EVALUATION OF DIAGNOSTIC IMAGING WORK-UP FOR PERIPHERAL ARTERIAL DISEASE

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VOOR PERIFEER ARTERIEEL VAATLIJDEN

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INTRODUCTION

BACKGROUND

The diagnosis of peripheral arterial disease (PAD) is established based on history taking, physical examination, and a decreased ankle-brachial pressure index. Diagnostic imaging work-up is necessary to localize the diseased arterial segment if percutaneous transluminal angioplasty with selective stent placement or bypass surgery is considered. Traditionally, intraarterial digital subtraction angiography (DSA) has been used as the sole pre-treatment imaging modality. It provides a roadmap of the arterial system and is still considered to be the reference standard ("gold standard"). A disadvantage of DSA is that it has a risk of mortality (3 out of 10,000) and morbidity (3 out 100) because of the intraarterial injection of iodinated contrast media.[1,2] Compared with other imaging modalities it is expensive and DSA requires a period of bedrest and observation after the procedure.

In the early eighties, duplex ultrasound (US) was introduced into clinical practice.[3,4] It is a non-invasive, inexpensive method, and duplex US machines are widely available. The sensitivity of duplex US is around 80 to 85% and the specificity above 95%[5] and with the addition of color-guidance the diagnostic accuracy improved.[6] However, the test results of duplex US are operator-dependent and uninterpretable in about 10% of patients.[7] Furthermore, duplex US does not provide a "roadmap" of the arterial system for planning treatment but nevertheless there are hospitals in which treatment is often planned based on duplex US findings with selective use of DSA.[7]

Magnetic resonance (MR) angiography became available for the diagnostic work-up of PAD in the early nineties.[8-10] With the addition of intravenously administered gadolinium MR angiography supplies high quality images[11] and the intravenous use of gadolinium is known to be safe.[12] Disadvantages are the costs that are still high nowadays and also contra-indications like having a pacemaker and being claustrophobic.

More recently, multidetector computed tomography (CT) angiography has become available for the work-up of PAD and the preliminary results are promising.[13-15] CT angiography is simple and fast, and the costs are relatively low. Disadvantages are the small dose of radiation and uninterpretable results due to calcifications of the arterial wall. Also other alternatives like MR angiography with blood pool agents[16], duplex US with contrast agents[17], and DSA with carbon dioxide[18] have been suggested as new imaging modalities for work-up of PAD.

The optimal diagnostic work-up strategy for patients with intermittent claudication is unknown. Some centers advocate the use of duplex US with selective use of DSA whereas others advocate the sole use of MR angiography. To determine the optimal diagnostic work-up strategy not only the diagnostic performance of the modalities should be taken into account but also risks of the modalities, consequences of false test results on treatment and follow-up, and the costs involved. Furthermore, patients' preferences for the different imaging modalities may be considered as a decisive factor in the determination of the

optimal work-up strategy.

Thesis outline

The main purpose of this thesis was to evaluate the currently used diagnostic imaging work-up for patients with intermittent claudication, namely intraarterial DSA, gadolinium-enhanced MR angiography, and color-guided duplex US. A systematic literature review was performed to collect data on color-guided duplex US and gadolinium-enhanced MR angiography (Chapter 2). The diagnostic performance of both modalities was summarized and compared by means of a summary receiver operating characteristic analysis.

To determine the cost-effectiveness of diagnostic work-up strategies not only the costs and effects of the work-up itself should be considered but also the costs and effects of subsequent treatment and follow-up. In Chapter 3 the cost-effectiveness of interventional and non-interventional treatment strategies for patients with intermittent claudication was evaluated for the United States.

The cost-effectiveness of DSA, duplex US, and MR angiography was evaluated in a decision-analytic model that incorporated data on diagnostic performance, risks, costs, and treatment and follow-up which were available from the medical literature and studies presented in this thesis (Chapter 4). Chapter 5 deals with the cost-effectiveness of management strategies including diagnostic work-up, treatment, and follow-up for patients with intermittent claudication. Since it is unclear if cost-effectiveness analyses are generalizable across countries the analysis in Chapter 5 was performed for the Netherlands.

Another important point is that the development of new imaging modalities is ongoing. Preliminary results of new imaging modalities in the work-up of PAD are promising but parameters like sensitivity and uninterpretable test results are not yet precisely known. Target values were estimated for which a new imaging modality would be cost-effective compared with the current work-up (Chapter 6).

In the assessment of the optimal diagnostic work-up strategy patients' preferences for the imaging modalities may also be considered. Chapter 7 describes a study in which patients' preferences for the three modalities were assessed by interviewing patients that underwent diagnostic work-up for PAD. A rating scale was used to assess a "utility", a willingness-to-pay technique was used to assess a monetary value, and a willingness to give up free time technique was used to assess a time value.

Imaging modalities are also used for the surveillance after vascular interventions to detect graft failures in an early stage so that an amputation of the limb can be prevented. In Chapter 8 the cost-effectiveness of different surveillance programs after infrainguinal autologous vein bypass graft surgery was evaluated. Finally, Chapter 9 summarizes the main findings of the preceding chapters and gives a general discussion on imaging work-up for PAD and the methodological issues involved.

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2

PERIPHERAL ARTERIAL DISEASE: GADOLINIUM-ENHANCED MR ANGIOGRAPHY AND COLOR- GUIDED DUPLEX US – A META-ANALYSIS

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ABSTRACT

Purpose: To summarize and compare the published data on gadolinium-enhanced magnetic resonance (MR) angiography and color-guided duplex US for the work-up of peripheral arterial disease.

Materials and Methods: Studies published between January 1984 and November 1998 were included if a) gadolinium-enhanced MR angiography and/or color-guided duplex US were performed for evaluation of arterial stenoses and occlusions in the work-up for peripheral arterial disease of the lower extremities, b) conventional angiography was the reference standard, and c) absolute numbers of true-positive, false-negative, true- negative, and false-positive were available or derivable.

Results: With a random effects model, pooled sensitivity for MR angiography (97.5% [95% CI: 95.7%, 99.3%]) was higher than that for duplex (87.6% [95% CI: 84.4%, 90.8%]). Pooled specificities were similar: 96.2% (95% CI: 94.4%, 97.9%) for MR angiography and 94.7% (95% CI: 93.2%, 96.2%) for duplex US. Summary receiver operating characteristic analysis demonstrated better discriminatory power for MR angiography than for duplex US. The regression-coefficients of MR angiography versus duplex US were 1.67 (95% CI: -0.23, 3.56) with adjustment for covariates, 2.11 (95% CI: 0.12, 4.09) without such adjustment, and 1.73 (95% CI: 0.44, 3.02) with a random effects model.

Conclusion: Gadolinium-enhanced MR angiography has better discriminatory power than does color-guided duplex US and is a highly sensitive and specific method, as compared with conventional angiography, for the work-up of peripheral arterial disease.

INTRODUCTION

The assessment of lifestyle-limiting intermittent claudication and critical ischemia prior to revascularization has traditionally been performed with conventional angiography. Conventional angiography is a widely used imaging modality that yields a "road map" of the vascular system, which is useful in choosing the optimal type and technique of revascularization procedure. Angiography is, however, an invasive procedure with a risk of morbidity and mortality.[1,2] When possible, noninvasive methods are used in the initial assessment of peripheral arterial disease.

Duplex US has been shown to be a reliable noninvasive modality with fairly good sensitivity and specificity.[3] The addition of color flow imaging to help guide duplex scanning improves the diagnostic performance.[4] Duplex US is, however, operator dependent and labor intensive and does not provide a road map equivalent to that obtained with angiography. Gadolinium-enhanced magnetic resonance (MR) angiography is a relatively new minimally invasive imaging method used in the work-up of peripheral arterial disease. Intravenous administration of a gadolinium chelate is considered to be safe, and MR angiography provides high-quality three-dimensional images of the vascular system in a short period of time with high sensitivity and specificity.[5-11] Disadvantages of MR angiography are the expense and the small number of cases in which the procedure is unsuccessful due to susceptibility artifacts or because the patient has claustrophobia.

A number of articles have recently been published on the topic of gadolinium-enhanced MR angiography, each a report of the experience from a single center with a limited number of patients. Before supporting MR angiography as a substitute for conventional (x-ray) angiography, the overall combined evidence should demonstrate whether MR angiography is a highly sensitive and specific modality. Furthermore, we were aware of no reports in which gadolinium-enhanced MR angiography was compared with color-guided duplex US. If a choice must be made between the imaging modalities, it should be largely dependent on the reported diagnostic accuracies of both methods, taking into account differences in applied positivity criteria and patient characteristics. A powerful tool for this kind of analysis is summary receiver operating characteristic (ROC) analysis.[12-14]

The purpose of this study was to summarize and compare the diagnostic performance of gadolinium-enhanced MR angiography and color-guided duplex US for the evaluation of arterial stenoses and occlusions in the work-up of peripheral arterial disease of the lower extremities and to compare both methods with conventional angiography.

MATERIALS AND METHODS

Data Sources and Data Extraction

A search was performed of the medical literature for articles on gadolinium-enhanced MR angiography and color-guided duplex US that were published between January 1984 and November 1998.[14] For the period between January 1984 and June 1994, we used articles on color-guided duplex US included in a previously published meta-analysis.[4,15-20] For gadolinium-enhanced MR angiography, we limited the search to articles published between January 1990 to November 1998 because gadolinium-enhanced MR angiography was introduced in the early 1990s. A Medline search was performed by using the following keywords and words related to these keywords: peripheral vascular, arterial occlusive, peripheral arterial, leg, limb, lower extremity, popliteal, femoral, and iliac, combined with MR angiography, magnetic resonance, duplex, Doppler, and ultrasonography. Additional references were obtained from bibliographies of reviews and original articles and experts in the field were consulted. PubMed was used to find the most recently published articles.

Articles[5-11,15-39] were included in the analysis if they met the following criteria: (a) Gadolinium-enhanced MR angiography, color-guided duplex US, or both were performed to demonstrate stenoses and occlusions of the arteries in the lower extremities; (b) results of conventional angiography were used as the reference standard; (c) the absolute numbers of true-positive (TP), false-negative (FN), true-negative (TN) and false-positive (FP) were available or could be derived for a defined cutoff criterion for angiography - usually a reduction in arterial diameter of more than 50%. In the case of multiple published reports by the same author(s) over a brief time, we tried to contact the author(s) to determine whether the patient populations overlapped. Use of the same patient population more than once in our analysis could bias the results. Among the articles[6,23,28,39-41] in which data were reported for the same patient population, we included those[6,23,39] with a research question most relevant to our meta-analysis. Moreover, we tried to contact the authors of articles that reported a measure of agreement (eg κ statistic) between the comparison modality and angiography rather than the absolute numbers of TP, FN, TN, and FP. One author[26] gave us the relevant data, but two authors[5,42] neglected to reply despite repeated requests (total of three requests to each).

