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Cost-effectiveness of Diagnostic Imaging Work-up and Treatment for Patients with Intermittent Claudication in The Netherlands

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Objective: *to determine the societal cost-effectiveness of various management strategies, including both the diagnostic imaging work-up and treatment, for patients with intermittent claudication in The Netherlands.*
Methods: *a decision-analytic model was used and included probability and quality of life data available from the literature. A cost-analysis was performed in a university setting in The Netherlands. Imaging work-up options included magnetic resonance angiography (MRA), color-guided duplex ultrasound, or intraarterial digital subtraction angiography (DSA) and treatment options were percutaneous transluminal angioplasty with selective stent placement if feasible or bypass surgery. Management strategies were defined as combinations of imaging work-up and treatment options. A conservative strategy with no imaging work-up and walking exercises was considered as reference. Main outcome measures were quality-adjusted life years (QALYs), lifetime costs (€), and incremental cost-effectiveness (CE) ratios. The base-case analysis evaluated 60-year-old men with severe unilateral intermittent claudication of at least one year duration.*
Results: *the range in QALYs and costs across management strategies that considered angioplasty as only treatment option was small (maximum difference: 0.0033 QALYs and €451). Similarly, the range was small across management strategies that considered angioplasty if feasible otherwise bypass surgery (maximum difference: 0.0033 QALYs and €280). MRA in combination with angioplasty (6.1487 QALYs and €8556) had a CE ratio of €20 000/QALY relative to the conservative strategy. The most effective strategy was DSA in combination with angioplasty if feasible otherwise bypass surgery (6.2254 QALYs and €18 583) which had a CE ratio of €131 000/QALY relative to MRA in combination with angioplasty.*
Conclusion: *the results suggest that the imaging work-up with non-invasive imaging modalities can replace DSA for the work-up of patients with intermittent claudication without a substantial loss in effectiveness and a minimal cost-reduction. Management strategies including angioplasty are cost-effective in the Netherlands but although strategies including bypass surgery are more effective, their incremental costs are very high.*

Key Words: Cost-effectiveness; Intermittent claudication; Magnetic resonance angiography; Duplex ultrasound; Digital subtraction angiography; Percutaneous transluminal angioplasty; Bypass surgery.

Introduction

Peripheral arterial disease (PAD) presenting as intermittent claudication is common among the elderly with a prevalence ranging from 0.6 to 7.0% and increasing with age.[1] The diagnosis of PAD is established based on the history, physical examination, and a decreased ankle-brachial pressure index. If a vascular intervention is considered, diagnostic imaging work-up is necessary. The current work-up may include intraarterial digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and color-guided duplex ultrasound (DUS). DSA is considered to be the reference ("gold") standard but involves small risks,[2,3] has contra-indications such as contrast media reactions and renal impairment, and is expensive compared with non-invasive tests. MRA is nearly as accurate as DSA but has contra-indications such as claustrophobia and the presence of a pacemaker whereas color-guided DUS

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has reasonable diagnostic accuracy and low costs but is operator-dependent.[4]

Treatment options for PAD include percutaneous transluminal angioplasty with selective stent placement, bypass surgery, or a more conservative approach with walking exercises. Angioplasty is a minimally invasive procedure and, compared with bypass surgery, both the complication risks and costs are lower but the rate of failure due to restenosis or occlusion is somewhat higher.[5–8] Walking exercise is regarded as an effective method for improving symptoms of claudication but not all patients benefit, and the costs are not as low as expected if patient time spent on walking is considered in terms of its monetary value.[9–12]

For the diagnostic imaging work-up and for the treatment of patients with intermittent claudication cost-effectiveness analyses have been performed for the United States.[13,14] It is, however, unclear to what extent cost-analyses, and thereby cost-effectiveness analyses, are generalizable across countries since differences exist in the finance systems and regulations of health care systems. In particular, it is unclear if the published cost-effectiveness analyses of the diagnostic work-up and treatment for patients with intermittent claudication can be applied to the situation in The Netherlands. The main purpose of our study was to evaluate the cost-effectiveness of management strategies, including the imaging work-up and treatment, for patients with intermittent claudication in The Netherlands. A second purpose was to study if the results from the previous cost-effectiveness analyses performed in the United States were generalizable to The Netherlands.

Methods

Decision models

For the current study we used a previously developed decision-analytic model evaluating the (societal) cost-effectiveness of diagnostic imaging strategies[14] and treatment strategies.[13] The model consisted of a Markov Monte Carlo model that was embedded in a larger decision-analytic model. The current study is a simulation study in which hypothetical patients were followed lifelong from the time that the initial diagnostic work-up was performed. We considered previously untreated patients presenting with severe unilateral claudication of at least one year duration who had at least one significant lesion ($>50\%$ arterial diameter reduction) that was located predominantly suprainguinal or infrainguinal.

