportion of the patients at higher risk of CV events (among PAD patients) was assumed to be 20% among the PAD patients and was varied in scenario analysis. A recent meta-analysis by Kleinegris et al. concluded that the PAD patients with elevated D-dimer are 2.3-times (95% CI: 1.43–3.68) likely to have a CV event than patients with normal D-dimer levels [18]. Since there is no data available for occurrence of CV events for low or high-risk PAD patients specifically, we have recalculated the transition probabilities of CV events separately in low and high-risk group of patients using REACH registry data (Supplementary Material; see online at www.futuremedicine.com/doi/full/10.2217/ BMM.14.45). In short, the recalculated transition probabilities are based on the relative risk of a CV event with D-dimer elevation reported by Kleinegris et al.
and the proportion of high-risk patients among PAD patients. CV event probabilities in the D-dimer strategy were derived using following formulas:

- Probability of CV events in low-risk PAD patients = probability of CV event in PAD patients/(1 - proportion high risk among PAD patients) + (proportion high risk among PAD patients × relative risk)

- Probability of CV events in high-risk PAD patients = probability of CV events in low-risk PAD patients × relative risk

We assumed that the hypothetical perfect biomarker will optimally identify the PAD patients who are likely to have CV events. Therefore, the remaining PAD patients (identified by the perfect biomarker as not being at high risk) were assumed to have the same risk of CV event rates as in the population with multiple risk factors reported in the REACH (Reduction of Atherothrombosis for Continued Health) registry [14]. Probability of CV events in low-risk PAD patients identified by the perfect biomarker was assumed to be equal to the probability of CV events in the ‘population at risk’. Probability of CV events in the perfect biomarker identified high-risk PAD patients was calculated as:

- = (Probability of CV event in PAD patients - (1 - proportion high risk among PAD patients × probability of CV events in low-risk PAD)) / proportion high risk among PAD patients

Patients on preventive treatment with ASA or with OAC have reduced CV morbidity and mortality but on the other hand, preventive treatments increase the risk of bleeding in the drug recipients. Relative risk of CV events in the recipients of ASA is assigned from a collaborative meta-analysis of randomized trials of antiplatelet therapies published by Antithrombotic Trialsists’ Collaboration [19]. Relative risk of CV events is calculated from the Dutch BOA study. Bleeding risks in ASA or OAC receiving patients were also assigned from the Dutch BOA study. In the Netherlands, acenocoumarol and phenprocoumon are frequently prescribed OACs and were used in the Dutch BOA trial [9].

Costs

The annual costs for an average PAD patient were published by van Asselt et al. [15]. Costs of amputation,
<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Value</th>
<th>Probability distribution</th>
<th>Moments of the probability distribution: β for BETA/min; max for BETA PERT distribution†</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discount rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost discount rate</td>
<td>4%</td>
<td>Fixed</td>
<td>–</td>
<td>[14]</td>
</tr>
<tr>
<td>Outcome discount rate</td>
<td>1.5%</td>
<td>Fixed</td>
<td>–</td>
<td>[14]</td>
</tr>
<tr>
<td>Costs (€)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of D-dimer test</td>
<td>20†</td>
<td>BETA PERT 15; 25</td>
<td>MUMC</td>
<td></td>
</tr>
<tr>
<td>Annual cost of PAD treatment</td>
<td>2369</td>
<td>GAMMA 325.09; 7.29</td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>Annual cost of aspirin</td>
<td>135</td>
<td>Fixed</td>
<td>–</td>
<td>[16]</td>
</tr>
<tr>
<td>Annual cost of acenocumarol including INR monitoring</td>
<td>310</td>
<td>Fixed</td>
<td>–</td>
<td>[16]</td>
</tr>
<tr>
<td>Costs of amputation</td>
<td>14,343†</td>
<td>BETA PERT 10683; 17804</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Cost of MI in first year</td>
<td>25,328</td>
<td>GAMMA 100; 253.27</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Annual costs of MI treatment in subsequent years</td>
<td>3584</td>
<td>GAMMA 99.92; 35.86</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Cost of stroke in first year</td>
<td>27,964</td>
<td>GAMMA 99.99; 279.66</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Annual costs of treatment of stroke in subsequent years</td>
<td>10,646</td>
<td>GAMMA 99.99; 106.47</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Costs of bleeding</td>
<td>3457</td>
<td>GAMMA 99.87; 34.61</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Event probabilities in ‘population at risk’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of amputation</td>
<td>0.003</td>
<td>BETA 21.8; 7832.17</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of MI</td>
<td>0.008</td>
<td>BETA 61.46; 8055.92</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of stroke</td>
<td>0.008</td>
<td>BETA 68.10; 8478.28</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of death</td>
<td>0.015</td>
<td>BETA 124.7; 8196</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Event probabilities in ‘PAD patients’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of amputation in PAD patients</td>
<td>0.016</td>
<td>BETA 61; 3694</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Probability of AMI in PAD patients</td>
<td>0.013</td>
<td>BETA 79; 6062</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Probability of stroke in PAD patients</td>
<td>0.019</td>
<td>BETA 112; 5795</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Probability of death in PAD patients</td>
<td>0.039</td>
<td>BETA 226.2; 5903</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Proportion of ‘high-risk’ PAD</td>
<td>0.2</td>
<td>Fixed</td>
<td>–</td>
<td>Assumption/expert opinion</td>
</tr>
<tr>
<td>Occurrence of events in low- &amp; high-risk PAD patients based on D-dimer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of CV events in elevated D-dimer patients</td>
<td>0.023</td>
<td>BETA 16; 665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of amputation in low-risk PAD patients</td>
<td>0.0128</td>
<td>BETA Calculated</td>
<td>Based on [19]</td>
<td></td>
</tr>
<tr>
<td>Probability of AMI in low-risk PAD patients</td>
<td>0.0102</td>
<td>BETA Calculated</td>
<td>Based on [19]</td>
<td></td>
</tr>
<tr>
<td>Probability of stroke in low-risk PAD patients</td>
<td>0.0151</td>
<td>BETA Calculated</td>
<td>Based on [19]</td>
<td></td>
</tr>
<tr>
<td>Probability of death in PAD low-risk patients</td>
<td>0.0293</td>
<td>BETA Calculated</td>
<td>Based on [19]</td>
<td></td>
</tr>
<tr>
<td>Probability of amputation in high-risk PAD patients</td>
<td>0.0295</td>
<td>BETA Calculated</td>
<td>Based on [19]</td>
<td></td>
</tr>
</tbody>
</table>

Occurrence of events in the current practice strategy is calculated using CV event probabilities in PAD patients and relative risk of CV events in PAD patients on ASA.

Supplementary Material

All costs were converted to 2012 Dutch costs using harmonized index of consumer prices (HICP).

† Mode for BETA PERT distribution.

AMI: Acute myocardial infarction; ASA: Acetylsalicylic acid; CV: Cardiovascular; INR: International normalized ratio; MI: Myocardial infarction; MUMC: Maastricht University Medical Centre; OAC: Oral anticoagulant; PAD: Peripheral arterial disease.
Cost–effectiveness of risk assessment & tailored treatment for peripheral arterial disease patients  

Research Article

The acute phase costs and subsequent costs of CV events (MI and Stroke) and costs of bleeding were taken from Thurston et al. [17]. All costs were converted to year 2012 Dutch costs using harmonized index of consumer prices data from the Dutch bureau of statistics [22].

Utilities
A Dutch EQ-5D-based utility score for the postbleed health state was published by Oostenbrink et al. [16]. In the absence of Dutch data on utility scores for the other health states used in our model, we used a catalog of EQ-5D scores published by Sullivan et al., providing EQ-5D scores for a variety of chronic conditions using UK-based preferences from a general population [19]. The utility scores for MI (post-MI health state), stroke (poststroke health state) and atherosclerosis (low and high-risk PAD health states) were used from this source. The utility of an amputee using wheel chair is published by Berry et al. and is based on standard gamble method in the UK population [21]. The utility score was used for the postamputation health state.

Analysis
The expected costs and QALYs of the strategies were based on the results of the probabilistic sensitivity analysis (PSA) with 1000 simulations. PSA allows systematic propagation of uncertainty in all model parameters.

Table 1. Model input parameters (cont.).

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Value</th>
<th>Probability distribution</th>
<th>Moments of the probability distribution: β for BETA/µ/min; max for BETA PERT distribution</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of events in low- &amp; high-risk PAD patients based on D-dimer (cont.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of AMI in high-risk PAD patients</td>
<td>0.0234 BETA</td>
<td>Calculated</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Probability of stroke in high-risk PAD patients</td>
<td>0.0347 BETA</td>
<td>Calculated</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Probability of death in high-risk PAD patients</td>
<td>0.0674 BETA</td>
<td>Calculated</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Probability of amputation in low-risk PAD patients</td>
<td>0.003  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of stroke in low-risk PAD patients</td>
<td>0.008  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of death in low-risk PAD patients</td>
<td>0.015  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of amputation in high-risk PAD patients</td>
<td>0.070  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of stroke in high-risk PAD patients</td>
<td>0.063  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Probability of death in high-risk PAD patients</td>
<td>0.125  BETA</td>
<td>Calculated</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td>Relative risk of CV events in PAD patients on ASA</td>
<td>0.810  BETA</td>
<td>Calculated</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Probability of bleeding in PAD patients on ASA</td>
<td>0.041  BETA</td>
<td>56; 1268</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Relative risk of CV events in PAD patients on OAC</td>
<td>0.720  BETA</td>
<td>Calculated</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Probability of bleeding in PAD patients on OAC</td>
<td>0.078  BETA</td>
<td>108; 1218</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>Utility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>0.652  BETA</td>
<td>144; 77</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.45   BETA</td>
<td>211; 258</td>
<td></td>
<td>[21]</td>
</tr>
<tr>
<td>Post MI</td>
<td>0.671  BETA</td>
<td>69; 34</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Poststroke</td>
<td>0.519  BETA</td>
<td>323; 300</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>0.581  BETA PERT</td>
<td>0.435; 0.725</td>
<td></td>
<td>[16]</td>
</tr>
</tbody>
</table>

Occurrence of events in the current practice strategy is calculated using CV event probabilities in PAD patients and relative risk of CV events in PAD patients on ASA. Supplementary Material: All costs were converted to 2012 Dutch costs using harmonized index of consumer prices (HICP).† Mode for BETA PERT distribution.‡ All costs were converted to year 2012 Dutch costs using harmonized index of consumer prices data from the Dutch bureau of statistics [22].

AMR: Acute myocardial infarction; ASA: Acetyl salicylic acid; CV: Cardiovascular; INR: International normalized ratio; MI: Myocardial infarction; MUMC: Maastricht University Medical Centre; OAC: Oral anticoagulant; PAD: Peripheral arterial disease.
COST-EFFECTIVENESS OF RISK ASSESSMENT AND TAILORED TREATMENT FOR PERIPHERAL ARTERIAL DISEASE PATIENTS

by assigning distributions to parameters and using a Monte Carlo simulation technique. ‘Beta’ distributions were assigned to the transition probabilities to various health states in the model and to the relative risk reductions by preventive treatments (ASA and OAC). The costs were assigned Gamma distributions in the Markov model. The BETA PERT distribution for model parameters (based on mode and ± 25% range) was used if confidence intervals or standard errors were not reported in the source literature. Fixed values such as the discount rate were not subject to the PSA.

A CE plane was used to graphically display the results of the PSA. The probability that D-Dimer is cost effective compared with usual care at different values of willingness to pay (WTP) thresholds was shown in a CE acceptability curve [23]. In order to further explore uncertainty, a series of scenario analyses were conducted varying the proportion of high-risk individuals among the PAD patients.