Each author independently extracted the data from all articles by using a standardized spreadsheet. The authors were not blinded with regard to identifying information of the individual manuscripts because this has been shown to be unnecessary.[43] Extracted data included variables related to study design, patient characteristics, diagnostic imaging protocol, and absolute numbers of TP, FN, TN, and FP (Table 1-4). The absolute numbers were most often available for arterial segments rather than for limbs or patients. If the results were tabulated for

Table 1 – Summary of MR angiography characteristics of included studies

Study*	Year of publication	Study location	MR Parameters†	Imager	Gadolinium Dose (mmol/kg)
Adamis et al[7]	1995	North America	2D fast inflow with steady-state precession (291/7, 60°-90° flip angle); subtraction MIP	1.5 T, body coil (Siemens Medical Systems, Erlangen, Germany)	0.3
Hany et al[6]	1997	Europe	3D spoiled GRE (4/1.9, 40° flip angle); MIP, multiplanar reformations	1.5 T, surface coil (Signa; GE Medical Systems, Milwaukee, Wis)	0.3
Ho et al[11]‡	1998	Europe	Moving-bed infusion-tracking 3D fast field echo (14.1/6.1, 50° flip angle); subtraction MIP	1.5 T, body coil (Gyroscan; Philips Medical Systems, Best, the Netherlands)	0.3§
Ho et al[10]‡	1998	Europe	3D fast field echo (20/6, 60° flip angle); subtraction and nonsubtraction MIP	1.5 T, body coil (Gyroscan; Philips Medical Systems)	0.2§
Laissy et al[34]	1998	Europe	2D fast low-angle shot (108/4, 65° flip angle); subtraction MIP	1 T, body coil (Magnetom; Siemens Medical Systems)	0.2
Poon et al[8]	1997	North America	3D GRE (32/5, 40° flip angle); MIP	1.5 T, body coil (Gyroscan; Philips Medical Systems)	0.3§
Quinn et al[38]	1997	North America	3D time of flight (25/6.9, 40° flip angle); MIP	1.5 T, body coil (Signa; GE Medical Systems)	0.2
Rofsky et al[9]	1997	North America	3D GRE (5/2, 30°-50° flip angle); subtraction MIP	1.5 T body coil (Vision; Siemens Medical Systems)	0.2
Snidow et al[5]	1996	North America	3D GRE (7/2.8, 60° flip angle); MIP	1.5 T, body coil (Edge; Picker, Highland Heights, Ohio)	0.2§
Cambria et al[26]‖	1997	North America	2D spoiled GRE (29/6.7, 45°-60° flip angle), gadolinium-enhanced 3D spoiled GRE (24/6.9, 40° flip angle); MIP#	1.5 T, body and head coils (Signa; GE Medical Systems)	0.3

Note. – The reduction in vessel diameter was considered to be greater than 50% in all studies.

* Number in parentheses is the reference number.

† Numbers separated by the virgule are repetition time msec/echo time msec. GRE = gradient recalled echo, MIP = maximum intensity projection, 2D = two-dimensional, 3D = three-dimensional.

‡ Studies did not include overlap patient populations (Ho KY, personal communication, 1998).

§ Dose is an estimate determined from reported volume of injection and assumption of 70-kg body weight.

‖ Study was used only for the sensitivity analysis.

In 37% of patients, 3D gadolinium-enhanced MR angiography was performed because of tortuosity or aneurysm of iliac arteries that caused severe saturation artifacts on 2D time-of flight images.

different readers, then the numbers of the first reader were used. If more than one examination technique was presented in the same article, we used the technique advised by the authors. US results of iliac segments were excluded if stenoses were indirectly determined on the basis of Doppler waveform analysis for the common femoral arteries. MR angiography results for segments examined with time-of-flight or phase-contrast techniques and without gadolinium-enhancement were excluded from the analysis.

Discrepancies in the data extraction between the two authors were noted and resolved at consensus. A κ value was calculated as a measure of agreement between extracted categoric variables in the analysis, and a correlation coefficient (*r* value) was calculated as a measure of agreement between extracted continuous variables in the analysis. The natural logarithm of the diagnostic odds ratio (D) was

Table 2 – Summary of duplex US characteristics of included studies

Study*	Year of Publication	Study Location	Diameter Reduction (%)
AbuRhama et al[22]	1995	North America	>50
Aly et al[23]	1998	Europe	>50
Arya[24]	1996	Asia	>50
Bergamini et al[25]	1995	North America	>50
Cossman et al[15]	1989	North America	>50
Davies et al[16]	1992	Europe	>50
Karacagil et al[30]‡	1996	Europe	>50
Karacagil et al[29]‡	1994	Europe	>50
Lai et al[33]	1996	Australia	>50
Larch et al[35]	1997	Europe	>50
Linke et al[36]	1994	Australia	>50
Moneta et al[17]	1993	North America	>50
Mulligan et al[18]	1991	North America	>50
Pinto et al[37]	1996	Europe	>50
Polak et al[19]	1990	North America	>50
Sensier et al[41]	1996	Europe	>50
Whelan et al[20]	1992	North America	>50
Zeuchner et al[21]	1994	Europe	>50
Sensitivity analysis			
Currie et al[27]	1995	Europe	>70§
Koelemay et al[31]‖	1997	Europe	Severe irregularities#
Koelemay et al[32]‖	1998	Europe	Severe irregularities#

* Number in parentheses is reference number.
‡ Patient populations assumed not to overlap because different scanners were used.
§ Reduction in area was greater than 50%.
‖ Period during which patients were included in the studies did not overlap.
Positive angiogram demonstrated severe vessel wall irregularities, diffuse luminal narrowing, isolated subtotal stenosis, or occlusion

calculated as follows: ln[(TP * TN)/(FP * FN)]. This value represents a summary measure of the diagnostic performance per study (ie, the discriminatory power of the examination). This was the measure of interest in the summary ROC analysis. The correlation between the natural logarithms of the diagnostic odds ratios as derived from the individual studies by the two authors was calculated to summarize the overall agreement in the data extracted by both authors.

Data Synthesis

Funnel plot

To detect publication bias, (ie, the bias resulting from studies with a positive result being published more often than studies with a negative result), we constructed a funnel plot.[44] In a funnel plot, the number of units measured per individual study (arterial segments, in this case) is plotted as a function of the

Table 2 – Continued

US Criteria†	Scanner and Manufacturer
PSV ratio > 2 or PSV > 200 cm/sec in iliac artery	Ultramark 9; ATL Ultrasound, Bothel, Wash
PSV ratio > 2	Model 128; Acuson, Mountain View, Calif
PSV ratio > 2, loss of reverse flow, or spectral broadening	Ultramark 9; ATL Ultrasound
PSV ratio > 2	QAD-1; Quantum Medical Systems, Woodland Hills, Calif
PSV ratio > 2 or PSV > 200 cm/sec	Model 128; Acuson
PSV ratio > 2, loss or reverse flow, or spectral broadening	Ultramark 9, ATL Ultrasound
PSV ratio > 2	Model 128; Acuson
PSV ratio > 2	Sonos 1000; Hewlett Packard, Andover, Mass
PSV ratio > 2 or PSV > 200/cm	Ultramark 9; ATL Ultrasound
PSV ratio > 2	Acuson
PSV ratio > 2 or PSV > 200 cm/sec	Model 128; Acuson
PSV ratio > 2 or PSV > 200 cm/sec in iliac artery	Model 128; Acuson
PSV ratio > 2	Model 128; Acuson
PSV ratio > 2, spectral broadening, or flattening of triphasic waveform	AU 590A or AU4; Esaote Biomedica, Genoa, Italy
PSV ratio > 2 or luminal narrowing	Acuson
PSV ratio > 2	Spectra; Diasonics, Tirat Carmel, Israel
PSV ratio > 2, PSV > 200 cm/sec, or loss of reverse flow	Model SSA 270 A; Toshiba, Tustin, Calif
PSV ratio > 2	Model SSA 270 A; Toshiba
Sensitivity analysis	
PSV ratio > 2.5	Ultramark 9; ATL Ultrasound
Vessel wall irregularities at B-mode US or luminal narrowing	Sonos 1000; Hewlett-Packard
Vessel wall irregularities at B-mode US or luminal narrowing	Sonos 2000; Hewlett-Packard

† PSV = peak systolic velocity. PSV ratio is PSV at stenosis divided by PSV distal to stenosis. Criteria for occlusion were absence of flow and/or color saturation.

measure of interest (the natural logarithm of the diagnostic odds ratio, in this case). In the absence of publication bias, the data points form a symmetric funnel-shaped distribution, whereas a skewed and asymmetric distribution indicates the presence of publication bias. Funnel plot symmetry was determined informally by means of visual inspection of the graph.

Weighted Pooled Analysis

Pooled values of effect size are often calculated by means of a weighted pooling of the individual effect sizes, with weights equal to the reciprocal of the variance of each study. To apply this method, the assumption of homogeneity of effect sizes must hold.[45,46] We checked the homogeneity of effect sizes with a statistical test, and only the sensitivity of MR angiography was homogeneous. We, therefore, used a random effects model, which can accommodate, heterogeneous as well as homogeneous, effect sizes. The pooled values based on this model

Table 3 – Clinical characteristics of included studies: MR angiography

Study*	No. of patients†	Mean Age (y)	Clinical indication			Arterial segments			Maximum time between Examinations (d)	Consecutive patients	TP	FN	TN	FP
			CL (%)	CI (%)	Other (%)	AI (%)	F-P (%)	IP (%)						
Adamis et al[7]	11 (75/25)‡	67	NR	NR	NR	NR	NR	NR	14	No	37§	0	111	19
Hany et al[6]	39 (72/28)	62	100	0	0	100	0	0	2	No	64	2	200	7
Ho et al[11]	28 (82/18)	62	100	0	0	24	46	30	7	Yes	90	7	240	4
Ho et al[10]	28 (75/25)	63	100	0	0	49	51	0	7	Yes	34	3	191	14
Laissy et al[34]	20 (85/15)	53	100	0	0	0	46	54	4	NR	113	0	393	14
Poon et al[8]	15 (80/20)	58	NR	NR	NR	67	33	0	NR	NR	12	0	78	0
Quinn et al[38]	30 (64/36)‡	NR	0	100	0	100	0	0	1	Yes	31	0	86	1
Rofsky et al[9]	15 (60/40)	66	0	100	0	NR	NR	NR	5	No	37	1	108	4
Snidow et al[5]	30 (98/2)‡	63‖	36#	38#	26	100	0	0	NR	No	27	0	117	6
Sensitivity analysis														
Cambria et al[26]	79 (56/44)	70**	43	57	0	16	24	60	NR	No	37††	8	195	16

Note. – All studies included blinded interpretation of both reference images and MR angiograms except that of Rofksy et al[9], who did not report whether readings were blinded. AI = aortoiliac, CI = critical ischemia, CL = intermittent claudation, F-P = femoropopliteal, IP = infrapopliteal, NR not reported.