Diagnostic work-up

The pre-treatment imaging work-up of patients with intermittent claudication consisted of localization of the lesion (predominantly suprainguinal or infrainguinal) and determining a treatment plan (angioplasty, bypass surgery, or walking exercise). The following imaging modalities for the pre-treatment work-up were evaluated: gadolinium-enhanced MRA, color-guided DUS, and intraarterial DSA. DSA was the reference standard in our analysis and we assumed that MRA and color-guided DUS could result in equivocal test results or could induce false test results. Equivocal test results were defined as a technical failure of the test, no treatment plan could be made on the basis of the test result, or the test could not be performed because of a contra-indication. A DSA was always performed for equivocal results and in the event that no lesion was localized.

False test results could lead to inappropriate treatment of patients. We assumed that if an angioplasty was incorrectly recommended to a patient that the diagnostic DSA performed as part of the angioplasty procedure would detect the false test result. If the angioplasty procedure had to be stopped the costs of the procedure equaled the costs of a diagnostic DSA plus some extra costs for inefficient use of personnel, equipment, and housing. An incorrectly recommended bypass surgery was not detected unless patients returned to the hospital with persistent symptoms of intermittent claudication after treatment of the incorrect location, at which time we assumed they would be re-evaluated with a DSA.

Treatment and follow-up

Treatment options for patients with intermittent claudication were supervised exercise (EX), percutaneous transluminal angioplasty with selective stent placement (PTA), or bypass surgery (BS). Of all patients, we assumed that 95% had lesions suitable for invasive treatment (angioplasty with selective stent placement or bypass surgery)[15] and the remainder of the patients entered a supervised exercise program. Feasibility of percutaneous treatment for suprainguinal or infraiguinal lesions was determined according to published guidelines.[16] Bypass surgery was considered if angioplasty was not feasible depending on the management strategy considered. A failure of invasive treatment was defined as a graft failure or restenosis in combination with severe claudication or progression to critical limb ischemia (defined as rest pain, ulcers or gangrene). A failure of supervised exercise was

defined as development of critical limb ischemia. Patients that developed critical limb ischemia were always treated invasively. Patients with failures underwent a DSA to determine appropriate treatment. In clinical practice invasive treatment for recurrent symptoms is not utilized in an unlimited fashion and we therefore limited the maximum number of interventions per limb to three. If the maximum number of interventions per limb was reached and the patient had critical limb ischemia then the affected limb was amputated.

The embedded model that evaluated treatment was a Markov decision model in which the patient's lifespan was modeled from the time of presentation with severe claudication until death, including treatment and follow-up. The following health states were considered: (1) asymptomatic or mild claudication; (2) severe claudication; (3) critical limb ischemia; and (4) amputation of the limb. Patients with severe intermittent claudication were distinguished from patients with no or mild claudication by a threshold maximum walking distance of less than 250 m, which was used in a previous analysis.[13] Maximum walking distance was defined as the distance at which the patient was forced to stop because of severe symptoms of intermittent claudication. To determine the maximum walking distance patients were asked to walk back and forth between two fixed points in the hospital corridors at a predetermined speed. Speed was held constant by monitoring the time needed to cover the distance (25 m) between these two points. The available data did not permit making a distinction between asymptomatic patients and patients with mild claudication. Implicitly, it was assumed that severe symptoms of intermittent claudication justified the use of invasive treatment. Patients could develop recurrent or contralateral symptoms during follow-up which would then be evaluated with a DSA and, depending on the management strategy, treated with angioplasty or bypass surgery.

Management strategies

The following management strategies were considered: (1) MRA in all patients and subsequent angioplasty for patients with suitable lesions otherwise patients entered a supervised exercise program ["MRA + PTA/EX"]; (2) MRA in all patients and subsequent angioplasty for patients with suitable lesions and bypass surgery for the remainder of patients ["MRA + PTA/BS/EX"]; (3) color-guided DUS in all patients and subsequent angioplasty for patients with suitable lesions otherwise patients entered a supervised exercise program ["DUS + PTA/EX"]; (4) color-guided DUS in all patients and subsequent angioplasty for patients with suitable lesions and bypass surgery for the remainder of patients ["DUS + PTA/BS/EX"]; (5) DSA in all patients and subsequent angioplasty for patients with suitable lesions otherwise patients entered a supervised exercise program ["DSA + PTA/EX"]; (6) DSA in all patients and subsequent angioplasty for patients with suitable lesions and bypass surgery for the remainder of patients ["DSA + PTA/BS/EX"]; (7) a conservative strategy as the reference strategy in which all patients entered a supervised exercise program ["Notest + EX"] and only evaluated further if critical limb ischemia developed. Strategies that started with supervised exercise for all patients and used imaging work-up with subsequent invasive treatment for patients who failed to respond to conservative treatment were not considered in the analysis since a previous analysis showed that there was virtually no difference in outcome compared with strategies that started with imaging work-up and invasive treatment.[13]