To assess the headroom for the perfect biomarker, societal WTP for a QALY is multiplied by the maximum QALY gain, in order to calculate the maximum additional cost of the new technology to remain cost effective [24]. Modeling a hypothetical perfect biomarker (optimal diagnostic accuracy and no cost) scenario for perfect identification of the high-risk PAD patients makes it possible to calculate the maximum QALY gain, thus the available headroom for such a biomarker. WTP threshold in the Netherlands varies between €20,000 per QALY [25] and a maximum of €80,000 per QALY proposed by the Dutch Council for Public Health and Health Care [31]. For our analysis

Table 2. Base case results.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean costs (€)†</th>
<th>Mean LYS†</th>
<th>Mean QALYs†</th>
<th>iCosts</th>
<th>iLYs</th>
<th>iQALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care</td>
<td>38,866</td>
<td>19.37</td>
<td>11.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-dimer risk stratification</td>
<td>38,056</td>
<td>19.53</td>
<td>11.68</td>
<td>-810</td>
<td>0.16</td>
<td>0.09</td>
<td>Dominant</td>
</tr>
</tbody>
</table>


Figure 2. Incremental cost–effectiveness plane. Usual care versus D-dimer.

iCost: Incremental cost; iQALY: Incremental quality-adjusted life year.
the Dutch informal WTP threshold was assumed to be €40,000 per QALY. The headroom was calculated as follows:

- Headroom = WTP × (QALYs gain by the use of perfect biomarker - QALYs gain by the use of usual care strategy)

A headroom scenario analysis was performed by varying the proportion of high-risk individuals among PAD patients.

Results

Usual care of all diagnosed PAD patients treated with ASA yielded on average 11.59 QALYs. Use of D-dimer for risk stratification followed by treatment of high-risk patients with OAC yielded on average 11.68. The total mean costs per patient were €38,866, for the usual care strategy and €38,056 for the D-dimer strategy. As a result, the D-dimer strategy dominated the usual care by producing higher mean QALYs at a lower mean cost. Detailed results for costs and outcomes associated with the usual care and currently available D-dimer are presented in Table 2. Figure 2 shows the incremental CE plane of D-dimer comparing to the usual care. The CE acceptability curves revealed that the D-dimer risk-assessment strategy has a high probability of being cost effective at a range of WTP thresholds. At a WTP of €40,000 per QALY, the D-dimer risk assessment had a 99.3% probability of being cost effective.

Use of the perfect biomarker for the accurate identification of the high-risk patients and their subsequent treatment with oral anticoagulants was expected to yield 2.09 incremental QALYs per patient in the base case scenario. The headroom available for the perfect biomarker was computed to be €83,877 for the base case (assuming 20% high-risk patients). The headroom for perfect biomarker decreases with the increasing proportion of high-risk patients and vice versa. The headroom for various proportions of high-risk individuals among PAD patients is shown in Figure 3.

Results of scenario analysis are shown in Table 3.

Discussion

We explored the the CE of risk assessment and treatment stratification by D-dimer and the headroom of a hypothetical perfect biomarker in PAD patients. As a result of this risk assessment, high-risk patients may be given stepped up secondary prevention by the use of OAC. The CE analysis results show that the use of currently available D-dimer to prescribe preventive treatment using OAC in the high-risk subset of patients is a cost-effective healthcare intervention. Therefore, correct identification of eligible and suitable patients for OAC treatment could change the current practice of universal ASA prescription to all PAD patients. We also assessed the commercial headroom available for developing biomarkers by modeling a hypothetical perfect biomarker and concluded that a risk assessment and treatment stratification for PAD patients could be financially attractive and societally cost effective. This economic modeling study clearly shows that it would be cost effective to identify high-risk PAD patients and subsequently give customized treatment with OAC therapy instead of a routine ASA treatment. Investment in laboratory and clinical studies for the development of biomarkers for this purpose is worth the cost as the commercial headroom available for biomarkers is large enough to accommodate the expected cost of the biomarkers. The results of this research may help regulatory bodies in reimbursement decision for biomarkers as they provide good societal value for the money.

Personalized healthcare with stratified and tailored treatment are the next echelon in healthcare [26,27]. Although medicine is inherently personal to each patient, personalized medicine denotes the use of technology enabling a level of personalization, which was previously not feasible. The aim of personalized medicine is to give each patient an individual therapeutically active drug while minimizing the adverse effects. Personalized medicine will only be successful when accurate diagnostic tests identify the patients who can benefit from targeted therapies and eventually reach the desired goal of prevention and prediction. Accurate risk prediction and identification of high-risk patients will provide the most optimal risk-benefit ratio for thromboprophylaxis.

The CE approach for biomarkers under development represents one direction that could be taken to improve the efficiency of use of new health technologies to the various stakeholders and improving public health at reasonable cost. The headroom method is a quick and useful way to consider the investment opportunity and
determines the maximum reimbursable price at a very early stage of technology development. The headroom analysis makes it possible to estimate the height of the future reimbursement opportunity by assessing the societal and commercial headroom for the biomarkers for risk assessment in PAD patients. The headroom method incorporates this demand-side reimbursement process (decision to buy) into supply-side investment decisions (decision to develop). It is to be used as early as possible, ideally at ‘concept’ stage of a new health technology. Although, the clinical and market context of the innovation is important, and should always be considered alongside the ‘headroom’, we believe that using CE principles will substantially assist in the process of biomarker valorization and guide the more detailed work that will be necessary to create complete and effective guidance in the later stages of development of biomarkers. Therefore, the early assessment of the health technology could be used as a learning tool, communication tool and a tool to shape the future research.

To the best of our knowledge, this study is unique to model risk stratification and treatment tailoring among diagnosed PAD patients. The relative risk of CV events in D-dimer elevated patients is an important model parameter in our study. Kleinegris et al. [10] have reviewed all the current evidences and report a 2.3-times increased risk of CV events in D-dimer elevated patients. It was found that the use of D-dimer for the risk assessment of arterial thrombosis was not very much studied and their meta-analysis was based on only four included studies. We have varied this parameter to the full range of the 95% confidence interval in our probabilistic analysis to incorporate the surrounding uncertainty. The results showed that the model results are robust and remain consistent while model parameters were varied.

International Society for Pharmacoeconomic and Outcomes Research (ISPOR) has formulated good research practice guidelines for the transferability of economic evaluations across jurisdictions. These guidelines address the issues surrounding the transferability of economic data [28]. PAD risk assessment and treatment stratification research has been done in the Dutch setting using Dutch costs for various modeled events. We have used CV event rates observed in the REACH registry in 44 countries and health states utility values are from the UK. REACH CV event rates were published by geographic regions comparing North America, Latin America, western Europe, eastern Europe, Middle East, Asia, Australia and Japan in another article based on REACH data [29]. However, CV events rates in PAD patients were not reported explicitly as those were reported by Steg et al. [18]. We do not expect a significant alteration in result by use of jurisdiction specific data, because the comparison of western European data with whole REACH population data shows no significant difference in CV events rates. The probabilities of CV events were included in the PSA, so the uncertainty surrounding the estimates in the total REACH population is reflected in our results. The utility values were also subjected to PSA.

This study shares the general limitations of economic modeling. Complex medical practice is difficult to transform into a decision model. Our model

| Table 3. Scenario analysis for different proportion of high-risk peripheral arterial disease patients. |
|---|---|---|---|---|---|
| Strategy | Mean costs (€)† | Mean LYs† | Mean QALYs† | iCosts | iQALYs | ICER |
| Proportion of high risk: 10% | | | | | |
| Usual care | 39,215 | 19.25 | 11.48 | | | |
| D-dimer risk stratification | 38,861 | 19.32 | 11.52 | -354 | 0.04 | Dominant |
| Proportion of high risk: 30% | | | | | |
| Usual care | 38,744 | 19.47 | 11.67 | | | Dominant |
| D-dimer risk stratification | 37,408 | 19.71 | 11.81 | -1336 | 0.14 | |
| Proportion of high risk: 40% | | | | | |
| Usual care | 38,720 | 19.44 | 11.61 | | | |
| D-dimer risk stratification | 36,821 | 19.76 | 11.83 | -1899 | 0.18 | Dominant |
| Proportion of high risk: 50% | | | | | |
| Usual care | 38,683 | 19.42 | 11.63 | | | |
| D-dimer risk stratification | 36,177 | 19.83 | 11.86 | -2506 | 0.23 | Dominant |

†Values discounted as per the health economics principles and guidelines.
attempts to reflect the true clinical practice as closely as possible and the model's robustness has been rigorously tested for changes in clinical and economic variables.

D-dimer-based PAD risk assessment and customized OAC treatment had high probability of being cost effective at various WTP thresholds. There is an implicit assumption that the WTP for health gain is identical to the willingness to accept (WTA) compensation for health loss. In practice, the perception of the value of public health intervention differs from the WTP and WTA perspective. This perception could also vary with the characteristics of certain individuals as age and socio-economic strata. There is a debate about what could be the appropriate measurement to determine the perception of value of a good or service when the enjoyment of the good or service already exists [30]. Therefore, the valuation of the risk assessment and OAC treatment in our setting (WTP perspective) may not be the same as the perspective of the WTA compensation.

However, the results of this study could be a step in the expansion of evidence for the use of OAC in PAD patients. This study provides a framework to evaluate several other factors associated with the individual response to OACs, for example, genetic factors, drugs, foods and environmental factors those can interact with these compounds. Additional research is warranted to explore and put together all the pieces of OAC jigsaw puzzle for a tailored and personalized care for PAD patients. An individualized approach taking into account the individual risk of CV events and risk of bleeding is needed to assess the best treatment option, and hopefully risk stratifying biomarker and new OACs will help to increase both efficacy and safety of the treatment.

In conclusion, PAD risk assessment and treatment tailoring based on D-Dimer is cost effective. Biomarkers-based identification of high-risk PAD patients and prescription of OAC in clinical practice is expected to save substantial healthcare costs and to improve chances of survival for high-risk PAD patients. However, further research of regarding accuracy and costs of future risk stratifying biomarkers is needed to support and strengthen the results of this modeling study.

**Conclusion & future perspective**

Peripheral arterial disease (PAD) patients are at greater risk of cardiovascular events and risk assessment followed by treatment customization may greatly impact their prognosis. PAD risk-assessment biomarkers have good future prospects. Biomarkers-based identification of high-risk PAD patients could provide good value for money. With the development of new safer oral anticoagulants in the coming years, PAD risk-assessment biomarkers may be used routinely to stratify patients in order to provide tailored secondary prevention.

**Executive summary**

**Peripheral arterial disease risk-assessment biomarker**

- High-risk peripheral arterial disease patients
  - Increased risk of cardiovascular events in the high-risk peripheral arterial disease (PAD) patients poses high economic burden over healthcare resources. Therefore, there is a critical need to identify high-risk subset of PAD patients vulnerable for cardiovascular events.
- D-dimer as a risk-assessment biomarker
  - Studies have shown that D-dimer could be used as a biomarker to identify the high-risk PAD patients enabling their treatment using more effective oral anticoagulants.
- Societal & economic value of D-dimer
  - Cost–effectiveness analysis shows that the D-dimer-based risk assessment and treatment stratification is a very cost-effective healthcare intervention which could improve the quality of life of PAD patients and could save valuable healthcare resources.
- Future development of PAD risk-assessment biomarkers
  - Accurate identification of high-risk PAD patients would result in more health gain and healthcare resources savings. There is significant commercial headroom available for the development of more accurate risk-assessment biomarkers.
References

Papers of special note have been highlighted as:
• of interest; ** of considerable interest


• Reporting the possible role of oral anticoagulants (OACs) in the management of peripheral arterial disease (PAD).


•• Reporting the possible role of OACs in the management of PAD.


• Reporting the role of D-dimer as a biomarker for risk stratification among PAD patients.


• In-depth review of the all the economic modeling studies performed in the field of PAD.


• Reporting the possible role of OACs after bypass surgery in severe occlusive arterial disease.