* Number in parentheses is the reference number.

† Numbers in parentheses are percentage of men/ percentage of women.

‡ Percentage of men and women was not reported for verified patients but only for the total number of patients described in the study.

§ Includes bypass graft results.

‖ Mean age was not reported for verified patients but only for the total number of patients described in the study.

Percentage with CL and CI not available because more than one symptom per patient was reported. Values are estimates on the basis of symptoms per site.

** Because 49.4% of patients were older than 70 years, the estimated mean age was 70 years.

†† F-P and IP segments were depicted on nonenhanced MR angiograms and were, therefore, excluded.

include an estimated component of variance due to interstudy variation.[45,46] We calculated the pooled sensitivity, specificity, and natural logarithm of the diagnostic odds ratio and constructed 95% CIs.

Summary ROC analysis

Summary ROC analysis is a meta-analytic method to summarize and combine the true- and false-positive rates for different diagnostic studies.[12-14] The method involved development of a regression model with the dependent variable being the natural logarithm of the diagnostic odds ratio from each study and the independent variable being a measure of the positivity criterion (S) of the study (ie, classification of an examination as positive): $S = \ln[(TP * FP)/(TN * FN)]$. With this method, one assumes that the differences in examination performance reported in the literature are due partly to variations in the positivity criterion used by different authors; the regression analysis thus allows one to adjust for these differences. Adjustment for important clinical variables and comparison of examinations are also possible. Examples of meta-analyses that used a summary ROC analysis can be found in De Vries et al[4] and Fleischmann et al[47].

The adjustment for clinical variables is accomplished by including them in the regression model. Inclusion of a dummy variable in the regression analysis for

Table 4 – Clinical characteristics of included studies: duplex US

Study*	No. of patients†	Mean age (y)	Clinical indication			Arterial segments			Maximum Time (d)	Blinded Reading of Reference Images/US images	Consecutive patients	TP	FN	TN	FP
			CL (%)	CI (%)	Other (%)	AI (%)	F-P (%)	IP (%)							
AbuRhama et al[22]	134 (58/42)	64	NR	NR	0	33	67	0	7	Yes/Yes	Yes	330	40	782	18
Aly et al[23]	90 (66/34)	68‡	90	10	0	20	46	34	7	Yes/Yes	NR	404	34	2,643	27
Arya[24]	23 (87/13)	44	NR§	NR§	0	NR	NR	NR	14	Yes/Yes	Yes	25	13	113	1
Bergamini et al[25]	44 (NR)	NR	66	34	0	0	91	9	61	Yes/NR	NR	94	24	273	13
Cossman et al[15]	61 (NR)	NR	NR	NR	0	0	89	11	NR	Yes/NR	NR	139‖	20	397	4
Davies et al[16]	52 (75/25)	64‡	100	0	0	0	100	0	14	NR	NR	45	0	20	0
Karacagil et al[30]	38 (45/55)	71	16	84	0	0	8	92	14	Yes/Yes	NR	211	36	186	47
Karacagil et al[29]	40 (NR)	NR	NR	NR	0	20	60	20	50	Yes/Yes	NR	66	6	227	36
Lai et al[33]	50 (NR)	NR	NR	NR	0	22	78	0	56	Yes/Yes	NR	124	42	354	38
Larch et al[35]	50 (52/48)	69	54	46	0	0	0	100	3	Yes/Yes	Yes	97	11	21	21
Linke et al[36]	25 (60/40)	68	100	0	0	0	100	0	33	Yes/Yes	Yes	41#	2	87	5
Moneta et al[17]	79 (98/2)	64	23	71	6	33	67	0	NR	Yes/Yes	Yes	188	25	236	4
Mulligan et al[18]	12 (100/0)	62	NR	NR	0	24	76	0	7	NR/Yes	No	25	3	89	6
Pinto et al[37]	167 (60/40)	63	55	45	0	8	64	28	14	Yes/Yes	Yes	330	15	343	26
Polak et al[19]	17 (77/23)	62	59	29	12	0	100	0	0	Yes/Yes	Yes	49	7	173	9
Sensier et al[41]	76 (58/42)	71‡	88	12	0	28	45	27	19	Yes/ Probably	Yes	298	81	1,201	78
Whelan et al[20]	51 (NR)	NR	NR	NR	16	0	84	16	0	Yes/Yes	Yes	112**	7	462	15
Zeuchner et al[21]	50 (55/45)††	70‡‡	22	78	0	39	61	0	1	Yes/ Probably	No	12##	4	305	1
Sensitivity analysis															
Currie et al[27]	92 (74/26)	64‡	97	3	0	100	0	0	42§§	Yes/ Probably	Yes	99	7	74	0
Koelemay et al[31]	23 (40/60)	71‡	9	91	0	0	18	82	1	Yes/Yes	No	136	52	48	23
Koelemay et al[32]	120 (61/39)	72‡	16	84	0	0	17	83	13	Yes/ Probably	No	733	257	344	99

Note. – AI = aortoiliac, CI = critical ischemia, CL = intermittent claudication, F-P = femoropopliteal, IP = Infrapopliteal, NR = not reported.

* Number in parentheses is the reference number.

† Numbers in parentheses are percentage of men/ percentage of women.

‡ Median age.

§ Percentage of patients with clinical indications was not reported for verified patients but only for the total number of patients described in the study.

‖ Aortoiliac disease inferred on the basis of Doppler waveform analysis of common femoral arteries; thus, aortoiliac segments were excluded.

Cases of aneurysm seen at angiography were excluded.

** Aortoiliac disease inferred on the basis of Doppler waveform analysis of common femoral arteries; thus, aortoiliac segments were excluded. One lesion in the superficial femoral artery was counted twice, and we subtracted this lesion from the analysis.

†† Percentages of men and women and mean age were not reported for verified patients but only for the total number of patients described in the study.

‡‡ IP segments were excluded because no grading of stenosis was reported.

§§ Mean number of days.

the type of diagnostic examination performed (1 for MR angiography, 0 for duplex US) makes it possible to compare the tests. The regression coefficient of this dummy variable is a measure of the difference in discriminatory power between the examinations. A positive regression coefficient indicates increased discriminatory power for MR angiography relative to that of duplex US whereas a negative regression coefficient indicates reduced discriminatory power.

To prevent undefined values for diagnostic odds ratios, positivity criteria, and their variances that result from zero values for TP, FN, TN, or FP, 0.5 was

added to each TP, FN, TN, and FP.[13] We assessed the effect of publication year, continent (North America vs other), mean age (65 years or younger vs older than 65 years), prevalence of diseased segments per study, blinded interpretation of the test result (yes or probably vs no or not reported), blinded interpretation of the reference test result (yes vs no or not reported), consecutive patients (yes vs no or not reported), type of imager (Ultramark [ATL] vs Acuson vs other for duplex US; Philips Medical Systems vs Siemens Medical Systems vs other for MR angiography), and dose of gadolinium (in millimoles per kilogram body weight) for MR angiography. A quality score was defined on the basis of the following criteria: blinded interpretation of MR or US images, blinded interpretation of the reference modality, and inclusion of consecutive patients. Studies fulfilling all criteria were given a quality score of 1; all others were given a score of 0. Also, a four-tiered rating of quality for diagnostic imaging studies, described by Kent et al[48], was determined for each study and analyzed by using three dummy variables.

Owing to missing data, the proportion of patients with intermittent claudication could not be analyzed as a covariate and was, therefore, excluded from all analyses. The proportions of femoropopliteal and infrapopliteal segments were missing for three articles, and only the subset of articles with complete data for the relevant variables was used. Age was not reported in six articles, and another three reported median age instead of mean age. The proportion of male patients was not reported in five articles. The maximum number of days between MR angiography or duplex US and conventional angiography was not reported in four articles. Estimates of missing values were calculated (imputed) with weighted means or with a best-subset regression analysis (Stata Reference Manual, vol 2, release 4.0; College Station, Tex: Stata Statistical Software) and were used to explore the effect of clinical variables by using all the available articles to ensure that no potentially important covariate was overlooked.

MR angiography and duplex US were first analyzed separately and subsequently compared in one model. Univariate analyses were performed to assess the effect of each clinical covariate by using the subset of articles with complete data for that variable and estimated values if necessary. The latter were used to select variables for the final analysis only if no or minor differences in the results between the subset of articles with complete data and the calculation with estimated values were found. Significant variables ($P < .05$) were subsequently assessed in a multivariate model per examination. Variables with a P greater than .05 but less than .10 were retained in the model if the explanatory power of the model increased substantially (adjusted R^2 increased by 0.05).

In the final multivariate analysis in which MR angiography and duplex US were compared, missing values for significant variables in the model were not substituted with estimates, and only the subset of articles with complete data for the selected variables was used. The selection of variables for the final model was performed by analyzing each variable in turn and considering significant variables

alone, so as to avoid exclusion of as few studies as possible. Also, interaction terms were incorporated in this analysis to allow for differential effects, depending on the examination. We tested for heterogeneity across studies by comparing the 95% CI of the observed values of the natural logarithm of the diagnostic odds ratio in each study with that of the predicted values of the diagnostic odds ratio by the final model. Finally, we re-analyzed the final summary ROC model with a random effects regression analysis (Stata Technical Bulletin no. 42, College Station, Tex: Stata Statistical Software) which took interstudy variability into account. All analyses were performed with SPSS for Windows (release 7.5.2, SPSS, Chicago, Illinois) and STATA (release 5.0, Stata Statistical Software) software.

Sensitivity analyses

A so-called jackknife type of sensitivity analysis of the final model was accomplished by performing multiple summary ROC analyses and excluding each article in turn. The jackknife sensitivity analysis is used to determine the contribution of the results in each article to the overall analysis. Three articles on duplex US used another definition of disease as determined at conventional angiography. Instead of 50% stenosis, 70% stenosis was used in one study[27], and severe vessel wall irregularities were used in two others.[31,32] In a sensitivity analysis, with dummy variables for the studies with another definition of disease, we determined whether these studies demonstrated a difference in diagnostic performance as compared with the other studies on duplex US. As before, a positive coefficient indicated increased discriminatory power, and a negative coefficient indicated reduced discriminatory power. In one study on MR angiography[26], the authors reported that gadolinium-based contrast material was administered only in selected patients, and we evaluated the results in this study by using a dummy variable for comparison with the other MR angiography studies.

