Cost-effectiveness of diagnostic imaging work-up and treatment for patients with intermittent claudication in the Netherlands


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The following alternative management strategies for patients with intermittent claudication were investigated.

Magnetic resonance angiography (MRA) in all patients and subsequent angioplasty for all patients with suitable lesions, otherwise patients entered a supervised exercise programme (MRA+PTA/EX).

MRA in all patients and subsequent angioplasty for patients with suitable lesions, bypass surgery for the remainder of patients, except for those non suitable who entered a supervised exercise programme (MRA+PTA/BS/EX).

Colour-guided duplex ultrasound (DUS) in all patients and subsequent angioplasty for patients with suitable lesions, otherwise patients entered a supervised exercise programme (DUS+PTA/EX).

Colour-guided DUS in all patients and subsequent angioplasty for patients with suitable lesions and bypass surgery for the remainder of patients, except for those non suitable who entered a supervised exercise programme (DUS+PTA/BS/EX).

Intra-arterial digital subtraction angiography (DSA) in all patients and subsequent angioplasty for patients with suitable lesions, otherwise patients entered a supervised exercise programme (DSA+PTA/EX).

DSA in all patients and subsequent angioplasty for patients with suitable lesions and bypass surgery for the remainder of patients, except for those non suitable who entered a supervised exercise programme (DSA + PTA/BS/EX).

A conservative strategy in which all patients entered a supervised exercise programme (Notest+EX) and were only evaluated further if critical limb ischaemia developed.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of previously untreated 60-year-old patients presenting with severe unilateral claudication of at least one year in duration, who had at least one significant lesion (>50% arterial diameter reduction) that was located predominantly suprainguinal or infrainguinal, an ankle brachial index pressure of 0.70 and no history of coronary artery disease.

Setting
The study setting was secondary care. The economic study was carried out in the Netherlands.
Dates to which data relate
The effectiveness data were derived from studies published between 1960 and 2002. The cost data would appear to relate to data published between 1995 and 2002. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
The authors used a model that had been developed already, which consisted of a Markov Monte Carlo model embedded in a larger decision-analytic model. The health states considered were asymptomatic or mild claudication, severe claudication, critical limb ischaemia, and amputation of the limb. Hypothetical patients were followed lifelong from the time that the initial diagnostic work-up was performed. The cycle length used in the Markov model was not clearly identified.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the sensitivities for MRA and DUS to detect a stenosis of more than 50%;
- the test characteristics of MRA and DUS to assess the treatment option (i.e. percentage of patients undergoing angioplasty versus bypass surgery versus lesions not suitable for invasive treatment given the test results);
- data on equivocal MRA and DUS results;
- the mortality and morbidity of DSA;
- the excess mortality for peripheral arterial disease (PAD);
- the mortality from vascular interventions for those patients at high and low risk;
- the risk of systemic complications;
- the 2-year patency in patients with intermittent claudication;
- the probability of suprainguinal disease;
- the suitability for angioplasty;
- the rate of critical limb ischaemia;
- the risk of amputation;
- the relative risk of severe intermittent claudication after stopping exercise and after graft failure; and
- the mean annual rate of contralateral symptoms.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.
Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 28 primary studies were included in the review (at least three of them were meta-analyses, and one was a case series).

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The sensitivities for MRA and DUS to detect a stenosis of more than 50% were, respectively, 0.98 (range: 0.96 - 0.99) and 0.88 (range: 0.84 - 0.91).

The probabilities that MRA and DUS results suggested angioplasty given that the lesion was suitable for angioplasty were, respectively, 0.79 and 0.60.

The probabilities that MRA and DUS results suggested angioplasty given that the lesion was suitable for bypass surgery were, respectively, 0.03 and 0.08.

The probabilities that MRA and DUS results suggested angioplasty given that the lesion was not suitable for invasive treatment were, respectively, 0 and 0.09.

The probabilities that MRA and DUS results suggested bypass surgery given that the lesion was suitable for bypass surgery were, respectively, 0.97 and 0.87.

The probabilities that MRA and DUS results suggested bypass surgery given that the lesion was suitable for angioplasty were, respectively, 0.14 and 0.36.

The probabilities that MRA and DUS results suggested bypass surgery given that the lesion was not suitable for invasive treatment were, respectively, 0 and 0.09.

The probabilities of additional work-up with DSA for equivocal MRA and DUS results were, respectively, 0.09 (range: 0.06 - 0.14) and 0.23 (range: 0.08 - 0.37).

The risks of major complications or death with DSA were 0.03 (range: 0.02 - 0.05) and 3.3 x10^-4 (range: 2.9 x10^-4 - 16.2 x10^-4), respectively.

The excess mortality for PAD was 3.14 (range: 2.74 - 3.54).