CHAPTER 5

Comparison of EQ-5D and SF-36 in untreated patients with symptoms of intermittent claudication

In submission
Comparison of EQ-5D and SF-36 in untreated patients with symptoms of intermittent claudication

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ABSTRACT

In order to make recommendations for public funding of treatments across different technologies and disease areas, comparability of the health related quality of life (HRQoL) measure across indications is important. In addition to the use for economic evaluations, HRQoL data can also be useful in monitoring an individual patient’s health status, the measurement of population health or the effect of therapies in clinical studies. This study compared HRQOL descriptions and utility scores in newly diagnosed, untreated and symptomatic peripheral arterial disease (PAD) patients, obtained by the two most widely used instruments, EQ-5D and SF-36. This study also explored the differences and relation between utility scores obtained with the EQ-5D and the SF-36 and clinical validity of these two instruments. Patients’ self-assessment of HRQoL was measured by the Dutch versions of the EQ-5D and SF-36 in the 204 patients. Mean utility scores ranged from 0.675 for SF-6D, 0.648 for the EQ-5D UK tariff and 0.715 for the Dutch EQ-5D tariff. Measurements by both instruments behaved in consistent manner. Both utility instruments differentiated between functional and clinical severity levels and the validity of both instruments in the Dutch PAD patient sample was supported by the results of this investigation. However, before using these two instruments interchangeably for HRQoL calculations and for health care resource allocation, a thorough sensitivity analysis is necessary to explore the preference value discrepancies. It is recommended that these two instruments in combination could provide a broad coverage of health dimensions and QOL scores for a variety of applications.

Keywords: Health related quality of life, Peripheral arterial disease, Short-Form 36, Euroqol 5D
Peripheral Arterial Disease (PAD) with its most classical manifestation of Intermittent Claudication (IC) is a sign of widespread atherosclerosis affecting multiple vascular beds simultaneously including coronary, cerebral and renal arteries. It is a relatively common disorder with a prevalence estimated at 16% in those aged over 55 years and up to 29% in high-risk groups (1). PAD patients have a significant reduction in Health Related Quality of Life HRQoL caused by impaired mobility and by cardiovascular morbidity (2). There is increasing acknowledgement of the clinical and economic benefits of (early) identification of PAD and its treatment. The Prevention of Athero-thrombotic Disease Network, an international, multidisciplinary network, has recommended a multi-pronged strategy to increase awareness, detection, and treatment rates of peripheral arterial disease (PAD) and have emphasized the need for greater resource allocation for PAD (3).

In order to make recommendations for public funding of treatments across different technologies and disease areas, comparability of the HRQoL measure across indications is important (4). The quality-adjusted life year (QALY) is a common measure to compare interventions across disease areas. The QALY integrates life expectancy and a utility value, representing the HRQoL adjusted expectancy (5). The cost per QALY of competing treatments can be a useful input into medical decision making and priority setting (6).

For instance, the National Health Care Institute (Zorginstituut Nederland) in the Netherlands and National Institute for Care and Excellence (NICE) in the UK recommend the use of QALYs as a measure of health benefit to enable a standardized approach for comparing economic evaluations across different healthcare areas (4, 7).

Several instruments exist to determine utility values for health states and two most widely used instruments are EuroQol 5D (EQ-5D) and Medical Outcome Study 36-item Short-Form Health Status Survey (SF36) derived SF-6D (8, 9). These instruments differ in their conceptualisation of HRQoL, the detail of their descriptive systems, their valuation techniques and the degree to which they invoke the assumptions of multi-attribute utility theory. Utility scores obtained from these instruments may vary due to these differences (10). Moreover, the acceptability of the cost-utility ratios based on utility scores from these two instruments differs as well (11).

Both the EQ-5D and the SF-36 have been used to assess QoL in patients with PAD (12-15). A large nationwide American study used SF-36 and was conducted in 25 cities at 350 primary care practices demonstrated that patients with PAD had a similarly low HRQoL as patients with other cardiovascular diseases (CVDs) (16). Other QoL studies in PAD patients using SF-36 have drawn similar conclusions (17, 18). Despite cost utility evaluations being required by different authorities, data on health state preferences or utilities of intermittent claudication patients are scarce in the Netherlands. There are two Dutch HRQoL studies in PAD patients that were conducted alongside the Dutch Bypass Oral Anticoagulant (BOA) trial and Dutch Iliac Stent trial (19, 20). These studies have a patient population with severe functional impairment requiring immediate revascularization. The Dutch BOA trial used both EQ-5D and SF-36 but did not compare
the results. Therefore to the best of our knowledge, the utility scores for newly diagnosed PAD patients in the Dutch population are not reported in the literature. Our study was motivated by a need to compare HRQOL descriptions and utility scores in newly diagnosed and untreated PAD patients with leg symptoms of intermittent claudication obtained by the EQ-5D and SF-6D. Additional research questions for this research were:
- What are the differences between health states descriptions obtained with the EQ-5D and the SF-6D;
- What are the differences and relation between utility scores obtained with the EQ-5D and the SF-6D;
- Do utility scores obtained with EQ-5D and SF-6D reflect functional and clinical severity of PAD (clinical validity)?
MATERIALS AND METHODS

Patients
Study subjects were consecutive patients with newly diagnosed PAD from three hospitals (Atrium Medical Center Heerlen, Orbis Medical Centre Sittard and the Maastricht University Medical Centre) in Limburg, the Netherlands. Patients were included between January 2009 and November 2013 after written informed consent of the patients was obtained. Medical ethics committee approval was granted for the study. The diagnosis of PAD was based on an in-hospital performed ankle brachial index (ABI) of ≤0.9. After initial clinical assessment with history taking, a physical examination was performed by the treating physician. Exclusion criteria for participation were the use of medication known to affect coagulation (e.g. cumarins, direct factor Xa-inhibitors and factor II-inhibitors, heparin), known coagulation disorders, age under 18 years, and the presence of active malignancy or chronic inflammatory diseases. Patients who underwent a cardiovascular intervention/arterial (peripheral) surgery within the past 6 months and patients with an episode of (unstable) angina pectoris, myocardial infarction, stroke or heart failure within the past three months were excluded as well.

Data collection
Patients were asked to participate in the study and subsequently included within three months after the initial diagnosis of PAD. On entry of the study, patients were seen by a study physician or research nurse and were questioned about their personal and medical history. In order to assess the patients’ clinical and functional status they were asked about rest pain, night pain, and pain free walking distance. Patients were classified using Fontaine classification reflecting the clinical and functional severity of the disease covering the entire spectrum of symptoms in PAD. There are five Fontaine stages: Stage I – Asymptomatic, Stage II – Intermittent claudication (patients usually have a very constant distance at which they have pain and this stage is subdivided into stage IIa and IIb) Stage IIa – Intermittent claudication after more than 200 meters of pain free walking and Stage IIb – Intermittent claudication after less than 200 meters of walking, Stage III – Rest pain and Stage IV – Ischemic ulcers or gangrene (21).

Quality of life assessment
Patients’ self-assessment of HRQoL was measured by the Dutch versions of the EQ-5D and SF-36.
The EQ-5D is a five dimensional instrument, the dimensions being mobility, self-care, usual activities, pain/discomfort and depression/anxiety. Each of these dimensions can be rated as 1 (no problem), 2 (some problem) or 3 (severe problem). There are 243 distinct health states described by the EQ-5D, and a sample of these has been valued by community samples from different countries using the time trade-off method. Country-specific algorithms have been developed based on societal preferences for health states. We have...
used the UK and the Dutch population specific scoring functions to derive the utility values based on the EQ-5D questions (9, 22-24). Utility scores calculated by the UK scoring function range from -0.59 (health state worse than death, severe problems in all dimensions, through 0 (health state equal to death) to 1 (full health, no problems in all dimensions). For the Dutch scoring function this range was -0.329 to 1. The EQ-5D instrument also includes a visual analogue scale (VAS), which records the respondent’s self-rated health status on a graduated (0–100) scale ranging from best to worst imaginable health.

The SF-36 includes 36 items that can be classified into the following eight health-status subscales: physical functioning, physical role limitations, bodily pain, general health perception, vitality, social functioning, emotional role limitations and mental health (25, 26). The SF-36 is a generic multidimensional instrument, which was reduced to six items by Brazier and colleagues to develop the SF-6D. The six items (each with 4-6 levels) in the SF-6D are physical functioning, role limitations, social functioning, pain, mental health and vitality (8). The SF-6D algorithm reduces the eight dimensions of the SF-36 to six by combining role limitations due to physical and emotional problems and omitting general health perceptions. The SF-6D describes 18,000 health states in all and 249 states were valued by a sample from the UK general public using the Standard Gamble (SG) method. The SF-6D utility scores range from 0.29 to 1.00. Regression models were used to estimate utility scores for all health states (8).

**Statistical methods**

Open Clinica software was used to store the data. This is open source clinical trial software for electronic data capture and clinical data management. All statistical analyses were performed with IBM SPSS statistics version 20.0 software (SPSS Inc, Chicago, IL). As recommended to handle missing HRQoL data, missing data on the EQ-5D and SF-6D were replaced using multiple imputation (27). For this purpose, five data were created using the ‘Markov Chain Monte Carlo’ algorithm. This method assumes normality and linearity. Variables were transformed before the imputation process and then back-transformed to create imputed values (28).

Demographic, risk factors, family history, medicine history and PAD related functional limitation data were summarized as number and percentage in each category.

Utility scores from SF-36 (UK) and EQ-5D (UK and NL) were derived using the published algorithms (8, 22, 27). To make comparison easier, all EQ-VAS scores were divided by 100 to generate values between 0.0 and 1.0. Summary of basic descriptive statistics including means, medians and ranges of utility scores were computed. Utility score distribution across instruments was charted. The differences between the mean and median utility scores obtained with the EQ-5D and SF-6D were tested using the paired samples t-tests and Wilcoxon signed rank test. The association between the EQ-5D and SF-6D utility scores was examined by Spearman rank correlation for non-parametric measures. The degree of agreement between the SF6D and the EQ5DUK utility scores was assessed by the Bland-Altman plot.
The empirical validity of the EQ-5D and SF-6D utility scores was assessed by hypothetically constructed preference rule that utility scores should differ significantly between self-reported functional status groups and should decrease monotonically with severity of symptoms (29). Mean values and 95% confidence intervals (CIs) of the utility scores from the EQ-5D (UK and Dutch tariffs) and SF-6D were compared for functional (rest pain, night pain, limitation of activities of daily life, pain free walking distance) and clinical (Fontaine classification) subgroups of patients.

Results
Of 250 patients included, 204 (81.6%) returned the survey instrument containing the SF-36 and EQ-5D. The participants who responded to the survey ranged in age from 46 to 86 years old, with an average age of 66.5 years. More than half of them were males, current alcohol and tobacco users and had limitations in the activities of daily life (ADL). Demographic and functional characteristics of 204 patients included in the study are shown in Table 1.

Table 1. Demographic and functional characteristics of 204 PAD diagnosed patients

From the instruments received, 75% SF-36 and 94% EQ-5D descriptive parts were completely filled in order to calculate the utility values, whereas 91% EQ VAS instruments were completely filled to obtain the VAS score. Using multiple imputation, utility scores and VAS scores could be obtained for all 204 patients. All results below are based on the imputed datasets. To follow the research questions posed in this article, the results are shown below in the following order: differences between health states descriptions obtained with the EQ-5D and the SF-6D, differences and relation between utility scores obtained with the EQ-5D and the SF-6D and clinical validity of EQ-5D and SF-6D in PAD patients.

Mean utility scores ranged from 0.675 for SF-6D, 0.648 for the EQ-5D UK tariff and 0.715 for the Dutch EQ-5D tariff. The mean EQ VAS score was 0.663. Detailed descriptive statistics of these values is presented in Table 2.

Table 2. Descriptive statistics of EQ-5D, and SF-6D utility scores and the EQ VAS score, n=204

Patients’ response distribution across severity levels of the EQ-5D and SF-6D dimensions are shown in the figure 1a and 1b.