RESULTS

Review of Studies

Our literature search resulted in 760 references, of which we retrieved 92 articles. Sixty-seven articles were excluded because (a) MR angiography was performed without gadolinium enhancement (n=37); (b) the absolute numbers of TP, FN TN, and FP results were not available or could not be derived (n=11); (c) duplex US was not color guided (n=7); (d) no standard of reference was used (n=4); (e) only treatment recommendations were reported (n=3); (f) authors reported on the same patients in more than one article (n=3); (g) no original data were reported (n=1); (h) or only results of aneurysms and vascular grafts were reported (n=1). None of the 160 non-English-language articles fulfilled the inclusion criteria of the meta-analysis. Thirty-one articles[5-11,15-39] met our inclusion

criteria, of which six[15-20] were available from a previous meta-analysis[4]. Three articles used another definition of disease[27,31,32], and in one MR angiography study[26], gadolinium enhancement was not used in all patients. These four studies were evaluated only in the sensitivity analysis, which resulted in nine articles on MR angiography and 18 articles on duplex US for the baseline analysis.

Table 5 – Discrepancies and measures of agreement between two authors for data extraction from 31 studies

Variable	No. of Discrepancies*	*r* Value	κ value
Year of publication	0 (0)	1.00	NA
Location of study	0 (0)	NA	1.00
Positivity criterion	2 (6)	NA	0.63
Percentage of men	0 (0)	1.00	NA
Mean age	0 (0)	1.00	NA
Blinded reading of MR or US results	5 (16)	NA	0.64
Blinded reading of reference images	1 (3)	NA	0.84
Consecutive patients	7 (23)	NA	0.67
Total no. of segments	12 (39)	0.99	NA
Time between MR or US and reference imaging	3 (10)	0.99	NA
Type of imager	0 (0)	NA	1.00
Natural logarithm of diagnostic odds ratio	8 (26)	0.92	NA
Overall	38 of 372 (10)	NA	NA

Note. – The Spearman *r* value was calculated for continuous variables; the κ value, for categoric variables.
NA = not applicable.
* Number in parenthesis is the percentage.

Overall 38 of 372 (10%) discrepancies in the data extraction occurred between the two authors and ranged from zero to 12 of 31 (0%-39%) for the different variables (Table 5). All discrepancies were resolved at consensus. In Tables 1 and 2, the examination characteristics of the 31 studies included in the meta-analysis are outlined; Table 3 and 4 represent the clinical characteristics. All studies but one[25] were judged to have been prospective. The MR angiographic results in 216 patients (from nine articles) were included in the baseline analysis. The mean age among patients who underwent MR angiography was 63 years; 72% were men, and 28% were women. Duplex US results reported in 18 studies with 1,059 patients were included in the baseline analysis. The mean age among patients who underwent duplex US was 65 years; 65% were men, and 35% were women. The funnel plot (Fig 1) for the number of analyzed segments as a function of the discriminatory power of the study (natural logarithm of the diagnostic odds ratio) demonstrated a symmetric funnel-shaped distribution for the duplex studies, which suggests that publication bias was unlikely to be present. Although the MR angiography studies were symmetrically distributed, there were a few with a large number of segments; therefore, publication bias could not be properly evaluated.

Weighted pooled analysis

On the basis of a random effects model, the pooled sensitivity for MR angiography (97.5% [95% CI: 95.7%, 99.3%] was higher than that for duplex US (87.6% [95% CI: 84.4%, 90.8%]. The pooled specificities were similar (for MR angiography, 96.2% [95% CI: 94.4, 97.9]; for duplex US, 94.7% [95% CI: 93.2%, 96.2 %]). The pooled value of the natural logarithm of the diagnostic odds ratio (Fig 1) was 6.43 [95% CI: 5.66, 7.19] for MR angiography and 4.99 [95% CI: 4.30, 5.68] for duplex US, which indicated that, overall, the discriminatory power of MR angiography was better than that of duplex US.

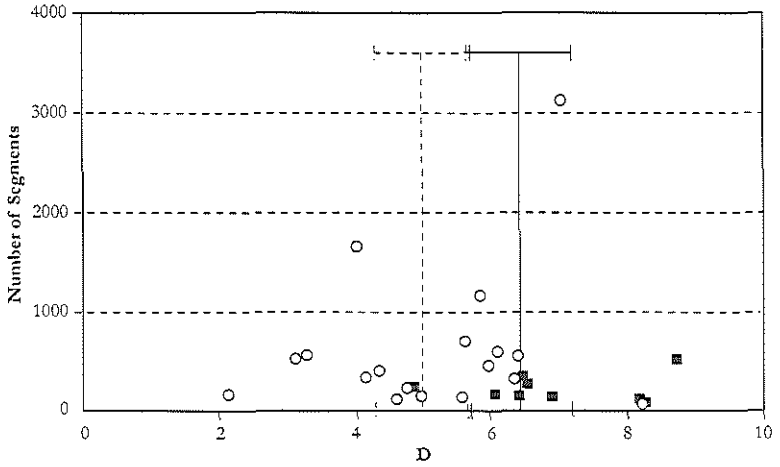

Figure 1 – Funnel plot shows discriminatory power (D, natural logarithm of diagnostic odds ratio) versus number of segments evaluated for pooled data from MR angiography (solid line) and duplex US (dotted line) studies. The pooled discriminatory power for MR angiography is greater than that for duplex US, which indicates that the diagnostic performance of MR angiography was better than that of duplex US. Horizontal error bars = 95% CIs, ■ = MR results from individual studies, O = US results from individual studies. The distribution of data points looks fairly funnel-shaped and symmetric for duplex US, which suggests that publication bias was unlikely. For MR angiography, there were too few studies with a large number of segments to enable evaluation of publication bias.

Summary ROC analysis

No significant predictors were demonstrated in the univariate analysis for MR angiography and no effect was demonstrated for different positivity criteria (regression coefficient, 0.16 [95% CI: –0.66, 0.98]; P = .65). The univariate analysis for duplex US demonstrated that as the maximum number of days between duplex US and conventional angiography increased, the discriminatory power of duplex US decreased (regression coefficient, -0.031 per day [95% CI: –0.060, –0.002]; P = .04]. In the same model the regression coefficient for the positivity criterion of duplex US was a significant predictor (regression coefficient, –0.66 [95% CI: –1.14,

–0.19]; P = .01). For both MR angiography and duplex US, neither the quality scores nor the individual covariates evaluating individual aspects of quality were significant predictors of diagnostic performance.

In the comparison analysis, without adjustment for covariates, the discriminatory power of MR angiography (regression-coefficient, 2.11 [95% CI: 0.12, 4.09]) was better than that of duplex US (P = .04). When we adjusted for each covariate in turn, the discriminatory power of MR angiography again was better than that of duplex US, with regression-coefficients of 1.18-2.27. In the comparison analysis, the time between duplex US and conventional angiography and the positivity criterion were significant predictors, with similar coefficients as in the analysis for duplex US alone. Age had a significant effect on the discriminatory power, with a regression coefficient of -0.13 per year (95% CI: -0.25, –0.003; P = .05).

In the final model with adjustment for multiple covariates, the discriminatory power of MR angiography was better than that of duplex US but with a slightly lower regression-coefficient of 1.67 (95% CI: –0.23, 3.56) that only approached statistical significance (P = .08). The interaction terms were included to allow for a duplex-specific effect for the maximum number of days between duplex US and conventional angiography (regression-coefficient, –0.031 per day [95% CI: –0.055, –0.006]; P = .02) and for the positivity criterion (regression-coefficient, –0.63 [95% CI: –1.05, –0.21]; P = .005) (Table 6). Age was not a significant predictor in the multivariate model. The adjusted R^2 of the final model was 0.41. Figure 2 presents the summary ROC curves on the basis of the final model for MR angiography and duplex US, adjusted to 0 days between duplex US and conventional angiography.

Table 6 – Final model for comparison between MR angiography and duplex US

Variable	Regression-coefficient*	P value	Adjusted R^2 value†
MR angiography versus duplex US	1.67 (-0.23, 3.56)	.08	NA
Time between duplex US and conventional angiography	-0.031 (-0.055, –0.006) ‡	.02	NA
Positivity criterion for duplex US	-0.63 (-1.05, –0.21)	.005	0.41

* Numbers in parentheses are the 95% CI
† NA = not applicable
‡ Value is the change per day.

Heterogeneity

The 95% CI of the observed discriminatory power of each examination was compared with the 95% CI of the values predicted with the final model. The predicted values from the MR angiographic studies all fell within the observed 95% CIs, which was indicative of homogeneity. The same was true for all but three of

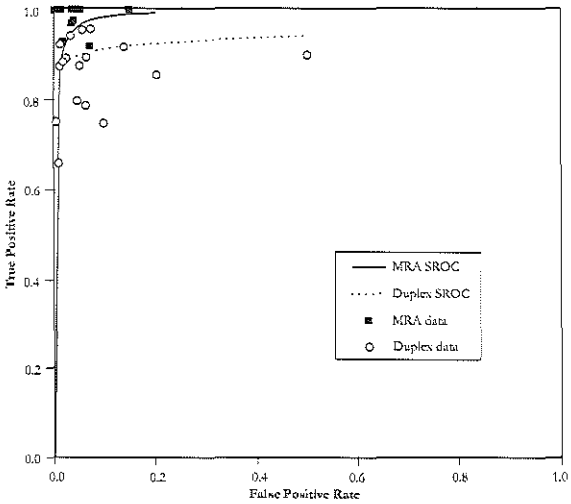

Figure 2 – Summary ROC (SROC) curves for MR angiography and duplex US based on the final model, adjusted to 0 days between duplex US and conventional angiography. The summary ROC curve for MR angiography is further to the upper left than that of duplex US, indicating that the discriminatory power of MR angiography was better than that of duplex US.

the duplex US articles. The three articles were by Pinto et al[37], who reported very high sensitivity (96%); Aly et al[23], who reported high sensitivity (92%) and specificity (99%); and Sensier et al[39], who reported low sensitivity (79%). Application of a random effects regression analysis to the final summary ROC model to account for the unexplained heterogeneity demonstrated that the discriminatory power of MR angiography was better than that of duplex US, with a regression-coefficient of 1.73 (95% CI: 0.44, 3.02; P = .009).