Data sources

Costs

The cost calculations were performed according to the Dutch guidelines for cost calculations in health care[17] and all costs relevant to society were considered. Direct medical costs included costs for personnel, materials, equipment, housing, hospital admission, and overhead. The costs for equipment were calculated by using the annuitization method with a 3% discount.[18] It was assumed that equipment had a lifetime of ten years and the yearly costs of maintenance of the equipment were 10%. Overhead was estimated at 15% of the costs for personnel, materials, and equipment. As direct non-medical costs we considered travel expenses and patient time. Patient time spent on interventions was included as a monetary cost by using the average gross earnings per year for men aged between 55 and 65 in The Netherlands (€32 000; 1997). The cost for radiological interventions were available from the Department of Radiology (1997) and the costs for surgical interventions were available from the Department of Surgery (1993), both from the University Hospital Maastricht. Costs of an one-day-admission (€167) were assumed to be half of an overnight admission (€333).[17] Costs for complications of invasive treatments and costs for follow-up after amputation of the limb were based on literature data.[19,20] All costs were updated with the consumer

price index to 1999 costs and converted to Euros (€) (2.20 Dutch Guilders = €1 = 1.06 US dollars, 1999 Dutch Bureau of Statistics) (Table 1).

Down-stream induced medical costs were not considered since the treatment of peripheral arterial disease does not prolong life but improves the quality of life of the patient. Also, friction costs (costs for productivity losses calculated as the costs of replacement of an employee) were not considered since most patients with peripheral arterial disease are retired.

Diagnostic work-up

Intraarterial DSA had a small risk of mortality and morbidity (Table 2).[2,3,21] For gadolinium-enhanced MRA and color-guided DUS no major complications or mortality were reported in the literature and, therefore, we assumed that non-invasive tests did not involve any risks. Sensitivities for MRA and color-guided DUS to detect a stenosis of more than 50% were available from a meta-analysis (Table 2).[4] Also the test characteristics of MRA and color-guided DUS to assess the treatment option (angioplasty vs bypass surgery vs lesions not suitable for invasive treatment) were available from the literature.[15,22–24] Data on equivocal MRA and color-guided DUS results were available from the literature.[4,15,22,24,25]

Exercise program

Estimates for the supervised exercise program were available from a study performed at the University

Table 1. Costs of interventions in 1999 Euros (€).

Variable	Baseline value (alternative values)	Source	United States costs (1998 $) §§
Interventions			
MRA	494	UHM	574
Color-guided DUS	184	UHM	243
Intraarterial DSA	1062 (605) *	UHM	1822 (1183) ‖ ‖
Planned angioplasty and stopped after angiography †	357	UHM	316
Angioplasty for suprainguinal lesions	1934	UHM	8290
Angioplasty for infrainguinal lesions	1655	UHM	4580
Bypass surgery for suprainguinal lesions	10 179	UHM	25 788
Bypass surgery for infrainguinal lesions	5452	UHM	18 108
Amputation above the knee	9817	UHM	15 830
Amputation below the knee	9379	UHM	8550
Supervised exercise program, time costs per year	1267	[13,28]	4147
Complications			
DSA ‡	666	Assumption	7393
Systemic complications §	6894	19	10 723
Mortality from vascular interventions ‖	2286	Assumption	12 758
Follow-up			
Long-term systemic complications ¶	1781	19	11 832
Follow-up visit including office visit, color-guided DUS and ABI measurement	298	UHM	392
Follow-up after amputation of the limb			
First year **	45 225	20 ‡‡	–¶¶
Subsequent years ††	11 079	20 ‡‡	–¶¶

UHM = University Hospital Maastricht

*The costs for hospitalization due to DSA were estimated based on the duration of hospitalization for 11 diagnostic DSAs performed in the University Hospital Maastricht between May 1999 and November 2000 (2 patients returned home after 6–8 h of bedrest and observation, 2 patients were admitted for one night, and 7 patients were admitted for two nights). The value between brackets represents the costs for a DSA with a short period of bedrest and observation after which the patient can return home. This value was used in the sensitivity analyses.

† Extra costs compared with a DSA for a planned but not performed angioplasty.

‡For complications of DSA it was assumed that the hospital admission was prolonged with two days.

§ Costs equaled the costs of treatment for myocardial infarction, which was used as a proxy for complications induced by vascular procedures.