The mortality from vascular interventions in high- versus low-risk patients ranged from 0.013 (range: 0 - 0.037) versus 0.001(range: 0, 0.029) when suprainguinal angioplasty with selective stent placement was performed to 0.098 (range: 0.077 - 0.119) versus 0.147 (range: 0.113 - 0.181) when amputation was performed in patients aged less than 75 years old versus those aged 75 or older.
The rate of systemic complications ranged from 0.013 (range: 0 - 0.035) when suprainguinal angioplasty with selective stent placement was performed to 0.38 (range: 0.377 - 0.383) when amputation was performed.

The 2-year patency in patients with intermittent claudication ranged from 0.67 when suprainguinal angioplasty with selective stent placement was performed in case of occlusion to 0.95 when aortic bifurcation grafts were performed.

The probability of suprainguinal disease ranged from 0.17 (range: 0.09 - 0.25) for subsequent interventions with prior infrainguinal disease to 0.56 (range: 0.12 - 0.85) for the first intervention.

The suitability for angioplasty in case of claudication ranged from 0.18 for a first intervention in a patient with infrainguinal disease to 0.51 for a first intervention in a patient with suprainguinal disease.

The annual incidence rates of critical limb ischaemia for patients aged less than 65 years old and for those aged 65 or older were, respectively, 0.017 (range: 0 - 0.039) and 0.036 (range: 0 - 0.075).

The 5-week probabilities following graft failure of pre-treatment symptoms/claudication and critical limb ischaemia were, respectively, 0.062 (range: 0 - 0.014) and 0.242 (range: 0.14 - 0.36).

The proportion of above knee amputations was 0.08 (range: 0.03 - 0.13).

The annual incidence rate of progression below-knee to above-knee amputation was 0.015 (range: 0 - 0.07).

The relative risks of severe intermittent claudication after stopping exercise and after graft failure were, respectively, 5.81 (range: 1.8 - 18.5) and 1.36 (range: 0.96 - 1.92).

The mean annual rate of contralateral symptoms was 0.149.

The health-related quality of life ranged from 0.20 (range: 0 - 0.40) in patients with above-knee amputation to 0.90 (range: 0.60 - 1.00) in patients with angina pectoris.

**Measure of benefits used in the economic analysis**

The summary measure of benefit used was the number of quality-adjusted life-years (QALYs). The health values for intermittent claudication were available from patients who participated in a supervised exercise programme, with the responses to the EuroQol being transformed into time trade-off values. For all other health states, time trade-off values were used from the literature. The time horizon considered for the estimation of health benefits was a lifetime. The health benefits were discounted at a rate of 3%.

**Direct costs**

The direct costs considered appear to have been those incurred by the health system and the patients. The direct medical costs were for personnel, materials, equipment, hospital admission, inpatient services and overheads. The direct non-medical costs included patient time spent on interventions and travel expenses. The costs were derived from the University Hospital Maastricht, data collected from the literature and authors’ assumptions. Resource use and the costs were not reported separately. Discounting was necessary, as the costs were incurred over the lifetime of the patient, and was appropriately performed at an annual rate of 3%. The study reported the average costs. All of the costs were updated with the Consumer Price Index to 1999 prices.

**Statistical analysis of costs**

The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**

Friction costs (i.e. costs for productivity losses, calculated as the costs of replacement of an employee) were not included in the analysis as most patients with PAD are retired.
Currency
Euros (Euro). The exchange rate used was Dutch guilders 2.20 = Euro1.00 = US dollars $1.06 (1999).

Sensitivity analysis
Sensitivity analyses were performed for diagnostic work-up parameters and also for the most influential parameters of treatment and follow-up, based on another analysis (de Vries et al. 2002, see ‘Other Publications of Related Interest’ for bibliographic details). The authors also considered a cohort of 40-year-old men and one of 70-year-old men with a history of coronary artery disease in order to assess the results for alternative populations.

Estimated benefits used in the economic analysis
The QALYs gained per patient with each management strategy were:

- 6.0606 with Notest+EX;
- 6.1465 with DUS+PTA/EX;
- 6.1487 with MRA+PTA/EX;
- 6.1498 with DSA+PTA/EX;
- 6.2002 with DUS+PTA/BS/EX;
- 6.2136 with MRA+PTA/BS/EX; and
- 6.2254 with DSA+PTA/BS/EX.

Cost results
The cost of each management strategy was:

- Notest+EX, Euro6,793;
- DUS+PTA/EX, Euro8,546;
- MRA+PTA/EX, Euro8,566;
- DSA+PTA/EX, Euro8,997;
- DUS+PTA/BS/EX, Euro18,720;
- MRA+PTA/BS/EX, Euro18,440; and
- DSA+PTA/BS/EX, Euro18,583.