Sensitivity analyses

Exclusion of all articles, one by one, from the final model did not have a large effect on the difference in discriminatory power between MR angiography and duplex US (regression coefficient range, 1.33-2.14). In a sensitivity analysis, we included three duplex US studies in which another definition of disease or another positivity criterion was used. The study with another percentage of diameter reduction as definition of disease[27] demonstrated better discriminatory power, but this difference was not significant in comparison with results from the other duplex US studies (regression coefficient, 2.66 [95% CI: –6.93, 12.25]; P = .56). The two studies by Koelemay et al[31,32] used irregularities of the vessel wall and luminal narrowing seen at duplex US as positivity criterion and severe vessel wall irregularities seen at conventional angiography as definition of disease. Results from these two studies demonstrated a discriminatory power that was lower than

those of the other duplex studies (regression coefficient, –2.16 [95% CI: –3.21, –1.10]; P = .001). In the study by Cambria et al[26], gadolinium-based contrast agent was administered only in selected patients, which decreased the discriminatory power relative to the other MR angiography studies (regression coefficient, –2.20 [95% CI: –3.92, –0.49]; P = .02).

Discussion

The current meta-analysis compared gadolinium-enhanced MR angiography and color-guided duplex US for the evaluation of stenoses and occlusions in the work-up for peripheral arterial disease of the lower extremities. The results suggest that the discriminatory power of MR angiography was better than that of duplex US, which was demonstrated both with the summary ROC results and with the pooled weighted estimates. In comparison with conventional angiography, both imaging modalities provided good diagnostic performance. Both had high specificity, but the sensitivity of duplex US was lower than that of MR angiography. The analysis also demonstrated that an increase in time between duplex US and conventional angiography resulted in a decrease in the discriminatory power of duplex US.

A limitation of pooling sensitivities and specificities is that different positivity criteria used in individual studies are not taken into account. Summary ROC analysis, on the other hand, allows adjustment for different positivity criteria. Furthermore, summary ROC analysis can be extended to a multivariate regression analysis to adjust for differences in patient characteristics, study design, and diagnostic test protocols. Adjustment for these differences was limited in our analysis, however, because not all articles included the relevant details. For example, the mean age of patients in the study was not always reported. The results based on comparative summary ROC analysis of the subset of studies in which mean age was reported suggested that both types of studies had lower discriminatory power in elderly patients, but firm conclusions about the effect of age cannot be made. Furthermore, the percentage of patients with intermittent claudication and the percentage of male and female patients could not be extracted from all articles. Finally, although most of the duplex US articles reported site-specific results, only five of the nine MRA articles did so, which made a comparative subgroup analysis by anatomic site impractical. We did, however, adjust for the proportion of femoropopliteal and infrapopliteal segments in our analysis and found no difference in effect with this adjustment.

As with all meta-analyses, the present study was limited by the ambiguity of the originally reported data. This ambiguity can lead to differences in interpretation and discrepancies in extraction of data. To minimize the bias due to this limitation, both authors extracted the data independently. Discrepancies occurred in 10% of

the extracted data points. Overall, the authors demonstrated good agreement with regard to extracted information, with κ values ranging from 0.63 to 1.00 and correlation coefficients (*r* values) ranging from 0.92 to 1.00.

Another limitation of meta-analyses is that the quality of the original studies may affect the results. L'Abbé et al[49] recommended that a quality-score be calculated for studies included in a meta-analysis. In our analysis, we evaluated the quality of the study design and reporting methods by distinguishing studies that fulfilled all quality criteria versus those that did not and by using a published rating score[48] for the quality of diagnostic imaging studies. In the summary ROC-analysis, neither the quality scores nor the individual covariates that constituted the quality score were significant predictors of diagnostic performance.

Publication bias may have affected our results. Although we demonstrated that publication bias was unlikely to be present among the duplex US studies, we cannot exclude such bias, because the limited number of data points could have decreased the power of detecting publication bias with the funnel plot. Moreover, the limited number of MR angiography studies, all of which included relatively small numbers of patients, did not enable us to detect whether publication bias was present. Another potential issue related to publication bias is that early reports of diagnostic test results generally are more favorable. This could have potentially biased the results against duplex US, because publications on duplex US have appeared since the early 1980s, whereas gadolinium-enhanced MR angiography was first performed in the early 1990s. To determine whether this may have influenced the results, we evaluated the effect of publication year and found that the discriminatory power of MR angiography and duplex US did not change over the years.

In general, the time period between MR angiography and conventional angiography was shorter (≤ 14 days; mean, 5 days) than that between duplex US and conventional angiography (≤ 61 days; mean, 17 days). With an increase in the period between the comparison examination (MR angiography or duplex US and the reference standard examination (conventional angiography), one would expect a greater change in the disease status due, for example, to progression of disease.[50] Thus, with an increase in the time between the comparison and the reference examinations, one can expect a decrease in the discriminatory power of the comparison examination, which was indeed demonstrated in this analysis for duplex US. In fact, the lower discriminatory power of duplex US as compared with MR angiography was explained in part by the longer time between duplex US and conventional angiography relative to that between MR angiography and conventional angiography. This implies that the comparison and reference examinations should ideally be performed on the same day and that comparisons between MR angiography and duplex US should take this factor into account, which we did by adjusting for this variable in the final model.

The reported sensitivities for duplex US span a broad range, which may be explained by the fairly long delay between US and conventional angiography (discussed in the preceding paragraph), operator dependency, differences in technique, variation among duplex US machines, or differences in patient populations. Results from a previous study[51] in which US assessment of carotid arterial stenosis was evaluated suggested that differences in the hardware or software of duplex US machines could cause discrepancies in measured velocities. We could not, however, detect a difference in diagnostic performance for different duplex US machines.

Questions have been raised concerning the use of conventional angiography as the reference standard for comparison with MR angiography. Owen et al[52] and Carpenter et al[53] reported that angiography may not be a good reference method for demonstrating runoff vessels, because MR angiography demonstrated more patent vessels than did conventional angiography. Thus, some authors[26,42] reported a measure of agreement (κ statistic) rather than the sensitivity and specificity for the comparison of MR angiographic results with conventional angiographic results. Cambria et al[26] reported κ values of 0.48-0.60, and Quinn et al[42] reported substantial to perfect (κ 0.61-1.00) agreement for nearly all anatomic segments.

The authors of three articles on MR angiography[8,10,38] compared different techniques for performing the examination. In our meta-analysis, we included only the results of gadolinium-enhanced MR angiography because gadolinium-enhancement has rapidly become the standard and has been shown to substantially improve the diagnostic performance of MR angiography.[8,38,54] With the ongoing technical development in MR imaging, one can expect future improvements in the discriminatory power of MR angiography. Major improvements in duplex US are less likely, although the use of intravascular contrast agents could potentially improve this method, as well. Such improvements may necessitate an update of the meta-analysis in the future.

Ideally, MR angiography and duplex US should be compared in the same group of patients or should be randomly assigned to groups of patients.[14] The literature search did not retrieve any articles in which gadolinium-enhanced MR angiography was compared directly with color-guided duplex US. It is possible that the demonstrated differences in our analysis of diagnostic performance between MR angiography and duplex US may reflect differences in study or patient characteristics. In fact, the current analysis suggests that part of the superiority in diagnostic performance of MR angiography, as compared with that of duplex US, was explained by such differences. Furthermore, it should be noted that both tests were performed in highly selected patient populations. Almost all studies were conducted in an academic setting in either North America or Europe and included patients usually scheduled for preinterventional work-up for peripheral arterial disease. Widespread use of MR angiography and duplex US in patients with

broader clinical indications might result in different diagnostic performance of these examinations; therefore, generalization of our results should be made with caution.

The goal of imaging in the work-up for peripheral arterial disease is not to discriminate between patients with and those without disease (the history and ankle-brachial index do that), but rather to discriminate between diseased and nondiseased segments, that is, to localize the disease. Thus, in determining the sensitivity and specificity of imaging examinations for peripheral arterial disease, data-analysis according to segment probably is the most relevant, and, in all articles but one[16], results were indeed reported according to segment rather than according to limb or patient. This would imply that multiple segments per patient were analyzed in each study and that observations within each study may have been correlated. Correlation of the observations within each study is a characteristic of the individual study results and does not imply that the data points used in the meta-analysis are correlated. In a meta-analysis, potential bias related to this problem can be adjusted if the correlations in the individual studies are known, which generally is not the case. Nevertheless, the fact that disease severity in arterial segments is correlated within a patient does not necessarily mean that the diagnostic performance is correlated as well.

Ultimately, diagnostic information according to segment must be integrated to enable treatment decision making for the patient. Evaluation and optimization of the decision-making process involved will require an extensive analysis that must take into account not only the diagnostic accuracies of the examination, as presented here, but also the effects of imaging on treatment planning, prognosis, quality of life, local expertise, availability of equipment, and costs.

In conclusion, our results suggest that the discriminatory power of gadolinium-enhanced MR angiography was better than that of color-guided duplex US and that MR angiography was a highly sensitive and specific method, as compared with conventional angiography, for the work-up for peripheral arterial disease, which implies that MR angiography could potentially replace duplex US and conventional angiography.

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3

COST-EFFECTIVENESS OF REVASCULARIZATION VS EXERCISE THERAPY IN PATIENTS WITH INTERMITTENT CLAUDICATION

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ABSTRACT

Purpose: To compare the costs, effectiveness, and cost-effectiveness of alternative treatment strategies for intermittent claudication.
Materials and methods: A Markov decision model was developed to evaluate the societal cost-effectiveness, combining data from the literature and original patient data. Patients presented with previously untreated intermittent claudication and treatment options were exercise, percutaneous transluminal angioplasty (with stent placement if necessary), and bypass surgery. Treatment strategies were defined by the initial therapy in combination with secondary treatment options should the initial therapy fail. Our main outcome measures were quality-adjusted life days, expected lifetime costs (1995 US dollars), and incremental cost-effectiveness ratios.
Results: Compared to an exercise program, revascularization (either angioplasty or bypass surgery) improved effectiveness with 33 to 61 quality-adjusted life days among patients with no history of coronary artery disease. The incremental cost-effectiveness ratio was $38,000 per quality-adjusted life year gained if angioplasty is performed whenever feasible compared with exercise alone and $311,000 for additional bypass surgery. The incremental cost-effectiveness ratios were sensitive to age, history of coronary artery disease, the estimated health values for no/mild vs. severe claudication, and costs of revascularization.
Conclusion: The results suggest that, on average, the expected gain in effectiveness achieved with bypass surgery for intermittent claudication is small in comparison to the costs. Angioplasty whenever feasible was more effective than exercise alone and the cost-effectiveness ratio was within the generally accepted range.

INTRODUCTION

Treatment strategies in patients with intermittent claudication have traditionally been conservative.[1,2] Few patients eventually develop limb-threatening symptoms and the risks of perioperative mortality and morbidity, at least for surgical procedures, are considerable.[3-5] Revascularization procedures are therefore generally postponed until initial conservative management has failed. Many physicians consider exercise an inexpensive and effective method for improving symptoms of claudication and recommend it as the initial treatment.[6-9] However, individual responses to exercise vary considerably and long-term compliance varies from 65 to 87%.[10,11] Furthermore, because patients must invest valuable time before reaping any reward, exercise may not be as inexpensive as it seems if the societal perspective is considered because this would require cost for time spent on exercising.