¶ Costs of survivors of myocardial infarction were used as a proxy for the costs of long-term systemic complications.

‖ Costs of dying from vascular procedures were assumed to equal the costs of two days of admission at an intensive care unit.

**Costs included rehabilitation, prosthesis, costs for time spent on rehabilitation, adjustments to the house, domiciliary care, and admission to a nursing home due to amputation of the limb, if necessary.

†† Costs included maintenance of prosthesis, domiciliary care, and admission to nursing home due to amputation of the limb, if necessary.

‡‡ In the study by Pernot *et al.*[20] 87 amputees were followed and data on their healthcare utilization was collected. With use of the Dutch guidelines for costs calculations, costs were allocated to the utilized care.

§§ United States costs were presented in 1998 US $. Updating the costs to 1999 € would slightly increase the presented figures.

¶¶ Costs for follow-up after amputation of the limb were not available for first year vs subsequent years.

‖ ‖ The number between brackets represents the costs of an outpatient DSA.

Table 2. Test characteristics of imaging modalities.

Variable	Base-case (range or alternative value) *	Source
MRA		
Sensitivity (stenosis $\geq$50%)	0.98 (0.96–0.99)	4
Additional work-up with DSA for equivocal MRA results	0.09 (0.06–0.14)	4, 15, 22
Probability that MRA result suggests angioplasty given that lesion is suitable for angioplasty	0.79 (0.87)	22, 15
Probability that MRA result suggests angioplasty given that lesion is suitable for bypass surgery	0.03 (0.065)	22, 15
Probability that MRA result suggests angioplasty given that lesion is not suitable for invasive treatment	0 (0.065)	22, 15
Probability that MRA result suggests bypass surgery given that lesion is suitable for bypass surgery	0.97 (0.87)	22, 15
Probability that MRA result suggests bypass surgery given that lesion is suitable for angioplasty	0.14 (0.65)	22, 15
Probability that MRA result suggests bypass surgery given that lesion is not suitable for invasive treatment	0 (0.065)	22, 15
Color-guided DUS		
Sensitivity (stenosis $\geq$50%)	0.88 (0.84–0.91)	4
Additional work-up with DSA for equivocal color-guided DUS results	0.23 (0.08–0.37)	4, 24, 25
Probability that color-guided DUS result suggests angioplasty given that lesion is suitable for angioplasty	0.60 (0.93)	23, 24
Probability that color-guided DUS result suggests angioplasty given that lesion is suitable for bypass surgery	0.08 (0.10)	23, 24
Probability that color-guided DUS result suggests angioplasty given that lesion is not suitable for invasive treatment	0.09 (0.24)	23, 24
Probability that color-guided DUS result suggests bypass surgery given that lesion is suitable for bypass surgery	0.87 (0.90)	23, 24
Probability that color-guided DUS result suggests bypass surgery giiven that lesion is suitable for angioplasty	0.36 (0.07)	23, 24
Probability that color-guided DUS result suggests bypass surgery given that lesion is not suitable for invasive treatment	0.09 (0.29)	23, 24
DSA		
Major complications	0.03 (0.02–0.05)	2
Mortality	$3.3 * 10^{-4}$ ($2.9–16.2 * 10^{-4}$)	3, 21

* Presented values are probabilities.

Hospital Groningen, The Netherlands.[26] In that study patients followed a supervised exercise program in which they were asked to walk a certain fixed distance each day and instructed to pause when symptoms of claudication appeared. During the first six months of the exercise program patients had four hospital visits.

Invasive treatment and follow-up

Invasive treatment of suprainguinal disease consisted of angioplasty with selective stent placement and aortic bifurcation surgery. Invasive treatment of infrainguinal disease consisted of angioplasty, femoropopliteal bypass surgery, and femoro-infrapopliteal bypass surgery. The invasive treatment options together represent approximately 85% of all interventions performed for PAD in the Brigham and Women's between 1990 and 1995. We used the distribution of treatment options of the United States for The Netherlands since the most often performed procedures in the United States are the same as in The Netherlands.[27] Most lesions being treated invasively for the first time were located suprainguinally and more suprainguinal lesions were suitable for angioplasty than infrainguinal lesions.[13,28] Risk of mortality and systemic complications for vascular interventions were available from the literature.[5,6,29–31] For patency estimates we used published meta-analyses[5–7] and in the model a time-dependent graft failure rate was used. Two-year patency estimates are shown as an illustration in Table 3. During follow-up patients could develop critical limb ischemia and/or symptoms in the contralateral limb for which incidence data were available from the literature.[13,32–36] Also age and gender adjusted estimates for the natural mortality rate and the excess mortality due to PAD were incorporated in the model.[33,34,37–39]

Health-related quality of life

The life expectancy of patients was adjusted with the quality of life. Mostly, health-related quality of life is

Table 3. Treatment and follow-up.