Figure 1. Distribution across severity levels of the EQ-5D dimensions.
Figure 2. Distribution across severity levels of the SF-6D dimensions.
Figure 3. Histogram showing utility frequency distribution across the measuring instruments

The relationship between the SF-6D, EQ-5D and EQ VAS scores is shown in Figure 4. SF6D and EQ5D UK showed the highest level of association. This was confirmed by Spearman coefficient, which was 0.63 for the association between SF6D and EQ5D (UK and NL),
0.45 for SF6D and VAS and 0.44 for EQ5D and VAS. The Bland-Altman plot showed wide limits of agreement between EQ5D and SF6D. Figure 5 shows the 95% limits of agreement varying from -0.36 to 0.41 with a mean difference in scale scores (SD) of 0.023 (0.019).

**Figure 4a-e. Relationship between measuring instruments scores (each dot representing a patient’s utility value across two instruments)**

**Figure 5. Bland-Altman plot of EQ-5D (UK) and SF-6D (each dot representing an average of EQ-5D, UK and SF-6D and delta for a patient)**

Mean utility scores were related to symptom, demographic characteristics and clinical classification (Fontaine). These subgroup analyses showed that the impact of PAD could be captured by SF-6D, EQ-5D and VAS (Figure 2). Both utility instruments differentiated between functional and clinical severity levels; the mean utility values from SF-6D, EQ-5D and VAS decreased with increased symptom severity. Utility distribution as per the measuring instrument is shown in figure 3.

**Figure 6a - 6f. Subgroup analyses based on functional, clinical and demographic characteristics, bars in figure are mean utility values and whiskers are 95% Confidence Interval.**
DISCUSSION

Generic HRQoL instruments currently have an important role in healthcare technology decision making in the Netherlands and in most of the developed world. In this study we made a detailed analysis of the relation between HRQoL, assessed with the generic preference based HRQoL instruments EQ-5D and SF-36, the severity of PAD and objective functional variables. Our results highlighted the negative impact that PAD has on HRQoL, which is consistent with the findings of other studies (16, 30).

In our comparative study of two widely used preference-based HRQoL instruments in PAD patients, we observed that the SF-6D scores were generally higher than the EQ-5D. This is consistent with current literature and may reflect floor effects associated with SF-36 (31, 32). We found a moderate correlation between the utility scores obtained from these instruments. The wide 95% limits of agreement in Bland-Altman plot signify this level of agreement between the instruments (12, 28).

Although EQ-5D and SF-36 intend to measure similar constructs, these instruments are quite different from each other in the assessment of HRQoL. Our research explored the likely association between the utility values generated by the SF-36 using algorithms developed by Brazier and colleagues and the utility value that would have been obtained from the EQ-5D. To the best of our knowledge, this is the first comparison of preference-based instruments in PAD population. Other studies have reported health state values derived from these HRQoL instruments (16, 30, 33, 34); however, ours included both of these instruments in diagnosed and symptomatic PAD patients. The ability to make reliable comparisons of health state utilities values measured by two most frequently used instruments would be of particular interest to health economists, researchers working in the field of PAD and decision makers, given the increasing importance of the quality adjusted life year as the standard metric of outcome in economic evaluation.

Utility scores were calculated and measurement properties were compared for two widely used HRQOL instruments EQ-5D and SF-6D in PAD patients with complaints of intermittent claudication. These two instruments show different utility score ranges and distributions. With vitality domain, SF-6D has 6 domains against five in EQ-5D; however, other domains of both instruments represent similar dimensions of health. The reference time frame used in the descriptive system varies for both the instruments. While answering EQ-5D patients describe their health status at that point of time while SF-6D has information on health status in last four weeks. The emphasis of EQ-5D is on physical functioning while social functioning has more weightage in SF-6D. However, the results of this study generally reinforced the construct validity of the EQ-5D and the SF-6D.

Both instruments measure HRQoL in PAD patients but selection of one instrument other is a difficult task as both instrument address physical limitation in PAD patients. It is important to consider the relative merits of each instrument when choosing measures of QoL.
Keeping in view the limited patient contact time available, collection of HRQoL information imposes an opportunity cost of reduction of time for other information. SF-36 is claimed to be completed in 5-10 min by the developers (35). However, in elderly PAD patients it may take on average 15 minutes to administer (36). On the other hand, EQ-5D could have an administration time less than 5 minutes with greater chances of completing the instrument (37). We received a significantly higher number of responses for EQ-5D (94%) than for SF-36 (75%) minimizing the need of imputation for missing data.

SF-6D has been reported to have a theoretical advantage over EQ-5D due to its larger SF-36-based descriptive system. However, SF-6D development team have suggested that future research should assess whether item selection for SF-6D caused limitations to its descriptive ability and indicates that SF-6D may not benefit from the descriptive richness of the original SF-36 (8). The EQ-5D presents health status as a simple 5-dimensional structure. This simplicity is one of its strengths, but would also be a limitation if it were used as a single measure of health status. Profile measures such as the SF-36 derived SF-6D may be better suited than the EQ-5D to capture certain facets of health status. With the use of algorithm developed by Brazier and colleagues, this instrument do provide an overall index score for respondents’ health, which can subsequently be incorporated into quality-adjusted life years and cost-utility analysis. However, revision of both these instruments is recommended to overcome their weaknesses, particularly in their descriptive systems (33). Convergent validity of EQ-5D and SF-6D could be measured by correlation but there is no consensus on the interpretation of various levels of correlations for this application. Since each instrument measures somewhat different concepts of health, modest correlation between them is not surprising. None of the instruments excelled uniformly, and the authors concluded that selection of the most suitable instrument for health status assessment should be guided by careful consideration of the special features of every study. In our study, the relationship and agreement between the SF-6D and EQ-5D utilities was not perfect. An observation in this study that the SF-6D scores were generally higher than the EQ-5D was also consistent with published literature and may reflect floor effects associated with SF-36(29)

The differences in utility measures need further confirmation by future research in patients with different levels of PAD severity and more research is needed to determine the relationship between the SF-36 and EQ-5D.

Since QALY (derived from utility score) provide the means to compare different types of interventions for allocation of resources in health care systems. The implications of this study are potentially profound. The utilities were higher for SF-6D utilities than for EQ-5D UK utilities. Thus, using SF-6D utilities in cost-effectiveness analyses would result in lower cost-effectiveness ratios than using EQ-5D utilities. It has been demonstrated that the choice of one of these instruments could significantly change the results of economic evaluations (38). We recommend use of composite outcome measures,
incorporating clinical indicators along with QOL indices for estimation of health benefit gain in these situations. There is also a need of raising awareness among policy makers of these methodological challenges when interpreting economic evaluations. The comparison of both instruments in order to inform an important debate on the choice of instrument is strength of this study. This allow us to investigate agreement between instruments without the potential confounding effects of intersubjective variations such as cultural differences in tendencies to report health problems (39). The present study has some methodological considerations that should be considered in interpreting the results. First, we have used cross-sectional data to assess the difference between instruments. As differences in change scores are likely to have a greater impact on pharmacoeconomic evaluations than changes in absolute scores, longitudinal studies should be conducted to quantify the magnitude of differences in change scores. Second, the study population consists of a convenience sample of patients diagnosed at hospital with PAD. Thus, it remains unknown whether these data are applicable for patients with all other asymptomatic or symptomatic PAD patients. Third, we delivered both instruments to each of our patients in the same order. It is unclear that if random order delivery would influence the results. Fourth, this study was performed in a small sample size and in a very specific disease area of PAD and with a specific symptom of intermittent claudication. In this case physical limitation is a prominent feature and was well represented in both instruments, EQ-5D and SF-6D. However, generalizability of these results to other diseases is unclear where a health dimension is not directly reflected by one of these instruments.

CONCLUSIONS

The impact of PAD on HRQoL can be evaluated using generic standardized instruments SF-36 and EQ-5D. The validity of both instruments in the Dutch PAD patient sample was supported by the results of this investigation. Measurements by both instruments behaved in consistent manner. However, EQ5D and SF6D measure different aspects of HRQoL. The difference in psychometric properties and the lack of agreement between them are significant. Before using these two instruments interchangeably for QALY calculations and for health care resource allocation, a thorough sensitivity analysis is necessary to explore the preference value discrepancies. Combining the two instruments would provide a broad coverage of health dimensions and would provide QOL scores for a variety of applications.
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Conflict of interest
None
REFERENCES

Legends – Tables
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Legends – Figures
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Figure 2. Distribution across severity levels of the SF-6D dimensions.

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Figure 4a-c. Relationship between measuring instruments scores (each dot representing a patient’s utility value across two instruments)

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Figure 6a - 6f. Subgroup analyses based on functional, clinical and demographic characteristics, bars in figure are mean utility values and whiskers are 95% Confidence Interval.
### Table 1

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Figure 1
Figure 2

![Bar chart showing categories of physical functioning, role participation, social functioning, pain, mental health, and vitality. Categories range from 1 (excellent) to 6 (very bad).]

Figure 3

![Graph showing the number of patients across different utility values. The graph includes categories for SF-6D, EQ-SUK, EQ-SD NL, and VAS.]
Figure 4

Figure 5

Bland-Altman plot

Average of EQ-5D UK and SF-36
Figure 6

6a-Rest pain

6b-Night pain

6c-Activity of daily life (ADL)

6d-Walking distance

6e-Gender

6f-Age
CHAPTER 6

High-sensitive troponin T assay for the diagnosis of acute myocardial infarction: an economic evaluation
High-sensitive Troponin T assay for the diagnosis of acute myocardial infarction: an economic evaluation

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Abstract

Background: Delayed diagnosis and treatment of Acute Myocardial Infarction (AMI) has a major adverse impact on prognosis in terms of both morbidity and mortality. Since conventional cardiac Troponin assays have a low sensitivity for diagnosing AMI in the first hours after myocardial necrosis, high-sensitive assays have been developed. The aim of this study was to assess the cost effectiveness of a high-sensitive Troponin T assay (hsTnT), alone or combined with the heart-type fatty acid-binding protein (H-FABP) assay in comparison with the conventional cardiac Troponin (cTnT) assay for the diagnosis of AMI in patients presenting to the hospital with chest pain.

Methods: We performed a cost-utility analysis (quality adjusted life years-QALYs) and a cost effectiveness analysis (life years gained-LYGs) based on a decision analytic model, using a healthcare perspective in the Dutch context and a life time horizon. The robustness of model predictions was explored using one-way and probabilistic sensitivity analyses.

Results: For a life time incremental cost of 30.70 Euros, use of hsTnT over conventional cTnT results in gain of 0.006 Life Years and 0.004 QALY. It should be noted here that hsTnT is a diagnostic intervention which costs only 4.39 Euros/test more than the cTnT test. The ICER generated with the use of hsTnT based diagnostic strategy comparing with the use of a cTnT-based strategy, is 4945 Euros per LYG and 7370 Euros per QALY. The hsTnT strategy has the highest probability of being cost effective at thresholds between 8000 and 20000 Euros per QALY. The combination of hsTnT and h-FABP strategy’s probability of being cost effective remains lower than hsTnT at all willingness to pay thresholds.

Conclusion: Our analysis suggests that hsTnT assay is a very cost effective diagnostic tool relative to conventional TnT assay. Combination of hsTnT and H-FABP does not offer any additional economic and health benefit over hsTnT test alone.

Keywords: Cost-effectiveness, Decision model, Acute myocardial infarction, High-sensitive troponin T

Background

Acute coronary syndrome (ACS) is a major cause of morbidity and mortality around the world. The most common manifestation of ACS is acute myocardial infarction (AMI). It is widely accepted that early detection and treatment of AMI has a major impact on AMI morbidity and mortality and therefore on associated costs [1-3]. According to the current guidelines, AMI is diagnosed on the basis of presenting symptoms (chest pain, shortness of breath, epigastric discomfort etc.), electrocardiographic (ECG) findings and dedicated blood biomarkers of cardiac necrosis [4]. However, less than 25% symptomatic patients are finally diagnosed with AMI [5], while ECG alone may remain non diagnostic in up to 50% of cases [6]. This makes cardiac biomarker testing an important additional measure for the diagnosis of AMI.