With the advent and development of percutaneous revascularization techniques, the interventional armamentarium for peripheral arterial disease (PAD) has expanded considerably. Because the risks of periprocedural mortality and morbidity for percutaneous revascularization are low, some physicians advocate such procedures at an early stage in the treatment of intermittent claudication.[12] Many patients with intermittent claudication eventually undergo revascularization, and earlier use of current low-risk alternatives might prevent unnecessary suffering. On the other hand, both percutaneous and surgical procedures are expensive and with a limited health care budget one needs to consider whether the gain in quality-adjusted life expectancy justifies the costs.

The medical literature does not provide a direct answer as to what would be the optimal comprehensive treatment strategy in patients with intermittent claudication. Research efforts have mainly been directed at comparing various initial revascularization procedures (for example: different types of material for aortic bifurcation grafts[13], primary vs. secondary stenting in iliac angioplasty[14], or bypass surgery vs. angioplasty in femoropopliteal arterial disease[15,16]). Two published clinical trials compared revascularization with exercise. One study found that the maximum walking distance was improved more with either bypass surgery or a combination of surgery and exercise than by exercise alone.[17] The other study found that exercise improved the walking distance more than angioplasty.[18,19] The number of patients in these two studies was small. Furthermore, treatment strategies in both were defined by the initial treatment only and the economic consequences of the strategies were not taken into account.

The purpose of the present study was to evaluate the costs, effectiveness, and relative cost-effectiveness of various comprehensive treatment strategies for the treatment of intermittent claudication, combining exercise, percutaneous transluminal angioplasty (PTA), and bypass surgery.

METHODS

A decision model was developed to estimate the quality-adjusted life expectancy, lifetime costs, and cost-effectiveness from the societal perspective[20] associated with five alternative treatment strategies for unilateral intermittent claudication. Therapeutic options included an exercise program, PTA, and bypass surgery. A treatment strategy was defined as the initial therapy combined with secondary treatment options should the initial treatment fail (Table 1). Treatment failure was defined as: [discontinuation of the exercise program in combination with severe claudication], or [graft failure or restenosis in combination with severe claudication], or [progression to critical limb ischemia]. We assumed that all patients would undergo general evaluation and treatment for other atherosclerotic disease and risk factor modification was not explicitly modeled. The treatment of critical limb ischemia (defined as restpain, ulcer, or gangrene) was the same for all strategies: in patients with suitable lesions angioplasty would be performed, in the others bypass surgery would be performed.

Table 1 – Treatment strategies evaluated

Strategy	Initial treatment	Secondary treatment*
(1) EX	EX	None
(2) EX±PTA	EX	PTA
(3) EX±PTA/BP	EX	PTA/BP
(4) PTA/EX†	PTA/EX	PTA
(5) PTA/BP/EX‡	PTA/BP/EX	PTA/BP

EX Exercise; PTA Percutaneous transluminal angioplasty, with stent placement if necessary; BP Bypass surgery
*Allowing for multiple secondary interventions, where necessary. The maximum number of possible revascularization procedures per limb was set to three, and varied from two to four in a sensitivity analysis.
†Only patients in whom PTA was not feasible entered the exercise program.
‡ For patients in whom PTA was not feasible BP was considered. If neither PTA nor BP was feasible the patient entered the exercise program.

The analysis combined data from the medical literature and original patient data from three different sources[3,14,21-52] (Table A and B of Appendix). Original patient data included a five-year consecutive series from the Vascular Registry Database at Brigham and Women's Hospital in Boston, Massachusetts (Boston-database, 1990-1995, 722 patients), the database of the exercise program at the University Hospital Groningen, Groningen, the Netherlands (Groningen-database, 329 patients), and a Dutch trial with oral anti-coagulants at the Dijkzigt Hospital, Rotterdam, the Netherlands (Rotterdam-database, 547 patients).[21] The protocols for these studies were approved by the appropriate institutional review boards and informed consent was obtained from the patients. Base-case values and ranges for the key-parameters of the model, technical details about the model structure, and data sources are presented in the appendix. Pertinent assumptions are summarized here.

Model structure

Figure 1 presents a schematic representation of the model. The model is a Markov model[53] that simulates individual disease histories, from presentation to death, for all alternative treatment strategies and keeps track of the time spent in various health states and the accumulated costs. Health states were defined by all possible combinations of symptom severity in each limb: (1) asymptomatic or mild claudication; (2) severe claudication; (3) critical limb ischemia; (4) below-knee amputation, including transmetatarsal amputations; (5) above-knee amputation. We did not define a separate health state for asymptomatic patients, because the available data did not allow distinguishing them from patients with mild claudication. Implicit in the definition of treatment failure (see above) is the assumption that no/mild claudication does not require treatment, other than general measures for atherosclerotic disease. A threshold maximum walking distance of 250 m was used to distinguish severe and no/mild claudication, which

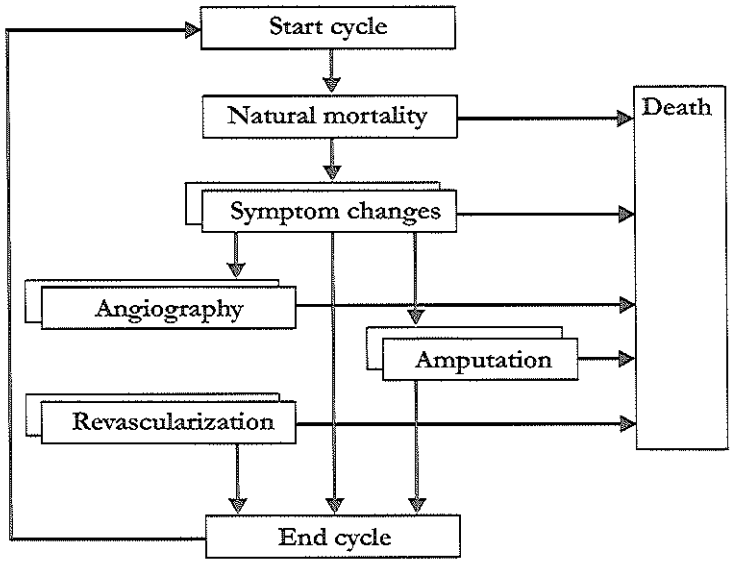

Figure 1 – Schematic representation of the decision model structure. The model is a state transition (Markov) model that defines a number of health states and possible transitions between those states (see Methods). The structure and parameter values define how patients may move from one health state to another during one time-cycle. Each box in this figure represents different possible events that may lead to such state-transitions. The box 'symptom changes', for example, represents possible changes in symptom severity, with the actual probabilities of these changes depending on whether a patient participates in an exercise program and on graft patency. Where events are modeled separately for each limb, two boxes are shown. Patients participating in an exercise program move from the 'start cycle' box through the 'symptom changes' box to the 'end cycle' box. These patients can only move to the 'angiography' box if invasive treatment (PTA or BP) is allowed for failure of exercise in alleviating claudication or if critical limb ischemia develops.

was the upper tercile value at presentation among the patient cohort in Groningen. In a sensitivity analysis we used the lower tercile of this distribution as a threshold (175 m). Apart from symptom severity, additional details of the disease history were modeled including age, sex, duration of the symptoms, history of angina pectoris or myocardial infarction, resting ankle-brachial index (ABI, lowest value of two limbs), patient compliance with exercise, the number of revascularization procedures performed, time since the last procedure, patency and predictors of failure, and the effects on quality of life and costs.

In the base-case analysis, we calculated the results for a 60-year old man presenting with a one-year history of severe unilateral claudication. We assumed that this patient had no history of coronary artery disease (i.e., angina pectoris or myocardial infarction) and that the initial ABI (lowest value of two limbs) was 0.70. Using a first order Monte Carlo analysis, the disease history of this patient was simulated multiple times (n=100,000) for each of the five strategies.[53] In Monte Carlo analysis, a computer-generated random factor is employed at each point in the model where chance plays a role. As a result, outcomes may differ from simulation to simulation, as in real life, where the outcomes for patients with the same characteristics may differ due to chance factors. The average outcome per strategy was used for further calculations. Strategies were ordered according to increasing effectiveness (QALYs) and a dominated strategy was defined as a strategy with a lower effectiveness and higher cost than another strategy. Next, dominated strategies were eliminated and incremental CE-ratios were calculated as the difference in mean lifetime costs divided by the difference in mean QALYs for each strategy compared to the next best strategy.[54]

Exercise program

We considered a six-month exercise program as developed at the Department of Internal Medicine of the University Hospital in Groningen.[41,51] In this program patients are asked to walk a certain fixed distance each day. The exact distance varies from patient to patient (2-6 km) and depends on his/her performance at baseline. Patients are instructed to pause when symptoms of claudication appear. There are four control visits at the hospital during the first six months. After these six months, patients continue with the exercises at home. We assumed that patients who discontinue the exercises do not re-enter the program.

Revascularization

Revascularization was assumed to be preceded by angiography. Findings on angiography, such as the level of disease and feasibility of PTA, were incorporated as possible events in the decision model. In a minority of patients (5%) findings at angiography are such that no revascularization will be considered unless patients develop critical limb ischemia. Of the remaining 95% of the patients, those with suitable lesions undergo PTA. A focal stenosis between 50-99% above the knee

joint was considered suitable for PTA. To make the problem tractable, we incorporated only the most commonly used procedures, i.e. PTA with selective stent placement and aortic bifurcation surgery for suprainguinal disease[14] and PTA and bypass surgery for infrainguinal disease. Thrombolysis was not considered as a treatment option. The maximum number of possible revascularization procedures per limb was set to three. More than three interventions per limb was rarely encountered in the Boston-database and in a sensitivity analysis we varied the number of interventions from two to four.

Quality of life

QALYs were calculated as the sum of the time spent in each health state, multiplied by a correction factor representing the quality of life in each of those health states. Correction factors are generally based on health value measures, instruments that aim to measure quality of life on a 0-1 scale. Examples of such instruments include the Standard Gamble and the Time Trade-off.[55] In the present study, we used Time-Trade-off estimates. For the health states 'no/mild claudication' and 'severe claudication', responses on the EuroQol-questionnaire modified to estimate Time-Trade-off values.[43,49] We used the EuroQol, because it was the best in discriminating between patients with different symptom severity. Values obtained with other instruments were used in sensitivity analyses. For patients with critical limb ischemia or with an amputation we used Time Trade-off estimates from the medical literature and explored a wide range of alternative values in sensitivity analyses.[42] With bilateral symptoms, we assumed that the most severe symptoms would determine the quality of life, ignoring possible additional effects on the quality of life of milder contralateral symptoms. The average Time Trade-off among survivors of a myocardial infarction were used as an approximation for the quality of life with a systemic complication[44], which was incorporated assuming a multiplicative relationship.