Variable	Base-case (range or alternative value) *	Source
Natural mortality		
Excess mortality for PAD (incidence rate ratio)	3.14 (2.74–3.54)	33, 35, 37–39
Mortality from vascular interventions, high risk/low risk †		
Aortic bifurcation grafts	0.044 (0.032–0.055)/0.007 (0.005–0.009)	6
Suprainguinal angioplasty with selective stent placement	0.013 (0–0.037)/0.001 (0–0.029)	5
Infrainguinal bypass surgery	0.047 (0.008–0.127)/0.008 (0.001–0.022)	29
Infrainguinal angioplasty	0.025 (0–0.264)/0.002 (0–0.021)	29
Amputation, Age < 75/Age ≥ 75	0.098 (0.077–0.119)/0.147 (0.113–0.181)	30
Systemic complications		
Aortic bifurcation grafts	0.083 (0.063–0.102)	6
Suprainguinal angioplasty with selective stent placement	0.013 (0–0.035)	5
Infrainguinal bypass surgery	0.085 (0.027–0.13)	29
Infrainguinal angioplasty	0.013 (0.002–0.110)	29
Amputation	0.38 (0.377–0.383)	31
Two-year patency in patients with intermittent claudication		
Aortic bifurcation grafts	0.95	6
Suprainguinal angioplasty with selective stent placement, stenosis/occlusion	0.84/0.67	5
Infrainguinal bypass surgery, autologous vein/PFTE, above-knee anastomosis/PFTE below-knee anastomosis	0.89/0.86/0.80	7
Infrainguinal angioplasty, stenosis/occlusion	0.75/0.46	7
Probability of suprainguinal disease		
First intervention	0.56 (0.12–0.85)	13
For subsequent interventions with previously suprainguinal disease	0.31 (0.13–0.49)	13
For subsequent interventions with previously infrainguinal disease	0.17 (0.09–0.25)	13
Suitability for angioplasty, claudication		
Suprainguinal disease, first intervention	0.51 (0.74)	13, 28
Suprainguinal disease, subsequent interventions	0.33 (0.74)	13, 28
Infrainguinal disease, first intervention	0.18 (0.50)	13, 28
Infrainguinal disease, subsequent interventions	0.23 (0.50)	13, 28
Critical limb ischemia		
Annual incidence rate, Age < 65/Age ≥ 65	0.017 (0–0.039)/0.036 (0–0.075)	33–36
Five-week probability following graft failure: pre-treatment symptoms, claudication/critical limb ischemia	0.062 (0–0.014)/0.242 (0.14–0.36)	13
Amputation		
Proportion of above knee amputations	0.08 (0.03–0.13)	13
Annual incidence rate of progression below-knee to above-knee amputation	0.015 (0–0.07)	13
Severe vs mild intermittent claudication		
Relative risk of severe intermittent claudication after stopping exercise	5.81 (1.8–18.5)	13
Relative risk of severe intermittent claudication after graft failure	1.36 (0.96–1.92	13
Contralateral symptoms		
Mean annual rate	0.149	32

ePTFE: expanded polytetrafluoroethylene.
* Presented values are probabilities unless stated otherwise.
† Patients that are aged over 65 years with critical limb ischemia and patients with history of coronary artery disease have a higher risk of mortality from vascular interventions.

measured on a scale from 0 (death) to 1 (perfect health). For intermittent claudication the health values were available from patients that participated in the supervised exercise program and the obtained responses to the EuroQol were transformed to time tradeoff values.[40] For patients with critical limb ischemia or an amputation time tradeoff values were used from the literature.[41] Health values for systemic complications and angina pectoris were incorporated by using a simple multiplicative relation.[42] Actual values are presented in Table 4.

Table 4. Health-related quality of life values.

Variable	Base-case (range)	Source
Asymptomatic or mild intermittent claudication	0.79 (0.75–0.83)	40
Severe intermittent claudication	0.71 (0.67–0.75)	40
Critical limb ischemia	0.35 (0.15–0.55)	41
Above knee amputation	0.20 (0.00–0.40)	41
Below knee amputation	0.61 (0.41–0.81)	41
Systemic complications	0.72 (0.60–0.90)	42
Angina pectoris	0.90 (0.60–1.00)	42

Cost-effectiveness analysis

Our primary outcome measures were quality-adjusted life years (QALYs) and lifetime costs (both discounted at 3%)[43] and management strategies were ordered by increasing QALYs. QALYs are a measure of the health outcome: to each period of time a weight ranging from 0 (health state equivalent to death) to 1 (optimal health) corresponding to the health-related quality of life during that period was assigned. These are then aggregated across time periods. Cost-effectiveness was determined by excluding (extended) dominated strategies and then calculating the incremental cost-effectiveness (CE) ratio. A strategy was considered to be dominated by another strategy if the latter yielded higher QALYs at a lower cost and a strategy was considered to be extended dominated by another strategy if the latter yielded higher QALYs and had a lower incremental CE ratio. The incremental CE ratio of a strategy was calculated as the difference in costs divided by the difference in QALYs compared with the next best strategy and represents the additional costs in Euros per additional QALY gained for a strategy compared with the next best strategy.