In current clinical practice cardiac troponin T (cTnT) is the preferred biochemical marker for myocardial cell necrosis [4]. Since elevated cTnT levels are detected only 8–12 hours after onset of ischemic symptoms, the low sensitivity of cTnT assay at time of presentation is a major drawback in its use [7]. The life threatening nature of AMI and the...
known inconsistency in cTnT test results at its early phase lead to over-triage of patients and substantial costs to the health system [2,8].

A recently published study has concluded that high-sensitive Troponin T (hsTnT) is a useful prognostic biomarker in patients with symptoms of chest discomfort suspected for ACS [9]. Two multi centre studies have suggested that high-sensitivity Troponin assays offer superior diagnostic accuracy for the early diagnosis of AMI compared to the conventional cTnT assay [7,10].

Another AMI biomarker, heart-type fatty acid-binding protein (H-FABP), was reported to appear in the blood within one hour of myocardial necrosis and peaks after 3–4 hours [11]. Although H-FABP is not recommended as stand-alone test for diagnosis of AMI[12], combined sensitivity of cardiac troponin and H-FABP is reported to be higher than cardiac Troponin alone [13].

In this study we assessed the cost effectiveness of the hsTnT assay and combination of hsTnT (fifth generation TnT assay) and H-FABP assays for the early diagnosis of AMI in comparison with the currently in clinical practice conventional fourth generation TnT assay. To the best of our knowledge, no economic evaluation study has yet been published in Eurozone on the conventional TnT assay based diagnostic approach versus new alternatives involving hsTnT and H-FABP assays.

**Methods**

**Decision analytic model tree**

This study was done in the Dutch context using a health care perspective. A decision tree was constructed to compare the costs and outcomes associated with three diagnostic strategies under evaluation in a hypothetical cohort (Figure 1).

**Diagnostic strategies**

1. cTnT assay at <6 hours of symptom onset, which will be repeated after <12 hours of symptom onset, in the case of negative test result and continuing symptoms.
2. hsTnT assay at <6 hours of symptom onset, which will be repeated after <12 hours of symptom onset, in the case of negative test result and continuing symptoms.
3. hsTnT and H-FABP assays at <6 hours of symptom onset, which will be repeated after <12 hours of symptom onset, in the case of negative test result and continuing symptoms.

Correct or incorrect diagnosis of AMI and subsequent events in the model are followed for patients with chest pain presenting to the hospital. This diagnostic work up

![Decision Tree Structure for Diagnosis of AMI](image)
of a chest pain patient by one of the above strategies will guide the treating physician to employ the therapeutic intervention i.e. primary percutaneous coronary intervention (PPCI). PPCI is the preferred therapeutic modality to treat AMI and in The Netherlands majority of patients are treated with PPCI [14,15].

The whole process will culminate into either death or survival of the patient during hospital admission. Patient endpoint can be either alive at the end of hospitalization or dead, after presenting to hospital for suspected cardiac chest pain. For the theoretical AMI survivor an average life expectancy was assigned from the literature [16], indicating the time horizon for this modelling study to be life time. Although the exact moment in time is unknown, patients who died during the period of hospitalization were assigned a life expectancy of zero. We assumed that the diagnosis of AMI is excluded in those patients who remained negative after 2 consecutive testing.

**Model input parameters**

Besides life expectancy and utility values, other parameters used in this model are probabilities of events and costs. Parameters fed into the model are computed from raw parameters obtained from the existing literature and from financial affairs department of Maastricht university medical centre (MUMC) (Table 1). The data for test accuracy of cTnT, hsTnT and hsTnT-H-FABP was determined from the diagnostic testing on the preserved blood samples

<table>
<thead>
<tr>
<th>Table 1 Model input parameters</th>
<th>Parameter</th>
<th>Deterministic values (min – max range)</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs &amp; event occurrence</strong></td>
<td>Cost of conventional cTnT test</td>
<td>€17.11 (12.8-21.4)</td>
<td>Beta PERT</td>
<td>Commercial price at MUMC</td>
</tr>
<tr>
<td></td>
<td>Cost of new hsTnT test</td>
<td>€31.5 (23.6-39.4)</td>
<td>Beta PERT</td>
<td>Time &amp; motion study*</td>
</tr>
<tr>
<td></td>
<td>Cost of AMI in 1st year</td>
<td>€ 12446 (9334-15557)</td>
<td>GAMMA</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Cost of AMI in subsequent year</td>
<td>€ 2002 (1569-2615)</td>
<td>GAMMA</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Utility score for AMI</td>
<td>0.725 (0.544-0.906)</td>
<td>BETA</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>Discount rate: cost</td>
<td>0.4</td>
<td>Fixed</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Discount rate: Effect</td>
<td>0.15</td>
<td>Fixed</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Prevalence of AMI among patients presenting with chest pain</td>
<td>0.30 (0.23-0.38)</td>
<td>Beta PERT</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Risk adjusted mortality ratio among inappropriately discharged AMI patients</td>
<td>1.9 (1.43-2.38)</td>
<td>Beta PERT</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>Life expectancy of AMI survivor (years)</td>
<td>8.3 (6.23-10.38)</td>
<td>Beta PERT</td>
<td>[16]</td>
</tr>
<tr>
<td><strong>Diagnostic accuracy</strong></td>
<td>cTnT sensitivity at ≤ 6 hours</td>
<td>0.44 (0.32-0.56)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cTnT sensitivity at ≤ 12 hours</td>
<td>0.93 (0.85-0.97)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cTnT specificity at ≤ 6 hours</td>
<td>0.92 (0.88-0.95)</td>
<td>BETA</td>
<td></td>
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<tr>
<td></td>
<td>cTnT specificity at ≤ 12 hours</td>
<td>0.85 (0.76-0.91)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT sensitivity at ≤ 6 hours</td>
<td>0.94 (0.87-0.98)</td>
<td>BETA</td>
<td></td>
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<tr>
<td></td>
<td>hsTnT sensitivity at ≤ 12 hours</td>
<td>0.95 (0.91-0.98)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT specificity at ≤ 6 hours</td>
<td>0.52 (0.39-0.65)</td>
<td>BETA</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>hsTnT specificity at ≤ 12 hours</td>
<td>0.51 (0.40-0.62)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT + hFABP sensitivity at ≤ 6 hours</td>
<td>0.97 (0.90-0.99)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT + hFABP sensitivity at ≤ 12 hours</td>
<td>0.97 (0.93-0.99)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT + hFABP specificity at ≤ 6 hours</td>
<td>0.39 (0.27-0.51)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hsTnT + hFABP specificity at ≤ 12 hours</td>
<td>0.38 (0.27-0.49)</td>
<td>BETA</td>
<td></td>
</tr>
<tr>
<td><strong>Event occurrence</strong></td>
<td>Average of AMI mortality among patients given PPCI within 4 hours of presentation</td>
<td>0.062 (0.0468-0.0780)</td>
<td>Beta PERT</td>
<td>Calculated from [3]</td>
</tr>
<tr>
<td></td>
<td>AMI mortality among patients given PPCI after 4 hours of presentation</td>
<td>0.103 (0.077-0.1288)</td>
<td>Beta PERT</td>
<td>[3]</td>
</tr>
<tr>
<td></td>
<td>PPCI procedure related mortality</td>
<td>0.0072 (0.0054-0.009)</td>
<td>Beta PERT</td>
<td>[18]</td>
</tr>
</tbody>
</table>

*Time & Motion study done at Pathology Laboratory, MUMC.
from Bad Nauheim Acute Coronary Syndrome II Registry, Germany as presented by Bongaerts et al. [17].

Event probability calculation
Application of Bayes’ Theorem allows us to interpret the test results. Pre-test probability or prior probability of presence/absence of a disease is calculated using Bayesian revision. Prevalence of AMI among symptomatic patients presenting at hospital and diagnostic test sensitivity and specificity are used to calculate various event probabilities. Prevalence of AMI among symptomatic patients presenting to hospital as reported in a large multi-centre study [5] is used in our model.

Post PPCI mortality among AMI patients is abstracted from the literature. Mortality increases with delay in PPCI and is reported from 15 minutes until 240 minutes delay in PPCI after presentation [3]. Average mortality, calculated from mortality reported at different points of time between 15 minutes to 240 minutes, is used in our model after initial biomarker testing at presentation. Average mortality for patients given PPCI within 4 hours of presentation is 6.24%. Mortality among patients in whom PPCI is delayed by ≥4 hours is assumed to be 10.3% based on the mortality figure reported in the literature for PPCI at 240 minutes.

Procedural mortality related to PPCI [18], post AMI life expectancy [16] utility score for AMI survivors [19] and mortality among patients in whom PPCI is delayed by ≥4 hours is assumed to be 10.3% based on the mortality figure reported in the literature for PPCI at 240 minutes.

Cost calculation
The cost of diagnostic cTnT test was 17.11 Euros (data obtained from the financial affairs department of Maastricht university medical centre (MUMC) database. MUMC publishes standard prices of health care products available at the MUMC every year in a freely available database [21]. Cost estimates for the new diagnostic tests hsTnT/hFABP (i.e. 21.50 euro), were based on the database, consultation with experts and an in-house time and motion study performed by a senior laboratory technician at the Pathology department of the MUMC who recorded the various stages of test procedure in a time sheet. The unit costs of resources identified for performing the assay was used to calculate the total cost per diagnostic test. Costs incurred in the first year of AMI survival are higher as the primary cost driver is PPCI as a therapeutic intervention. The Dutch costs for the AMI survivors for first year and subsequent years were taken from the published literature [22].

All costs used in the model were converted to Year 2012 costs using harmonized index of consumer prices data from the Dutch bureau of statistics [23].

Longer term costs and outcomes are discounted as per the Dutch pharmacoeconomic guidelines [24].

Outcome measures
The effectiveness of diagnostic test strategies is measured in terms of survival probabilities in AMI patients during hospitalization and incremental life years gained (LYGs) by AMI survivors. Quality adjusted life years (QALYS) are derived by multiplying LYGs with the Post AMI utility score reported in the literature [19].

Analyses
The expected costs and outcomes of all the three strategies were calculated and incremental cost effectiveness ratios were determined. Cost effectiveness analysis (CEA) and cost-utility analysis (CUA) are approaches to compare the costs and health outcomes of a new intervention with the existing practice [25]. An incremental cost effectiveness Ratio (ICER) is calculated by dividing differential costs with differential effects between existing practice and the new health technology. When more than one, ‘new technologies’ are under evaluation then the more costly technology is compared with the less costly technology [26].

The probabilistic sensitivity analysis (PSA) considers uncertainties in all the model parameters simultaneously. Probabilistic sensitivity analysis quantifies the uncertainty in the ICER, by placing a probability distribution over parameter values. Test accuracy parameter values were varied in the full range of their reported 95% confidence interval (CI). Other parameter values were varied between 75% and 125% of their point estimates. The model parameters were assigned BETA distribution and BETA Pert distribution was used if confidence intervals or standard errors were not reported in the source literature. BETA Pert distribution is a version of the Beta distribution. The costs of AMI treatment were assigned GAMMA distribution. Probabilistic sensitivity analysis of the model parameters with 1,000 iterations using Monte Carlo simulation technique yields a range of health outcome results. Net monetary benefit (NMB) framework was applied to Monte Carlo simulation data to construct the cost effectiveness acceptability curves (CEACs). This framework offers an advantage of unambiguously sorting out the acceptability of an individual simulation trial on cost effectiveness plane, for a range of ‘willingness to pay’ values [25,27].