Costs

Both medical and non-medical costs were included. Medical costs included the costs of all diagnostic and therapeutic procedures, professional fees, short- and long-term care after complications, follow-up visits, and rehabilitation and long-term care for patients with an amputation. Estimates of the hospital-costs for each of the revascularization procedures were obtained from the Boston-database.[46] Future medical costs for unrelated diseases were not considered because none of the proposed treatment strategies offer any significant survival advantage. By including these medical costs all strategies would be equally affected and the incremental CE-ratio would not change. Non-medical costs included transportation costs and the opportunity cost of patient time invested in, for example, undergoing a procedure or exercising. In a sensitivity analysis we set the cost of patient time spent on exercise to zero which assumes the patient enjoys the

activity. Costs associated with productivity changes were considered to be negligible and not to differ across strategies. All costs were converted to 1995 US dollars by using the medical care specific consumer price index (Bureau of Labour Statistics).[56] Both costs and QALYs were discounted at an annual rate of 3%.[20] The discount rate was varied from 0-10% in a sensitivity analysis.

RESULTS

Base-case analysis

In the base-case analysis, we calculated the outcomes for a 60-year-old man, with no history of coronary artery disease. The model predicts a lower probability of severe claudication with increasingly intensive treatment efforts (Figure 2) and, correspondingly, a higher probability of having no/mild claudication (not shown). The difference in predicted probability of severe claudication between the treatment strategies that considered revascularization as a primary option and the corresponding strategies that considered the same revascularization procedure(s) as a secondary option after a trial of exercise (i.e. PTA/EX vs. EX±PTA and PTA/BP/EX vs. EX±PTA/BP) is initially large, but disappears quickly over time

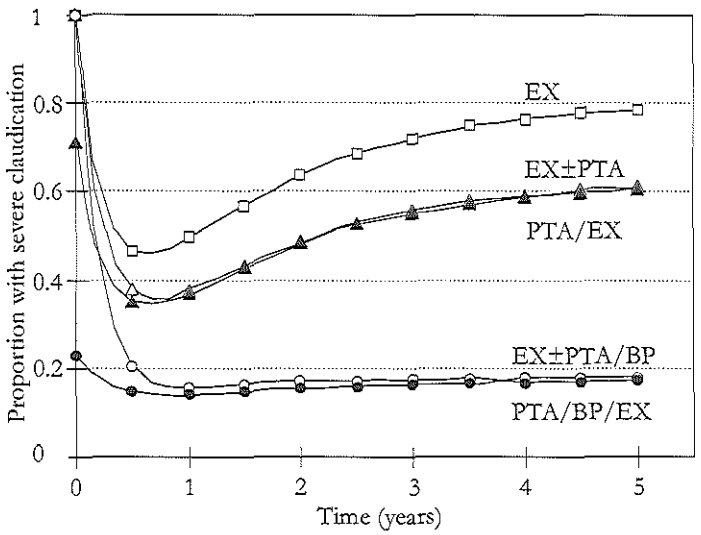

Figure 2 – Proportion of patients with severe claudication during the first five years of follow-up, conditional upon survival (base-case analysis). The model predicts a lower probability of severe intermittent claudication for strategies that consist of more invasive treatment options. Initially, the difference between the strategies EX±PTA/BP and PTA/BP/EX was large because invasive treatment was directly successful in many patients and walking exercises may take some time before reaping any reward but over time the difference disappears. Strategies: □=EX, ▲=PTA/EX, Δ=EX±PTA, ●=PTA/BP/EX, ○=EX±PTA/BP. (For an explanation of the strategies see Table 1)

(Figure 2). Invasive treatment of patients can be directly successful while patients starting with walking exercises have to invest valuable time before reaping any reward. With the two strategies that include bypass surgery, the probability of severe claudication drops sharply during the first year and increases only slightly during subsequent years. The two bypass surgery strategies were, however, associated with a substantially higher risk of periprocedural mortality (Figure 3) and morbidity (not shown) than the other strategies. For the base-case, this did not substantially affect the unadjusted life expectancy: without quality-adjustment or discounting estimates ranged from 10.37 years for strategy PTA/BP/EX to 10.40 years for strategy EX±PTA. Estimates of QALYs varied more substantially, ranging from 6.05 for strategy EX to 6.22 for strategy EX±PTA/BP (including discounting). Generally, with increasing QALYs the expected lifetime costs also increased (Figure 4). Strategy EX±PTA was inferior to strategy PTA/EX by dominance, and strategy PTA/BP/EX was inferior to strategy EX±PTA/BP by dominance. The differences, however, between the dominant and dominated strategies were minimal. The incremental CE-ratios of the two remaining revascularization strategies were: $38,000 per QALY gained for strategy PTA/EX (compared to strategy EX) and $311,000 per QALY gained for strategy EX±PTA/BP (compared to strategy PTA/EX).

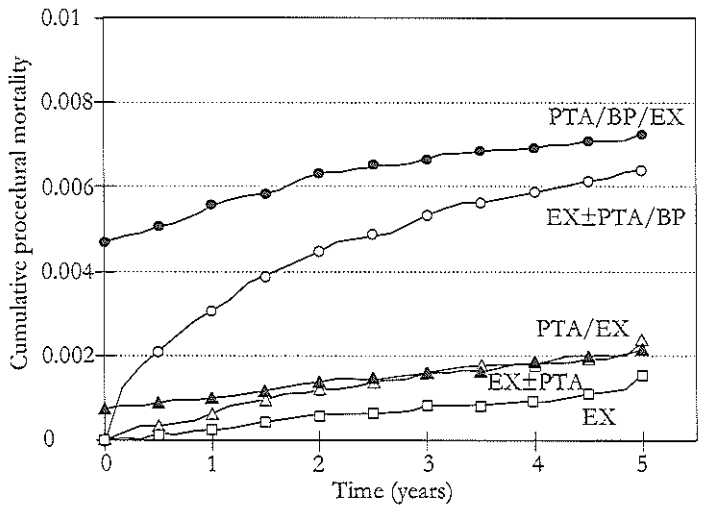

Figure 3 – Cumulative procedural mortality (i.e., mortality from angiography, amputation, bypass surgery, or a percutaneous intervention) during the first five years of follow-up (base-case analysis) including mortality from initial invasive treatment (at time = 0) for strategies PTA/EX and PTA/BP/EX. Strategies including bypass surgery have a higher risk of procedural mortality than other strategies. Strategies: □=EX, ▲=PTA/EX, Δ=EX±PTA, ●=PTA/BP/EX, ○=EX±PTA/BP. (For an explanation of the strategies see Table 1)

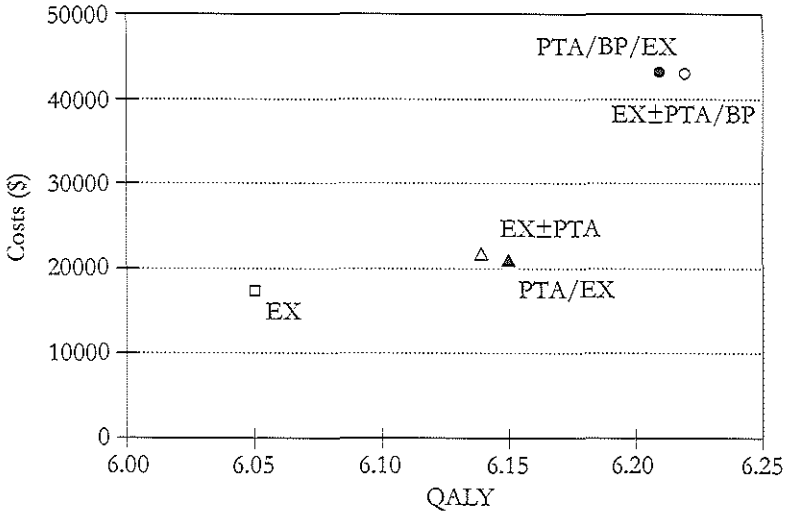

Figure 4 – Expected lifetime costs vs. quality-adjusted life years (QALY) (base-case analysis). With increasing QALYs the lifetime costs also increased. Strategies EX±PTA and PTA/BP/EX were inferior by dominance. Strategies: □=EX, ▲=PTA/EX, Δ=EX±PTA, ●=PTA/BP/EX, ○=EX±PTA/BP.

Sensitivity analysis

For most parameters we found that alternative assumptions did not substantially affect the outcomes or that they affected all strategies similarly, without substantial effects on the incremental CE-ratios. For example, the discount rate was varied from 0 to 10%, which affected both costs and effects for all five strategies, but the incremental CE-ratios hardly changed. Similarly, a higher or a lower risk of mortality associated with PAD did not substantially affect the incremental results.

The results were, however, particularly sensitive to varying the health values for severe vs. no/mild claudication (Table 2). The smaller was the difference between the health values of severe vs. no/mild claudication, the higher were the incremental CE-ratios, whereas a larger difference between the health values resulted in lower incremental CE-ratios. Also the results of strategies that included bypass surgery were sensitive to the quality of life of a patient with systemic complications. For example, if the quality of life for systemic complications was lower then the incremental CE-ratio for strategy EX±PTA/BP increased. The effects of varying the health values for angina pectoris, above- or below-knee amputation, and critical ischemia were minimal.

For all strategies, the expected lifetime costs were sensitive to the costs of revascularization procedures. By varying these costs between 50% and 150% of the original estimates resulted in incremental CE-ratios for strategy PTA/EX ranging

from $25,000 to $46,000 per QALY gained and $266,000 to $453,000 for strategy EX±PTA/BP. By assuming that the patient enjoyed walking (time costs for exercise were set to zero) the total costs for strategies that started with exercise reduced with approximately $3500, resulting in an incremental CE-ratio of $63,000 per QALY gained for the strategy PTA/EX and $230,000 for EX±PTA/BP.

Assuming a small survival benefit among patients who participate in the exercise program did not affect the results substantially. Using a threshold maximum walking distance of 175 m instead of 250 m to distinguish severe from no/mild claudication increased the incremental CE-ratio for strategy PTA/EX ($53,000/QALY gained) and strategy EX±PTA/BP ($359,000/QALY gained). Assuming that initially the proportion of lesions suitable for PTA would be 50% higher than during subsequent years decreased the incremental CE-ratio for strategy PTA/EX ($31,000/QALY gained) and increased the incremental CE-ratio for strategy EX±PTA/BP ($1,504,000/QALY gained). Alternative assumptions concerning the effect of exercise or the effect of bifurcation grafts on the development of contralateral symptoms did not change the results substantially. For all five strategies, the outcomes under alternative assumptions regarding the maximum number of procedures per limb (varied from two to four) were essentially the same.

