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 wide spread atherosclerosis also 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.](image-url)
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 Philips 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 Philip's 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 Janu-ary 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 Muradin 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 preoperative 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, nitrofuryl 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.

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<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>就可以</th>
<th>Setting</th>
<th>Population</th>
<th>Type of analysis/ Unit of outcome</th>
<th>Diagnostic/ Therapeutic</th>
<th>Comparators</th>
<th>Model type</th>
<th>Perspective</th>
<th>Diagnostic/ Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yin (25)</td>
<td>1995</td>
<td>US</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>D</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>MRA, Angiography</td>
</tr>
<tr>
<td>Hunink (16)</td>
<td>1995</td>
<td>US</td>
<td>Peripheral arterial occlusion</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Payer's</td>
<td>Markov model</td>
<td>PTA, No treatment, PTA-PTA, BS-No treatment, BS-ANGIO</td>
</tr>
<tr>
<td>Sculpher (18)</td>
<td>1996</td>
<td>UK</td>
<td>25 years</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree + Markov model</td>
<td>Payer's</td>
<td>Societal</td>
<td>CUA/QALY</td>
</tr>
<tr>
<td>Bosch (11)</td>
<td>1998</td>
<td>NL</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>Laser assisted angioplasty, conventional surgery</td>
</tr>
<tr>
<td>Bosch (10)</td>
<td>2000</td>
<td>US</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>PTA, selective stent placement, repeated PTA, PTA with selective stent placement, PTA with selective stent placement, primary stent placement, No revascularization, Angioplasty device</td>
</tr>
<tr>
<td>De Vries (13)</td>
<td>2001</td>
<td>NL</td>
<td>IC</td>
<td>NL</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Visser (22)</td>
<td>2002</td>
<td>NL</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Visser (24)</td>
<td>2003</td>
<td>US</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Visser (26)</td>
<td>2003</td>
<td>NL</td>
<td>IC</td>
<td>NL</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Markov model</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Treesak (21)</td>
<td>2004</td>
<td>US</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Guest (14)</td>
<td>2005</td>
<td>US</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Hillel (15)</td>
<td>2006</td>
<td>NL</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Coffi (12)</td>
<td>2008</td>
<td>NL</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Sigut (19)</td>
<td>2011</td>
<td>NL</td>
<td>IC</td>
<td>IC</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
<tr>
<td>Squires (20)</td>
<td>2011</td>
<td>NL</td>
<td>IC</td>
<td>NL</td>
<td>CUA/QALY</td>
<td>T</td>
<td>Decision tree</td>
<td>Societal</td>
<td>CUA/QALY</td>
<td>D + T</td>
</tr>
</tbody>
</table>

US = United States of America, NL = The Netherlands, UK = United Kingdom, IC = Intermittent Claudication, D = Diagnostic, T = Therapeutic, DUS = Duplex Ultrasonography, MRA = Magnetic Resonance Angiography, PTA = Percutaneous Transluminal Angioplasty, PGE1 = Prostaglandin E1 infusion, BS = Bypass Surgery, EX = Exercise rehabilitation, CUA = Cost Utility Analysis, CEA = Cost Effectiveness Analysis, QALY = Quality Adjusted Life Years, ICER = Incremental Cost Effectiveness Ratio, ACE-I = Angiotensin Converting Enzyme Inhibition, L.E.A.D. = 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>
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<tbody>
<tr>
<td>Yin (25)</td>
<td>There is a gain of 0.0044 in quality-of-life value for a patient undergoing preoperative evaluation when MR angiography replaces conventional angiography as preoperative planning modality. ICER was reported to be 25895/QALY.</td>
<td>MR angiography may be a cost-effective alternative to conventional angiography in patients with limb-threatening LEAD.</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>Sculpher (18)</td>
<td>The ICER for laser assisted angioplasty in claudicants was 3040 pounds and in patients with rest pain/laceration was 1810 pounds per QALY.</td>
<td>Secondary use of laser assisted angioplasty is worth funding in the UK.</td>
</tr>
<tr>
<td>Bosch (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 caused by an iliac arterial stenosis.</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 bypass surgery 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 is small compared with the costs. Angioplasty performed whenever feasible was more effective than was exercise alone, and the cost-effectiveness ratio was within the generally accepted range.</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>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>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 with 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 pain, 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>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>
Services (NHS) UK, cilostazol is the most cost-effective strategy for improving the maximal walking distance at 24 weeks after starting the treatment (14).

A Markov model (16) referred to in three other articles (10, 11, 17) was comprised of the following health states: the procedure performed, any resulting complication, post-procedural patency, being amputated, and death. The time horizon in this model is lifetime. Hunnink et al. compared angioplasty with bypass surgery in patients with femoropopliteal disease. Angioplasty was found to be the preferred initial treatment in patients with disabling claudication while bypass surgery is preferred treatment for patients with chronic critical ischaemia and an occlusion (16). Bosch et al. compared primary stent placement, Percutaneous Transluminal Angioplasty (PTA) and PTA with selective stent placement using Dutch iliac stent trial (DIST) data. This study suggested that PTA with selective stent placement is a cost-effective strategy for the treatment of iliac arterial occlusive disease (11). Similar study was conducted in the United States setting and obtained a similar conclusion (10). In the Markov model developed by Hunnink et al. (16) another treatment option of a hypothetical endovascular device was added by Muradin et al. (17). Target cost and patency rates for this hypothetical device were estimated in this study, and this device was found to be cost-effective in comparison of current therapies (17).

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 diagnostic 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. No 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 can 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-occlusion of 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-occlusion 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

<table>
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<tr>
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<th>Results</th>
<th>Conclusions</th>
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<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>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>Sigvant (19)</td>
<td>Statin, aspirin, non-aspirin platelet therapy and ACE-I treatment yielded a 26%, 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 the most cost effective compared with other vasoactive drug and no vasoactive drug.</td>
</tr>
<tr>
<td>Squires (20)</td>
<td>Pentoxifylline and Cilostazol are dominated by Naftidrofuryl oxalate and has an incremental cost per QALY gained of around 6070 pounds.</td>
<td>Naftidrofuryl oxalate is the most cost effective compared with other vasoactive drug and no vasoactive drug.</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.
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.

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**Figure 2: Methodological grading of the included studies.** Methodological appraisal of the included studies has been done using Philip’s check-list containing 60 items. The x-axis of the figures shows the number of items from the check-list while y-axis lists the included studies assessed against these items. Colour coding for each study bar shows total responses and should be interpreted as Y=yes, Y/N=yes and no (check-list item is partially answered; described but not justified), NA=not applicable, N=no.
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 the 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 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 health economic evaluations of new interventions to inform the allocation of resources.

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Conflict of interest
None declared.

References