We performed one way sensitivity analyses to assess the degree of change in results with variation of one model input parameter value at a time. All parameters were varied in the full range of their reported 95% confidence interval (CI) or between 75% and 125% of their point estimates.

Results
Base case
The expected values for the three strategies namely conventional cTnT, hsTnT and combination of hsTnT and...
H-FABP, regarding costs and outcomes are shown in Table 2. The constructed model predicts that when a diagnosis is made using hsTnT instead of conventional TnT, a hypothetical AMI survivor will live 0.006 years (Life Year Gain-LYG) longer and will have additional 0.004 QALYs for an incremental cost of 30.70 Euros. It should be noted here that hsTnT is a diagnostic intervention which costs only 4.39 Euros/test more than the cTnT test. The ICER generated with the use of hsTnT based diagnostic strategy comparing with the use of a cTnT-based strategy, is 4945 Euros per LYG and 7370 Euros per QALY. Combination strategy of the hsTnT assay with the H-FABP assay is the next more costly new technology and as per the decision modelling guidelines it is compared with less costly hsTnT [26]. Comparison of combination arm with hsTnT alone arm shows 0.0037 and 0.0025 additional LYGs and QALYs respectively, at an incremental cost of 55.91 Euros leading to an ICER of 15286 per LYG and 22781 Euros per QALY. Details of costs, outcomes and increments for all strategies are presented in the Table 2.

### Table 2 Base-case results costs and effects

<table>
<thead>
<tr>
<th>Diagnostic strategies</th>
<th>Increments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hsTnT vs cTnT</td>
</tr>
<tr>
<td>Discounted cost</td>
<td>€ 30.70</td>
</tr>
<tr>
<td>Discounted LYGs</td>
<td>0.006</td>
</tr>
<tr>
<td>Discounted QALYs</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**ICER**

<table>
<thead>
<tr>
<th>hsTnT vs cTnT</th>
<th>Reference strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT</td>
<td>4945 Euros per LYG</td>
</tr>
<tr>
<td>hsTnT + H-FABP vs cTnT</td>
<td>8780 Euros per LYG</td>
</tr>
<tr>
<td>hsTnT + H-FABP vs hsTnT</td>
<td>15286 Euros per LYG</td>
</tr>
</tbody>
</table>

**Probabilistic sensitivity analysis**

The probabilistic results of the decision model are similar to the deterministic results hsTnT as cost effective diagnostic strategy. Figure 2 shows the probability in the PSA that each strategy is cost effective at various thresholds of willingness to pay ranging from zero to 20000 Euros. hsTnT strategy has the highest probability of being cost effective at thresholds between 8000 and 20000 Euros per QALY. The combination of hsTnT and h-FABP strategy’s probability of being cost effective remains lower than hsTnT at all willingness to pay thresholds and was not analysed further by one way sensitivity analysis.

**One way sensitivity analysis**

The constructed model was robust to all one way sensitivity analyses and ICER remains less than 12000 Euros per QALY which is far below the acceptable willingness to pay per QALY limit of 20000 Euros in The Netherlands. The results of one way sensitivity analyses are graphically displayed as a tornado diagram in the Figure 3. This figure

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**Figure 2** Cost effectiveness acceptability curve(s) shows likelihood that a strategy would be cost effective for a range of maximum acceptable ceiling ratios society is willing to pay for the gain of one QALY, assessed with 1000 Monte Carlo simulations.
Figure 3 One way sensitivity analysis: Tornado diagram.

Discussion
This modelling study assessed the cost effectiveness of two biomarker strategies for the early diagnosis of AMI i.e. hsTnT and the combination of hsTnT and H-FABP. Economic and clinical consequences of using these new tests instead of conventional cTnT test were extrapolated by decision modelling. Our findings suggested that hsTnT is a cost effective tool to diagnose AMI at the Emergency Department in patients presenting with chest pain. Use of hsTnT diagnostic assay resulted in gain of additional QALYs compared with the existing 4th generation diagnostic cTnT test. A combination strategy of performing the 5th generation hsTnT and H-FABP assays simultaneously did not bring any additional benefit and even incurred higher costs.

This study was performed with a health care payer’s perspective. The societal perspective for this study was not considered because the average age of AMI patients in The Netherlands is 66.7 years [28]. Therefore, productivity loss in this age group may not be significant and impact of this effect was not weighed or included. Indirect costs associated with time spent by family members for the care of these patients are also difficult to estimate for the societal perspective.

A potential limitation of this study is that the probabilities of clinical outcomes in our model are derived from diagnostic accuracy estimates for hsTnT and H-FABP from a single cohort with relatively small number of patients from Bad Nauheim Acute Coronary Syndrome II Registry, Germany. However, in sensitivity analysis our test accuracy data was varied between full ranges of confidence interval (CI) limits to test the robustness of the model. Application of the net monetary benefit (NMB) framework revealed the dominance of hsTnT strategy showing highest net monetary benefit for it. Furthermore, a recently published meta-analysis [29] for diagnostic accuracy of cTnT and hsTnT at the time of patient’s presentation to the emergency department has similar accuracy figures as our source article by Bongaerts et al. [17].

This study shares the general limitations of economic modelling. Complex medical practice is difficult to transform into a decision tree model. This applies to our model as well. All test positive patients will not undergo PPCI in real life situation. Repeated biomarker testing, clinical judgment and ECG findings play a crucial role in decision making on invasive intervention. Our decision tree model attempts to reflect the true clinical practice as closely as possible and the model’s robustness has been rigorously tested for changes in clinical and economic variables. All the model assumptions and uncertainties were addressed by performing one way sensitivity analysis and state-of-the-art Probabilistic Sensitivity Analysis. PSA is one of the most sophisticated methods to address uncertainty allowed systematic propagation of uncertainty in all model parameters and offered a statistical interpretation of the joint distribution of incremental costs and effects. The model outcomes (expected costs and QALYs of the strategies) were based on the results of the probabilistic sensitivity analysis (PSA) with 1,000 simulations. The results of our study are in line and are comparable to the recently published National Institute for Health Research (NIHR) UK, document showing the value of hsTnT based early diagnosis of AMI. This document also concludes that there
is currently insufficient evidence to support routine use of alternative biomarkers alongside troponin [30].

Our estimation of post PPCI mortality is based on averaged mortality figures reported by Rathore et al. and covers the 15–240 min delay from diagnosis to PPCI after arrival to hospital [3]. The study by Rathore et al. [3] shows that more than 80% of patients underwent a PPCI within 120 minutes of hospital arrival, implying that the applied average mortality rate in our model may be an overestimation. Lower mortality rate will shift ICER more in favour of hsTnT and would make hsTnT even more cost effective.

Our model conforms to the principles of good practice for decision analytic models with use of transparent data and modelling technique as per the guidelines laid by the international society for pharmacoconomics and outcome research (ISPOR) task force [31]. Strength of this model is its potential transferability as model inputs can be adapted to a new setting easily. Inter- or intracountry variations in costs, prevalence of AMI and therapeutic intervention outcomes caused by availability and accessibility of health care can be incorporated into the model. Using cost effectiveness threshold from WHO-CHOICE (world health organization – CHOosing Interventions that are Cost Effective) project for ceiling ratio in a particular country, cost effectiveness analysis can be performed for that country [32].

The newly introduced hsTnT biomarker assay significantly contributes to the early diagnosis of AMI and appears to be a promising diagnostic intervention for AMI. Although a multi-marker approach using hsTnT and H-FABP may allow an early rule out of the disease but economic modelling of cost and consequences for this combination predicts its inferiority to hsTnT alone. Moreover, in a non ST elevation AMI patients study by Giannitsis et al. showed that a doubling of the hsTnT concentration within 3 hours with the second concentration above the 99th percentile value is associated with a positive predictive value for AMI of 100% and a negative predicting value of 88% [33]. This indicates that with the hsTnT assay within 3 hours instead of the 6 hours examined in this study, a definitive outcome can be obtained.

Conclusions
This economic evaluation concludes that hsTnT assay is a cost effective alternative for the diagnosis of AMI to the existing diagnostic marker assay in clinical practice. Combination of two biomarkers, hsTnT and H-FABP for the diagnosis of AMI does not bring any added advantage. Future replacement of cTnT with hsTnT in clinical practice is expected to save substantial health care costs and to improve Health Related Quality of Life among AMI patients. However, data for hsTnT and its combination with other biomarkers from further research is needed to support and strengthen the results of this modelling study.

Abbreviations
ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; ECG: Electrocardiogram; cTnT: Cardiac troponin; hsTnT: High-sensitive troponin; H-FABP: Heart type fatty acid binding protein; PPCI: Primary percutaneous coronary intervention; MUMC: Maastricht university medical centre; LYG: Life year gained; QALY: Quality adjusted life years; CEA: Cost effectiveness analysis; CUA: Cost utility analysis; PSA: Probabilistic sensitivity analysis; CI: Confidence interval; NMB: Net monetary benefit; ICER: Incremental cost effectiveness ratio; CEAC: Cost-effectiveness acceptability curve; CHOICE: CHOosing interventions that are cost effective.

Competing interest
The authors declare that they have no competing interests.

Authors’ contributions
Conceived and designed the economic evaluation: AV and JLS. Data: BWCB and EALB. Wrote the paper: AV, JLS, EALB. Critical revision of the manuscript: KBJMC, PJN, LH and MDV. Final approval of the manuscript for publication: JLS and EALB. All authors read and approved the final manuscript.

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CHAPTER 7

General discussion
The overall aim of this dissertation as introduced in chapter 1, was to assess the value of strategies for screening, diagnosing and/or treating AVDs (PAD and MI) by performing economic modelling. This aim was achieved by exploration into three objectives. First, to provide a general overview of the methodological quality of economic evaluations published in the field of PAD; second, to perform economic evaluations of biomarkers associated with PAD and MI; third, to assess the health related quality of life (HRQoL) in PAD patients using two most widely used instruments. The shortcomings and merits of the individual studies presented have been discussed in the previous chapters. In this chapter, a summary of the main findings is presented. Subsequently, some methodological issues and areas of future research are discussed followed by a section considering clinical and policy implications.

Summary of main findings of the dissertation

Chapter 2 is a systematic review of all the model-based economic evaluations conducted and published in peer reviewed sources in the field of PAD. Sixteen identified studies were assessed by using the Philips’ checklist for their methodological quality. Eleven models compared therapeutic health technologies; three models compared diagnostic tests and two models compared a combination of diagnostic and therapeutic options for PAD. Results of this systematic review revealed an acceptable to low methodological quality of the included studies. Methodological diversity and insufficient information posed a challenge for valid comparison of the included studies. Based on these findings, it was recommended that future economic evaluations in the field of PAD need to be transparent, methodologically comparable and scientifically credible. Use of Philip’s check-list was recommended during the designing phase of a study that may help the researcher to conduct a good quality and transparently reported economic evaluation. Future modelling studies should include clinically and economically important cardiovascular outcomes to reflect the wider impact of PAD on individual patients and on society.

In chapter 3 a model-based economic evaluation was performed to explore the effectiveness and cost effectiveness of PAD screening. This study assessed the impact of PAD screening using long term clinical and economic outcomes. The results show that targeted ankle-brachial index (ABI) screening and consequent secondary prevention of cardiovascular events using low dose aspirin or clopidogrel is a cost-effective strategy. These results expand the evidence for advocating PAD screening and targeted treatment. Implementation of targeted PAD screening and subsequent treatment in primary care practices and in public health programs is likely to improve societal health and save health care costs by reducing catastrophic cardiovascular events.