The baseline analysis evaluated a cohort of 60-year-old men that presented with unilateral severe symptoms of intermittent claudition of at least one year duration, an ankle brachial index pressure of 0.70, and no history of coronary artery disease. We also considered 40-year-old men (all other characteristics similar to the base-case) and 70-year-old men with a history of coronary artery disease (all other characteristics similar to the base-case). Bypass surgery was not performed in patients with a history of coronary artery disease because of high complication rates unless critical limb ischemia developed.

The Markov Monte Carlo model embedded in the larger model was modeled in a C++ based programming language. The complete model was modeled and analyzed in DATA™ (Decision Analysis by TreeAge, version 3.5.7, Treeage Software Inc., Williamstown, MA, U.S.A.). Sensitivity analyses were performed for diagnostic work-up parameters and also for the most influential parameters of treatment and follow-up based on a previous analysis.[13]

Results

Base-case analysis

For the base-case (60-year-old male patients with severe unilateral claudication for one year and without a history of coronary artery disease) the conservative strategy ("Notest + EX") was the least effective and least costly (6.0606 QALYs and €6793). The strategy "MRA + PTA/EX" was more effective and more costly (6.1487 QALYs and €8566) and had an incremental CE ratio of (rounded off) €20 000/QALY compared with the conservative strategy. The strategy "DSA + PTA/BS/EX" was the most effective strategy but was also expensive (6.2254 QALYs and €18 583) and had an incremental CE ratio of €131 000/QALY compared with "MRA + PTA/EX". All other management strategies were inferior by (extended) dominance meaning that another strategy was more effective against lower costs (or with a lower incremental cost-effectiveness ratio) (Table 5). Figure 1 shows that the range in costs and effectiveness across management strategies that considered angioplasty as the only invasive treatment option was small. The same applied but to a lesser degree to strategies that considered both angioplasty and bypass surgery as treatment options.

Alternative patient cohorts

For 40-year-old male patients the incremental CE ratios of "MRA + PTA/EX" and "DSA + PTA/BS/EX" decreased (€13 000/QALY and €98 000/QALY, respectively). For 70-year-old male patients with a history of coronary artery disease only management strategies with angioplasty as treatment option were considered and it was found that

Table 5. QALYs, costs, and incremental CE ratios of management strategies for patients with intermittent claudication.

Management strategies	QALYs *	Cost (€)	Increm CE ratio (€/QALY) §
Notest + EX	6.0606	6793	–
DUS + PTA/EX †	6.1465	8546	ED
MRA + PTA/EX †	6.1487	8566	20,138
DSA + PTA/EX †	6.1498	8997	ED
DUS + PTA/BS/EX ‡	6.2002	18 720	D
MRA + PTA/BS/EX ‡	6.2136	18 440	ED
DSA + PTA/BS/EX ‡	6.2254	18 583	130 557

QALYs = Quality adjusted life years; Increm. CE ratio = incremental cost-effectiveness ratio; DUS = color-guided duplex ultrasound; MRA = magnetic resonance angiography; DSA = digital subtraction angiography; EX = supervised exercise program; PTA = percutaneous transluminal angioplasty with selective stent placement; BS = bypass surgery; D = dominated; ED = extended dominated.

* Strategies were ordered by increasing effectiveness.

† Patients with lesions suitable for angioplasty underwent angioplasty otherwise patients entered a supervised exercise program.

‡ Patients with lesions suitable for angioplasty underwent angioplasty otherwise patients underwent bypass surgery. Patients with lesions not suitable for invasive treatment entered a supervised exercise program.

§ Numbers could differ slightly from calculations based on figures available in the table because of rounding.