Synthesis of costs and benefits
The cost-effectiveness was determined by excluding (extended) dominated strategies and then calculating the incremental cost-utility ratio. A strategy was considered to be dominated by another strategy if the latter yielded higher QALYs at a lower cost. A strategy was considered to be extended dominated by another if the latter yielded higher QALYs at a lower incremental cost-utility ratio. The incremental cost-utility ratio of a strategy was calculated as the difference in QALYs compared with the next best strategy, which represented the additional costs per additional QALY gained for a strategy compared with the next best strategy.
The strategy MRA+PTA/EX had an incremental cost-utility ratio of Euro20,138/QALY compared with the Notest+EX strategy.

The strategy DSA+PTA/BS/EX had an incremental cost-utility ratio of Euro130,557/QALY compared with the MRA+PTA/EX strategy.

All other management strategies were inferior by either dominance or extended dominance.

For 40-year-old male patients, the incremental cost-utility ratios of MRA+PTA/EX (compared with Notest+EX) and DSA+PTA/BS/EX (compared with MRA+PTA/EX) decreased (Euro13,000/QALY and Euro98,000/QALY, respectively). For 70-year-old patients with a history of coronary artery disease it was found that the DUS+PTA/EX strategy had an incremental cost-utility ratio of Euro48,000/QALY compared with the Notest+EX strategy, while MRA+PTA/EX had an incremental cost-utility ratio of Euro75,000/QALY compared with DUS+PTA/EX.

The results were found to be sensitive to an increase in the costs of MRA. When the number of patients with intermittent claudication having lesions suitable for angioplasty was increased, the effectiveness of all strategies increased. In addition, the costs increased for management strategies with angioplasty as the only invasive treatment option, but decreased for management strategies with both angioplasty and bypass surgery.

Authors’ conclusions
For patients with severe unilateral intermittent claudication of at least one year in duration, noninvasive imaging modalities could replace intra-arterial digital subtraction angiography (DSA) without an important loss in effectiveness and at a minimal cost-reduction. Management strategies including angioplasty were cost-effective in the Netherlands and, although strategies including bypass surgery were more effective, their incremental costs were very high.

CRD COMMENTARY - Selection of comparators
The authors compared seven different management strategies for patients with intermittent claudication in the Netherlands and chose Notest+EX as the comparator (although no explicit justification was given for this choice). As the authors stated, medical therapy and smoking cessation were not considered as separate treatment options, but rather as a part of the general management of all patients. All these strategies appear to have covered the available diagnostic and treatment options for this group of patients. You should decide if these are widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature had been undertaken to identify relevant research and minimise bias. They also failed to report any methodology of their review, such as the sources searched, study designs for inclusion and synthesis of the results from different studies, and whether they investigated any differences between the primary studies. Despite this, the authors included approximately 28 studies in their review, and a range of values (or an alternative value) was given for each point estimate to allow sensitivity analyses. Further, sensitivity analyses were performed for diagnostic parameters and for the most influential parameters of treatment and follow-up, based on the results from a prior analysis.

Validity of estimate of measure of benefit
The estimation of benefit was modelled. The decision analytic model used to derive the health benefits appears to have been appropriate. The fact that QALYs were used as the measure of benefit enables comparisons of the study results with results from different interventions. The estimated benefits were discounted, although there is controversy in the health economics literature about whether health benefits should or should not be discounted.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted appear to have been included in the analysis, although
some relevant costs were omitted. Down-stream induced medical costs were not considered since the treatment of PAD did not prolong life but improved the quality of life of the patient. In addition, although the stated perspective was societal, friction costs were not considered since most patients with PAD are retired. The costs and the quantities were not reported separately, which will limit reflation exercises to other settings. The costs were derived from the authors’ setting, published sources and from several assumptions. Appropriate sensitivity analyses of the costs were performed. Discounting was necessary, as the costs were incurred over the lifetime of the patient, and was appropriately performed at 3% per annum. The price year was reported, which will aid any possible inflation exercises.

Other issues
The authors made appropriate comparisons of their findings with those from other US studies, finding that the incremental cost-utility ratios for the USA were higher than those for the Netherlands. Despite this, the authors reported that the implications for both countries were the same. The issue of generalisability to other settings was addressed in the sensitivity analysis, and by the fact that the authors explicitly compared their results with those from other studies with US settings. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of limitations to the study. First, they assumed that DSA would be performed for recurrent or contralateral symptoms instead of MRA or colour-guided DUS, which may not be the case in current clinical practice. However, they commented that the results would only change minimally and that the conclusions would not change. Second, several secondary data sources were used as input data for the parameters, with limiting assumptions having to be made.

Implications of the study
The authors do not appear to have recommended strategies with bypass surgery, compared with angioplasty, as their additional gain in effectiveness does not justify the additional expense.

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Other publications of related interest


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