In chapter 4 the cost-effectiveness of risk assessment and treatment stratification by D-dimer and the headroom of a hypothetical perfect biomarker in PAD patients were explored. As a result of this risk assessment high risk patients may be given stepped up secondary prevention by the use of an oral anti-coagulant (OAC), either alone or on top of antiplatelet therapy. The cost-effectiveness analysis results show that the use of currently available D-dimer assays to guide such preventive treatment using OAC in the
high-risk subset of patients might be a cost-effective health care intervention. Therefore, correct identification of eligible and suitable patients for OAC treatment could change the current practice of universal antiplatelet therapy prescription to all PAD patients. We also assessed the commercial headroom available for developing biomarkers by modelling a hypothetical perfect biomarker and concluded that a risk assessment and treatment stratification for PAD patients could be financially attractive and societally cost-effective. The results of this research may help regulatory bodies in reaching decisions on reimbursement for biomarkers as they provide good societal value for the money.

In chapter 5 quality of life in PAD patients was assessed with two well validated and widely used generic quality of life questionnaires: EQ-5D and SF-36. In this study a detailed analysis of the relation between quality of life, the severity of PAD, and objective functional variables was performed. This research explored the likely association between the utility values generated by the SF-36 using algorithms developed by Brazier and colleagues and the utility value that would have been obtained from the EQ-5D. The validity of both HRQOL measurements in the PAD population sample was supported by the results of this investigation. Measurements by both instruments behaved in consistent manner; however, the differences in psychometric properties between them are significant. EQ5D and SF6D measure different aspects of HRQoL and the emphasis of EQ-5D is on physical functioning while social functioning has more weightage in SF-36. Moreover, there is a difference in the preference weighting, as EQ-5D is based on TTO and SF-36 is on standard gamble. [1] The results of HRQoL studies in PAD patients emphasize the close relationship between physical disability and HRQoL [2-4].

Assessment of the physical dimension of HRQoL is an important criterion in PAD care as objective disease indicators are not reflective of the subjective health state in these patients. HRQoL domain analysis indicated that the psychological distress in PAD patients played a secondary role. The domain analysis of SF-36 in the HRQoL study presented in this dissertation clearly shows that the domains like social functioning; mental health and role participation are much less affected in PAD patients. Due to the length of the SF-36 lower response rates and higher missing values were also observed with the use of SF-36.

The EQ-5D could be a reasonable option for a generic health measure in old and frail PAD patients; it is an easy-to-fill questionnaire with greater emphasis on physical functioning which is one of the most affected HRQoL dimensions in PAD patients. Advantages of the EQ-5D (five dimensions) include its brevity and simplicity, while the advantages of the SF-36 include its broader coverage, but this is only an advantage if all these dimensions are relevant for a particular research question. On one hand, use of the EQ-5D is less taxing for the patient and the researcher and on other hand it has shown to have a comparable sensitivity and specificity to more lengthy questionnaires in PAD patients [5]. Previously reported head-to-head comparisons of the two measures demonstrated that the EQ-5D is better at discriminating between individuals in poor health [6]. Our study contributes to the evidence that researchers should choose a measurement tool
that best fits the condition under investigation as well as their study design and there may not be an instrument superior to the other.

**Chapter 6** is a model based economic evaluation assessing the cost effectiveness of early diagnosis and treatment of MI using high sensitive Troponin (hsTnT) as a biomarker of myocardial necrosis. This economic evaluation concluded that the hsTnT assay is a cost effective alternative for the diagnosis of AMI as compared to the existing diagnostic Troponin T assay in clinical practice. Future replacement of conventional biomarker with hsTnT in clinical practice is expected to save substantial health care costs and to improve health related quality of life among AMI patients.

**Methodological considerations**

Based on the findings of the studies included in this thesis the following methodological considerations are discussed: suboptimal reporting of economic studies; multiple screenings, therapeutic options and confounding; and research efficiency and data issues.

**Sub optimal reporting of economic studies**

By doing the systematic review it was found that the methodological diversity and insufficient reporting of information posed a challenge for valid comparison of included studies. Suboptimal reporting of model-based CEAs hampers knowledge transfer and thus innovation. As per the evidence the quality of reporting of economic evaluations varies widely, and could potentially benefit from improved quality assurance mechanisms [7, 8]. There are multiple checklists available to appraise the quality of economic evaluations. A systematic review has identified 10 such appraisal checklists [9]. To consolidate and update previous efforts into a single useful reporting guidance a consolidated health economic evaluation reporting standards (CHEERS) statement was developed by a task force supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). This was part of a broader initiative to facilitate and encourage the exchange of expert knowledge in this field and to promote the best practices. This checklist containing 24 items, is a useful and practical tool to improve economic evaluation reporting by researchers and for editors and peer reviewers evaluating their publication potential [10]. However, to ensure the scientific quality of studies, and to facilitate the comparison and transferability of economic evaluation results, methodological standards for health economic evaluations should not only be established, but also followed. With the growing number of published health economic evaluations, more transparent and complete reporting of methods and findings will be increasingly important to facilitate interpretation and comparison of studies. HTA journals could encourage authors to stick to the latest CHEERS checklist and could incorporate this guidance in their ‘Instructions to Authors’ and implement its use during the peer review process to strengthen the methodological quality and reliability. Lack of print space could hamper the transparency in reporting but it could be encountered by encouraging online appendices by the journals.
Multiple therapeutic options and model limitations

The cost-effectiveness study of PAD screening (Chapter 3) indicates that ABI is a highly cost-effective diagnostic tool to be applied in primary care to select patients for treatment with low dose aspirin or clopidogrel. However, the model represents outcomes based on screening done at one point in time based on an average prevalence, and targeted treatment with platelet inhibitors (low dose aspirin or clopidogrel). The outcomes of this cost-effectiveness model only provide a starting point for additional, more refined studies as this model does not factor in repeated screening and multiple treatment options. Though the diagnostic accuracy of the ABI test is high, repeated periodic ABI screening could identify PAD patients missed on initial screening but its benefits against additional cost need to be investigated. No study, so far provided evidence about the intervals for screening for PAD with the ABI [11]. Similarly, modeling the effects of various pharmaceutical therapeutic options (other than platelet inhibitors) used for PAD e.g. lipid lowering drugs (statins) or angiotensin-converting enzyme inhibitors, could provide additional estimates on quality of life due to positive treatment effects and adverse events [1-3, 11, 12]. The model also does not include exercise and smoking cessation programs that are effective in a long-term strategy [13-15].

Research efficiency and data issues

Use of biomarkers could improve estimation of patients' risks, which could personalize treatment management decisions and could better predict response to therapy or a potential for adverse events. Thus, reduced wastage of health resources and cost-effective patient-tailored treatment prescriptions could be achieved. However, single biomarkers can have a very wide range of possible applications, and it is a challenging task to select the applications that should be investigated in depth, as it may not be feasible or efficient to develop decision models for every application. Decision analysis in the very early stage of biomarker development is also typically challenged by a lack of data. Therefore, it is necessary to make assumptions, and sometimes researchers, and thus decision makers, have to rely on scenario analyses in the absence of a 'best guess'. This refers to the scenario uncertainty where a range of possible outcomes are known, but the probability of a particular outcome is not. Use of formal scenario analysis or other foresight methods is recommended in such situations [16].

The HRQoL study among PAD patients is a cross sectional study conducted with most of the participants in Fontaine stage II. Our assumptions about the stability of intra-individual response standards may not be valid. As people can vary, so can their values. This variability may reflect informative shifts in an individual's internal standards, in values and priorities, or in the conceptualization of perceived QOL, in addition to changes in actual health state. The validity of the study would be enhanced by test-retest analysis to evaluate the reliability. This should be done by allowing an appropriate time between tests [17]. This was not done because of practical and time restraints but would be of great interest in further research.
Although correlation between instruments is often used as a measure of convergent validity, there is no consensus on the interpretation of various levels of correlations for this application. Low correlations between EQ-5D and SF-36 is reported by Suarez-Almazor who suggested that these instruments measure somewhat different concepts of health[18]. It is not surprising that various tools would reach only modest correlations as they have been developed for different purposes. On the other hand, McDowell and Newell [19] describe in their review that a correlation of 0.60 can be viewed as extremely high, (0.63 in our study between EQ5D and SF-36); they argued that when two measurements are compared, the maximum correlation between them is the square root of the product of their reliabilities. Where the reliability coefficients are known, the observed correlation may be compared with the maximum correlation that is theoretically obtainable; this helps in interpreting the convergent validity coefficients between two scales.

These findings indicate that essentially the same construct is measured by EQ-5D and SF-6D. The same authors also explained that the correlations are influenced by the range of the scale: wider ranges tend to produce higher correlations.[19].

SF-36 and EQ-5D aim to measure the preference-based measure of health. They do not generate equivalent values for patients. This is not surprising due to differences in their valuation techniques, classification systems, dimensions and items covered. One potential limitation of our study is that it did not explore the effects and extent of valuation method on health state values.

Similarly, the extent to which a change in instrument order would influence baseline health state values is unknown as our study did not allow us to estimate an instrument order effect.

**HTA, clinical decisions and policy making**

HTA is a field of scientific research to inform policy and clinical decision making on the introduction and use of health technologies. Health technologies include pharmaceuticals, devices, diagnostics, procedures and other clinical, public health and organizational interventions. In health systems throughout the world, HTA increasingly plays an essential role in supporting decision making.

This dissertation reports several examples of use of HTA in clinical and policy decision making, defining the role of new health technologies, their appropriate use, and their contribution to better health outcomes.

A) In addition to its ability to detect PAD, ABI is a useful predictor of cardiovascular morbidity and mortality. Better discrimination or calibration of existing cardiovascular events risk assessments could be achieved by ABI measurement. Therefore, the overall benefit of ABI testing includes appropriate risk reclassification facilitating treatments targeted at improved clinical outcomes[11]. Cost effectiveness analysis of ABI screening included in this dissertation suggests that this instrument could be a highly cost-effective option for population based identification and treatment of high-risk for PAD individuals in clinical practice.
A 2005 recommendation by the U.S. Preventive Services Task Force (USPSTF) against routine screening for PAD was based on the rational that screening using the ABI would not provide information “beyond treatment based on standard cardiovascular risk assessment” [20]. The USPSTF guidelines advocate against PAD screening because of the low likelihood of reducing leg morbidity, while screening asymptomatic adults could lead to increased harm due to “false-positive results and unnecessary work-ups. However, these recommendations are too narrow in focus and overlook the fact that the point of screening is not symptom relief, but prevention of cardiovascular events and mortality. Furthermore, ABI screening has high specificity; the percentage of false-positives is relatively low. ABI can serve as a prognostic marker for cardiovascular events and functional impairment. It can be used to stratify the risk of individuals initially classified as intermediate risk on the basis of cardiovascular risk scores (e.g. Framingham Risk Score.[21-23] The American Heart Association’s scientific statement recommended cost effectiveness analyses of targeted ABI screening [24]. Chapter 3 of this dissertation shows that the ABI screening for PAD could be a highly cost-effective option for population based identification and treatment of high-risk individuals and could be useful in weighing the balance between potential harms and benefits of a national screening policy.

B) In current practice, oral anticoagulants are not given to patients with PAD and most patients with PAD receive antiplatelet therapy. Antiplatelet therapy reduces the risk of cardiovascular events in PAD patients by approximately one-third [25]. However, it is estimated that up to 10–20% of these patients are still at risk of cardiovascular events.[26] Research has focused on reducing this remaining risk by using oral anticoagulants, the rationale being that the process of thrombus formation in PAD patients is based on the combination of platelet activation and plasmatic hypercoagulability contributing to the formation of fibrin in the atherothrombotic lesion [26]. With a considerable unmet medical need, there is renewed interest in the anticoagulants therapy in these patients. Research presented in this dissertation shows that the biomarker based (d-dimer) risk assessment of PAD patients and identification of patients with greater risk of cardiovascular events could lead to a stepped up secondary prevention. Use of anticoagulants in the high-risk subset of patients is shown to be a cost-effective healthcare intervention.