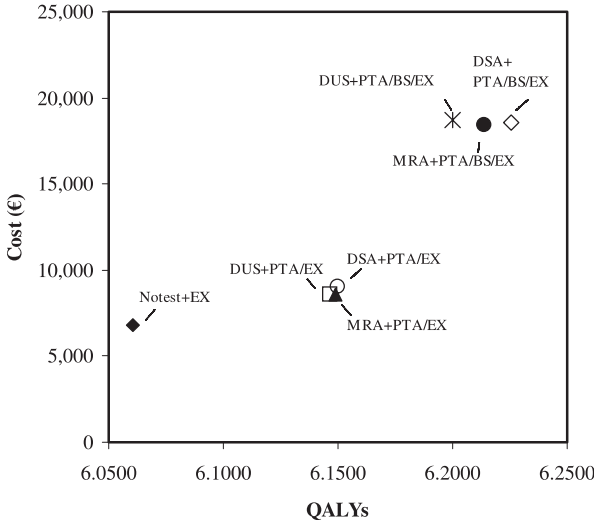

Fig. 1. Quality adjusted life years (QALYs) vs lifetime costs for the base-case analysis.

"DUS + PTA/EX" had an incremental CE ratio of €48 000/QALY compared with the conservative management strategy and "MRA + PTA/EX" had an incremental CE ratio of €75 000/QALY compared with "DUS + PTA/EX".

Sensitivity analysis

The results were sensitive for the costs of MRA. Compared with the conservative strategy the incremental CE ratio of "MRA + PTA/EX" increased from €20 000/QALY (base-case) to €31 000/QALY with an increase of the costs of MRA to €544 and to €115 000/QALY if the costs of MRA were assumed to be 150% that of baseline (€741). The results were not sensitive for lower costs of MRA: the incremental CE ratio decreased to €17 000/QALY if MRA cost €247. Using alternative estimates for the treatment recommendations made by color-guided DUS (Table 2), "MRA+ PTA/EX" was dominated and "DUS + PTA/EX" had an incremental CE ratio of €20 000/QALY.

Criteria for the suitability of lesions for percutaneous interventions vary across centers. In a sensitivity analysis we assumed that more patients with intermittent claudication had lesions suitable for angioplasty (0.74 for suprainguinal lesions and 0.50 for infrainguinal lesions, Table 3). For all strategies the effectiveness increased (range of the gain: 0.0603 to 0.0951 QALYs) whereas the costs increased for management strategies with angioplasty as the only invasive treatment option (range of increase: €1197 to €1243) but decreased for management strategies with both angioplasty and bypass surgery (range of decrease: €1739 to €2072). The incremental CE ratios of "MRA+ PTA/EX" and "DSA + PTA/BS/EX" decreased slightly to €17 000/QALY and €110 000/QALY, respectively.

Performing an angioplasty in conjunction with a diagnostic DSA did not change the incremental CE ratios of the base-case analysis but the effectiveness increased with 0.007 QALYs and the cost decreased with €91 for strategies with DSA as first imaging modality ("DSA + PTA/EX" and "DSA + PTA/BS/EX", respectively). On the other hand, the incremental CE ratios and order of strategies changed if all patients could return home after a short period of observation and bedrest after a DSA (cost for a DSA decrease to €605, Table 1). In this case the incremental CE ratios were €17 000/QALY for "DUS + PTA/EX" compared with the conservative strategy, €47 000/QALY for "DSA + PTA/EX" compared with "DUS+ PTA/EX", and €126 000/QALY for "DSA + PTA/BS/EX" compared with "DSA + PTA/EX".

Discussion

The current study evaluated different management strategies for patients with intermittent claudication. We found that management strategies that limited invasive treatment to angioplasty were all similar in costs and effectiveness irrespective of the imaging modality performed. Management strategies that also included bypass surgery had a clearly higher cost than strategies that limited treatment to angioplasty and there was a marginal gain in effectiveness. DSA with angioplasty and bypass surgery was the most effective management strategy but the differences with the strategies that started with MRA or color-guided DUS was small. Apparently, the diagnostic work-up had minor influence on the cost-effectiveness using the assumptions and management strategies as described.

At first glance, the differences in costs, risks, and diagnostic accuracy between the considered imaging modalities seem large but if all relevant lifetime effects and costs are taken into account then these differences become almost negligible. Treatment of PAD improves the patients' quality of life by treating the symptoms and does not prolong life expectancy of patients with intermittent claudication. Therefore, only a small gain in quality-adjusted life years (QALYs) will be found. Furthermore, a small cost-reduction could be achieved if no overnight admissions are necessary after a DSA and all patients could return home after a period of observation and bedrest. The choice between one-day admissions and overnight admissions are mainly determined by hospital policies but also by individual

patient characteristics and the condition of the patient after the DSA. Finally, if the flexibility of the interventional team and the workflow allow for planning of a diagnostic DSA in conjunction with an angioplasty without knowing if lesions are suitable for angioplasty then the effectiveness will increase and the costs will decrease. These latter effectiveness gains and cost-savings are, however, so minimal that one should carefully weigh their advantage against making changes in the work process.