C) Conventional Troponin T sensitivity is suboptimal in the initial hours of MI after symptom onset. As a consequence, MI cannot usually be ruled out within a typical emergency department length of stay, and hospital admission is often required. The development of high-sensitivity troponin assays has raised the possibility that repeated troponin testing and hospital admission could be avoided with an associated reduction in pressure on acute beds, and consequent cost savings. The positive results of the cost effectiveness analysis for the use of high-sensitive troponin for the diagnosis of MI in this dissertation may initiate a change in cardiology practice, leading to acceleration of MI diagnosis and improved outcomes. HTA has the potential to function as a mediating mechanism between policy and
research domains by providing a problem oriented systematic overview of research. However, this is dependent upon HTA producers having a thorough and detailed knowledge of policy-making and its conditions, and its users being aware of the use of HTA. The linking policy and research through HTA has some basic barriers to be dealt with. One important issue is that researchers and policy-makers represent two very different communities with different values, ideologies, languages, backgrounds, institutional settings, reward systems etc. These two communities have very different interests which influence the traditionally expected output from research and the demands for input to policy. These challenges can be tackled by mandated information sharing, coordination and joint actions. Therefore, the utilization of HTA in policy-making depends very much on mutual understanding and responsiveness to user needs [27, 28].

CONCLUSIONS

This dissertation presents early assessments of the costs, effects and cost-effectiveness of novel screening, diagnosis and treatment modalities of AVDs. Despite methodological challenges and a lack of data, the studies showed it is feasible to inform policy makers, healthcare professionals and researchers on the potential cost-effectiveness of these interventions. This information may improve clinical and policy decision making; contributing to better and more efficient health care.
REFERENCES


CHAPTER 8

Summary
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SUMMARY

Arterial vascular diseases (AVDs), such as peripheral artery disease (PAD) and myocardial infarction (MI), are caused by fatty deposits on the arterial walls. Patients with AVDs may require treatment in primary or secondary care. For the majority of patients, treatment is aimed at reducing the risk from cardiovascular events.

AVDs are of major public health concern causing considerable burden on the population and incurring large costs to the health care system. PAD remains an underdiagnosed and undertreated disease. Significant morbidity and mortality in PAD patients warrant early diagnosis by screening and stratified treatment based on risk profiles of patients. With limited healthcare resources, it is important to inform decision makers to make appropriate and efficient decisions about the use of health care resources. Health technology assessment (HTA) aims to assess the medical, social, economic and ethical implications of health technologies, and is therefore extremely useful to guide health policy decisions. The aim of this dissertation was therefore to review economic evidence and to provide new perspectives for screening, diagnosis and stratified treatment of patients with AVDs. In the research presented economic modelling is used to assess the value of strategies for screening, diagnosing and/or treating PAD and MI.

Chapter 2 presents a systematic review of existing model-based economic evaluations of PAD. The methodological quality of the appraised studies shows several weaknesses, including insufficient reporting of the study details and limited adherence to good practice guidelines. Methodological diversity and insufficient information posed a challenge for valid comparison of the included studies. Based on these findings, it was recommended that to ensure the scientific quality of studies, and to facilitate the comparison and transferability of economic evaluation results, published methodological standards for health economic evaluations should be followed.

PAD is a common but under recognized cause of morbidity. Although intermittent claudication is the classic symptom of PAD, the vast majority of those affected is asymptomatic and could be diagnosed by ABI screening. Chapter 3 of this dissertation uses health economic modeling to show that the ABI screening for PAD could be a highly cost-effective option for population based identification and treatment of high-risk individuals. This study assessed the impact of PAD screening using long term clinical and economic outcomes. The results show that targeted ABI screening and consequent secondary prevention of cardiovascular events using low dose aspirin or clopidogrel in patients at high risk is a cost-effective strategy. Implementation of targeted PAD screening and subsequent stratified treatment in primary care practices and in public health programs could save health care resources by reducing cardiovascular events.
Chapter 4 reports on the cost-effectiveness of risk assessment and treatment stratification by an existing biomarker ‘D-dimer’ and the headroom of a hypothetical perfect biomarker in PAD patients. The model-based study shows that the use of D-dimer in detection of PAD patients at a relatively higher risk of cardiovascular events and treating them with more aggressive treatment options (oral anticoagulants) is cost-effective. The commercial headroom for a hypothetical biomarker suggests that the development of more accurately stratifying biomarkers (with higher sensitivity and specificity) for the risk assessment and treatment stratification for PAD patients could be financially attractive.

In chapter 5, health related quality of life in PAD patients was assessed using two well validated and widely used generic quality of life questionnaires: EQ-5D and SF-36. PAD is associated with limited physical capacity and impaired functional status. In this study a detailed analysis of the relation between quality of life and severity of PAD was performed. This research also explored the difference between the utility values generated by the SF-36 and the EQ-5D. Mean utility scores ranged from 0.675 for SF-6D, 0.648 for the EQ-5D UK tariff and 0.715 for the Dutch EQ-5D tariff. Both utility instruments differentiated between functional and clinical severity levels; the mean utility values from SF-6D and EQ-5D decreased with increased symptom severity. However, EQ-5D was more sensitive to the functional and clinical severity represented by the rest pain, night pain, activity of daily life and walking distance.

Clinical researchers could use multiple outcome measures for assessing patient outcomes, including both clinical and patient reported outcomes, which could have an impact on subsequent health and wellbeing.

High sensitive Troponin (hsTnT) as a biomarker of myocardial necrosis is extremely sensitive, allowing earlier and faster recognition of AMI patients and giving clinicians an avenue to more quickly diagnose and treat patients appropriately. In chapter 6, a model based economic evaluation shows that the hsTnT assay is a cost effective alternative for the diagnosis of AMI as compared to the existing diagnostic Troponin T assay in clinical practice. Use of hsTnT could save lives and healthcare resources and could improve health related quality of life among AMI patients.

The findings of this dissertation can have several implications for decision making, clinical practice and future/further research. First, the review of economic evidence around AVDs shows that in order to be a useful evidence for decision makers the quality of reporting needs to be improved significantly. Second, this dissertation raises awareness about and provides insight into the value of screening, diagnosis and stratified treatment of patients with AVDs in clinical practice. Finally, this dissertation gives several directions for future research including modelling of multiple AVDs interventions to inform the policy decisions for comprehensive secondary prevention. Cost effectiveness research
into the AVDs screening and management using multiple pharmaceutical and non-pharmaceutical modalities; use of more accurate biomarkers for cardiovascular event risk assessment and stratified treatment with newer anticoagulants; and research into the patient reported outcomes measures in PAD patients in different stages of clinical classification is warranted.
VALORISATION

Innovation is clearly the engine of our social and economic development. Success of innovation should be measured not only in terms of commercialization but, more broadly in terms of valorization. This is a coherent framework for transforming health research into action, improving the quality of life and stimulating economic development through discovery and innovation. Valorization of health research could lead to health improvement, increased productivity and improved quality of life.

This dissertation included several analyses about the economic value of screening, diagnosis and treatment of arterial vascular diseases (AVDs) that could be useful and used by the patients, health care providers, health care policy makers and health care budget holders. Based on the results of peripheral artery disease (PAD) screening study and tailored treatment study, the debate is restarted regarding the active detection and use of aggressive treatment with anticoagulants for a subgroup of patients. Optimizing the screening, diagnosis and management of AVDs based on the evidence presented in this dissertation could lead to the reduction in the catastrophic cost associated with expensive cardiovascular consequences of AVDs, saving the resources for the health care system and for the society as a whole. The study on reporting economic evaluations can be helpful for researchers as well as for policymakers, as they provide an overview of the possible improvements that should be taken into account in order to perform a good evaluation or to rate an evaluation more adequately. Common minimum reporting standards that are followed by all researchers in the field are important, as it increases confidence in and the usability of economic evaluations. We hope that our article and recommendations to use CHEERS checklist for economic evaluations will stimulate the discussion among other researchers to use this ISPOR taskforce checklist for appraisal of economic evaluations. Societal relevance, target audience, business and innovation and valorization process for this research are elaborated below.

Societal relevance: Due to high prevalence of AVDs, screening, treatment and secondary prevention of AVDs has huge societal impact. The modelling of the status quo of AVDs management in this thesis predicts poor clinical, functional and financial outcomes and highlights the importance of timely detection, aggressive treatment and secondary prevention. On one hand this will improve functional status, cardiovascular profile and quality of life of these patients and on the other hand it will reduce health care resource consumption and will save money. This research contributes to the expansion of the evidence base supporting prevention of AVDs in order to improve societal health and reduce the high costs associated with management of cardiovascular events and disability in AVD patients. In this era of steadily rising health care costs on one side and austerity on the other, prevention is having a greater role than ever in the health care arena. This research also suggest cost effective improvement in the quality of care of
AVDs patients by advocating personalized management of disease, based on their cardiovascular risk profile.

**Target audience:** The research presented in this dissertation has a broad audience base ranging from AVD patients, manufacturers of pharmaceuticals, health care providers, health care policy makers and health care budget holders. The clinical and financial consequences of the diagnosis and treatment of AVDs are modelled to raise awareness in the target audience. This research could provide an economic lens to the target audience and suggests the means to cut the cost of consequences for AVDs and to improve the quality of care.

**Business and innovation:** Research and modelling for the biomarkers identifying patients having higher risk of cardiovascular events have great business potential. In status quo, standard regiment is prescribed for secondary prevention in all patients. However, biomarker based high risk patient identification is a game changer leading to prescription of more aggressive regimen and better health outcomes for these patients. This dissertation modelled an existing biomarker and also calculated the commercial headroom available for more refined future products for this purpose. Commercial viability of future biomarkers shown by this research will encourage manufacturers to invest resources in this filed. Commercialization of these models to the relevant stakeholders could inform product development portfolios and guide investment decisions.

**Valorization process:** Through dissemination of the research findings to the relevant stakeholders, namely patients, health care providers, policy makers and manufacturers, are critical to the valorization process. This could be achieved by scientific publication, policy briefs, study newsletter, press release, media coverage, flyers, posters, brochures, seminars and conferences. Economic models developed in this research could have a user’s interface to incorporate new clinical and economic information of future biomarkers and these models could be reused by the relevant stakeholders. Manufacturers could use the models to predict the commercial success of a biomarker under development, policy makers to assess the value of a newly available biomarker and clinical bodies to update the clinical guidelines for the management of AVDs.

To conclude, studies presented in this dissertation could be useful for patients, manufacturers, decision makers and clinicians in efforts to manage the AVDs. Development of an efficient screening and secondary prevention program for AVDs and a better incorporation of patient preferences in policy and clinical decision making could definitely be useful in tackling the increasing burden of AVDs. In addition, this research could serve as case to raise awareness amongst the primary and secondary care providers and general population regarding the efficient and early secondary prevention of AVDs.
It might be just a small step, and there are still barriers to overcome, but bringing study results from health economics to various stakeholders is something this dissertation might have contributed to.
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ABOUT THE AUTHOR

Anil Vaidya was born on 17th February 1970 in Gwalior, India. He was practicing physician in India before joining Erasmus Mundus European Public Health master program sponsored by the European Commission. He received Master of Public Health degree in 2007 from the Sheffield University, UK and Master of Science in Health Economics from Jagiellonian University, Krakow, Poland in 2008. He also received his dual master EUROPUBHEALTH diploma from École des hautes études en santé publique, (EHESP School of Public Health), Rennes, France. In 2009, he joined Health Services Research department at Maastricht University in the Netherlands. He started his PhD in 2010 at the department of Clinical Epidemiology and Medical Technology Assessment of the Maastricht University Medical Center. Topics of special interest to Anil are health technology assessment, economic evaluation, patient reported outcomes, value communication and market access.

Currently, Anil is working as research associate at the Health Technology and Policy unit of School of Public Health at the University of Alberta, Canada. He is also co-founder and partner of O-ZONE 2.0 Health Economics and Outcomes Research (HEOR) consultancy.

Anil and his wife Param have two boys Anmol (1998) and Shourya (2000).
LIST OF PUBLICATIONS

International peer reviewed journals