A limitation of our analysis was that we assumed that DSA would be performed for recurrent or contralateral symptoms instead of MRA or color-guided DUS. We made that assumption because non-invasive imaging modalities were not as often used during the mid-90's (i.e., the time the decision models were developed) as nowadays. However, the results would only change minimally and probably not change the conclusions if we were to assume that non-invasive modalities would have been performed in case of recurrent or contralateral symptoms. This is because, first, in the current analysis we compared alternative management strategies for patients with intermittent claudication and the main outcome measure is the difference in costs and effects between the alternative strategies. In all alternative strategies DSA would be performed for symptoms during follow-up and the differences in the proportion of patients whom would undergo DSA during follow-up across the alternative strategies is minimal and would thereby not affect the differences between strategies. Second, replacing DSA with non-invasive modalities would give a cost-reduction and avoids the risk of an invasive modality but this should be weighed against the consequences of false test results induced by non-invasive tests. Third, although MRA and color-guided DUS are often indicated as initial imaging work-up there will always be some patients in whom DSA would be preferred. Proceeding to DSA immediately is particularly efficient if it is likely that percutaneous treatment can be performed in conjunction with the DSA or if the patient has critical limb ischemia. Both situations are more likely in patients with recurrent symptoms. In summary, although our assumption is not completely valid for today's clinical practice, we believe that it did not have a major impact on the results and conclusions of the presented study.

Other limitations of our study were limitations that are inherent to decision models and cost-effectiveness analyses. Several secondary data-sources available from the literature were used as input data for the parameters in the decision-analytic model. For instance, different data-sets were used to model changes in the severity of claudication. Where possible we adjusted the data for important potential confounders. In addition, assumptions had to be made to keep the problem manageable. Health states for intermittent claudication, for example, were divided into mild vs severe claudication by an arbitrary cutoff in maximum walking distance and this subdivision did not take into account a patient's lifestyle and occupation. Furthermore, it was assumed that DSA was the reference standard in the diagnostic work-up for PAD which is often done[4] but can be questioned since some studies reported that MRA yielded better results in the detection of patent runoff vessels than DSA.[44,45] Lastly, we did not consider medical therapy and smoking cessation as separate treatment options but rather considered these as a part of the general management of all patients with intermittent claudication independent of the imaging and revascularization strategy considered.

The Dutch costs for vascular interventions were lower than the United States costs but not all costs decreased by the same ratio (Table 1). A previous cost-effectiveness analysis focusing on the same clinical problem as in this study using United States costs showed that the differences between imaging strategies were small.[14] The incremental CE ratio for MRA with angioplasty as the only invasive treatment option compared with the conservative strategy was $35 000/QALY (US costs, 1998) whereas the CE ratio for DSA with both angioplasty and bypass surgery relative to MRA with angioplasty as treatment option was $345 000/QALY (US costs, 1998). Therefore, the incremental CE ratios for the United States were higher than the CE ratios for The Netherlands and adjustments for inflation and currency (€1 = $1.06, 1999) would make the differences even larger.

The current analysis showed that cost-effectiveness analyses across countries do not necessarily yield the same results. The order of the optimal strategies was the same but the magnitude of the incremental CE ratios differed between the United States and The Netherlands. The generally reported range of CE ratios for the United States varies between $10 000 and $100 000/QALY.[46] Applying this range to the previously published cost-effectiveness analysis based on US cost data we would conclude that management strategies that limit invasive treatment to angioplasty for claudication are cost-effective but that bypass surgery for claudication is not warranted. For The Netherlands the approximate threshold incremental CE ratio can be deduced from the fact that heart transplantation at a cost of €33 000/QALY (72 000 Dutch guilders per QALY)[47] is considered acceptable whereas lung transplantation[48] at a cost of €54 000/QALY (118 000 Dutch guilders per QALY) is considered too

high in comparison to the effectiveness to justify widespread implementation. Applying a threshold incremental CE ratio of between €33 000/QALY and €54 000/QALY, the same conclusion concerning management strategies for patients with intermittent claudication in The Netherlands would be drawn as in the United States. Therefore, although the incremental CE ratios for the United States were higher than for The Netherlands, the practical implication for this particular clinical problem is the same. One marginal note on the comparison of CE ratios between countries is that we assumed that effectiveness was equal across countries. As long as the demographic and epidemiologic factors are comparable this seems a reasonable assumption since biological variation between people is small.

In conclusion, the results suggest that for patients with severe unilateral intermittent claudication of at least one year duration non-invasive imaging modalities can replace DSA without an important loss in effectiveness and a minimal cost-reduction. In addition, compared with angioplasty, the additional gain in effectiveness with bypass surgery does not justify the additional expense. Furthermore, although absolute incremental CE ratios were different between The Netherlands and United States, the implications for both countries are the same.

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