For most patient characteristics the effects on the incremental results were modest, except for age and history of coronary artery disease. Generally, the incremental CE-ratios for the interventional strategies increased with increasing age or a positive history of coronary artery disease. The latter was associated with a significantly shorter life expectancy for interventional strategies due to the increased procedural risk in patients with cardiac ischemia, especially for the strategies that include bypass surgery.

Table 2 summarizes the combined effects on the incremental CE-ratios for strategies PTA/EX and EX±PTA/BP of those variables that showed significant effects in one-way sensitivity analyses: age, history of coronary artery disease, costs of revascularization, and the health value difference between no/mild claudication and severe claudication. Each cell in Table 2 is based on simulating 100,000 disease histories for each treatment strategy under the given parameter values. For example, assuming an age of 40, a positive history of coronary artery disease, revascularization costs that are 50% lower than our base-case estimates, and a health-value difference of 0.08 between no/mild vs. severe claudication, our analyses indicate that the incremental CE-ratio for strategy PTA/EX is approximately $36,000 per QALY gained, whereas strategy EX±PTA/BP is dominated by the other two strategies. Table 2 suggests that, especially for 80-year olds and those with a history of coronary artery disease, strategy EX±PTA/BP is unattractive under most circumstances, either because it is dominated by strategy EX or PTA/EX, or because the incremental CE-ratios are exceptionally high.

Table 2 – Results* of a 4-way sensitivity analysis based on age, history of coronary artery disease, revascularization costs, and health value difference between no/mild claudication and severe claudication.

			PTA/EX				EX±PTA/BP			
CAD	Age	Costs	Health value difference†:				Health value difference†:			
			0.04	0.08	0.12	0.16	0.04	0.08	0.12	0.16
No	40	50%	39,187‡	17,103	11,119	8,242	PTA/EX	196,685	72,704	44,221
		100%	49,295	21,514	12,445	9,225	PTA/EX	239,872	89,216	54,264
		150%	53,097	23,119	14,286	11,247	PTA/EX	288,462	106,918	64,045
	60	50%	52,995	25,307	17,461	13,145	PTA/EX	265,713	102,078	59,035
		100%	76,141	36,360	24,386	18,358	PTA/EX	359,948	140,054	80,997
		150%	95,109	46,319	31,947	24,188	PTA/EX	452,851	175,152	102,228
	80	50%	114,912	61,315	49,692	37,982	PTA/EX	2,285,963	208,865	130,330
		100%	181,209	96,690	80,732	61,707	PTA/EX	3,594,454	327,320	204,245
		150%	245,534	129,918	108,995	84,630	PTA/EX	4,978,633	451,569	277,653
Yes	40	50%	470,891	35,807	18,699	12,573	EX	EX	837,319	104,038
		100%	578,047	43,955	23,173	15,582	EX	EX	1,036,061	128,732
		150%	685,136	52,098	27,466	18,468	EX	EX	1,237,523	153,763
	60	50%	305,840	52,879	27,587	19,121	EX	EX	PTA/EX	199,618
		100%	434,018	75,040	37,736	26,155	EX	EX	PTA/EX	276,732
		150%	572,654	98,406	48,890	34,094	EX	EX	PTA/EX	353,623
	80	50%	620,887	167,466	80,962	50,606	EX	EX	PTA/EX	434,891
		100%	1,005,651	271,245	127,903	79,947	EX	EX	PTA/EX	685,366
		150%	1,375,211	373,200	177,199	109,564	EX	EX	PTA/EX	931,353

CAD: history of coronary artery disease
Age: age in years
Costs: revascularization costs, as a percentage of the base-case estimates
EX: strategy EX and PTA/EX are superior to EX±PTA/BP by full dominance
PTA/EX: strategy PTA/EX is superior to EX±PTA/BP by full dominance.
* Results are presented as incremental cost-effectiveness ratios (US$/QALY gained) compared to the next best strategy (i.e., PTA/EX was compared to EX and EX±PTA/BP was compared to PTA/EX).
† Difference between health value for no/mild claudication and that for severe claudication. For base-case estimates see Table B, Appendix.
‡For a 40-year-old man without CAD, costs of revascularization equaled 50% of the base-case estimates, and a difference in health value of 0.04 between no/mild claudication and severe claudication, the incremental CE ratio was $39,187/QALY relative to the strategy EX.

Discussion

The advent and development of percutaneous procedures for PAD during the last two decades have stirred up the debate about the optimal treatment strategy in patients with intermittent claudication.[1,2,12,57-59] In this study we addressed the question whether the traditional conservative approach to treating claudication can still be justified in the present era of low risk revascularization procedures. The results suggest that, from a societal perspective and considering cost-effectiveness, a fairly conservative approach is warranted. The net effect on the quality-adjusted life expectancy of revascularization was relatively small, not only because of the modest difference in health values between patients with no/mild vs. severe claudication, but also because the benefits of revascularization

in terms of symptom severity were partly offset by the risks of procedural mortality and morbidity, especially for bypass surgery. The expected lifetime costs of revascularization, especially strategies including bypass surgery, were substantially higher than those of exercise therapy alone. Furthermore, the results of strategies with a revascularization procedure as a possible initial step (strategies PTA/EX and PTA/BP/EX) were very similar to those of the corresponding strategies that considered the same procedure(s) as a secondary option after a trial of exercise (strategies EX±PTA and EX±PTA/BP, respectively). The results of the sensitivity analysis emphasize that the expected gain in quality of life should be a crucial factor in the choice of treatment for intermittent claudication. We found that the CE-ratios of the revascularization strategies depended to a large extent on the health values for no/mild and severe claudication. The quality of life values for no/mild and severe claudication in the current analysis were based on the results of a previous study[43], which agreed closely with the values obtained in other studies.[47,60] The difference in the average observed EuroQol values (which were used in our analysis) for patients with no/mild vs. severe claudication was only modest (0.08), leading to high CE-ratios for the revascularization strategies. With other quality-of-life instruments differences between groups were even smaller which would have resulted in even higher CE-ratios. The estimated health values were, however, average values assuming that patients can be divided into fairly homogenous groups based on their walking distance. The impact of a change in walking distance from e.g. 300 to 150 meters may for some patients have a far larger impact on their quality of life than the average we estimated. Thus, whereas our results suggest that bypass surgery is not cost-effective given the average observed difference in quality of life values between no/mild and severe claudication, the sensitivity analysis supports the use of bypass surgery in exceptional cases where the difference is very large.

With constant improvements in the technique of percutaneous treatment more lesions will be suitable for PTA. Under those circumstances our model predicted that the incremental CE-ratio of the strategy with angioplasty as only and initial invasive treatment decreased slightly and the incremental CE-ratio of the strategy with bypass surgery would increase tremendously. We also assumed that invasive treatment was always preceded by an angiography. Nowadays, angiography is often replaced by non-invasive imaging modalities such as magnetic resonance angiography and duplex ultrasound. These modalities involve lower costs and risks compared with angiography but could lead to false test results.

The CE-ratios of more than $200,000 per QALY gained is outside the generally reported range of CE-ratios[61] implying that bypass surgery for intermittent claudication is an inefficient use of the limited resources in health care. Although practice patterns vary considerably, in many centers bypass surgery is currently performed not only for limb-threatening symptoms but also for severe claudication. Our analysis suggests that bypass surgery, even only as a secondary

option, is very expensive compared to the achieved gain in effectiveness. The incremental CE-ratios for angioplasty were within the range of those reported for currently accepted technologies. For example, Wong et al. found that coronary artery bypass surgery for three-vessel disease in patients with severe angina cost $105,000 per QALY gained (adjusted to 1995 dollars).[62] Compared to CE-ratios for coronary angioplasty for severe angina ($10,000 - $18,000 per QALY gained[62]), the CE-ratios for peripheral angioplasty were, however, somewhat unfavorable.

Our study is a synthesis of the existing knowledge of the risks, benefits, and costs of different therapeutic options in patients with PAD. Limitations of our study reflect shortcomings in the current knowledge and the necessity to make several simplifying modeling assumptions to keep the problem tractable. To test the robustness of our conclusions, we examined, where possible, the effect of choosing alternative assumptions on the outcomes of our study. For many assumptions we found that either the alternatives did not change the results substantially, or that they changed the results for all strategies similarly, implying that the conclusions remained the same. However, a number of significant points of discussion remain.

The primary limitation of our study is that differences between the various sources of evidence that we used may have biased the results. For example, we used two different data-sets to model changes in the severity of claudication, one for patients participating in an exercise program and one for the situation after revascularization. We adjusted the transition probabilities from both data sets for important potential confounders, including age, ABI, the presence of angina, and the duration of the symptoms. Similarly, we corrected other parameter estimates for potential confounders where possible. Thus, a formal decision analysis offers opportunities to truly integrate information from different sources as an alternative to just comparing the outcomes of different studies. Nevertheless, in terms of *prevention* of confounding, our analysis cannot replace a properly conducted randomized controlled trial. In our own view, the current analysis is a prelude to, rather than a true alternative for such a future trial, and the presented results may help focus the question and trial design.

Another limitation related to cost-effectiveness analysis using decision models is the use of fixed values for the parameters in the model assuming that all these values are precisely known. For example, in the model we incorporated that 8.3% of patients undergoing aortic bifurcation bypass surgery would suffer from systemic complications. This value, however, is uncertain and could also be 7% or 10%. Thus, not only is there uncertainty as to whether an event will occur, which is modeled with probabilities, but there is also uncertainty surrounding the value of all the model parameters. We explored the effect on the decision of the uncertainty in the model parameters by performing sensitivity analysis, in which all estimates were varied over a plausible range of values. Sensitivity analysis was performed varying up to four parameters simultaneously which provided insight into the

uncertainty surrounding the results.

To take it one step further, we could have assessed the uncertainty in the model with probabilistic sensitivity analysis using second order Monte Carlo analysis.[63,64] In second order Monte Carlo analysis simulations are performed with a set of parameter estimates drawn from pre-specified distributions and this process is repeated multiple times, each time drawing a new set of parameter estimates from the distributions. The results provide a distribution of the effectiveness and cost outcomes. Although useful at times, second order Monte Carlo analysis increases the complexity of the methods and results and does not provide more insight into which parameters are driving the decision. Moreover, a decision which treatment strategy to use in clinical practice would still need to be made and, according to welfare economics would still be best made based on the incremental CE ratios calculated using the means of the parameter estimates.[65]

We recognize that our definition of health states, especially that of no/mild and severe claudication, is a simplification of a more complex clinical reality. Most recommendations regarding revascularization procedures for intermittent claudication distinguish between 'disabling' and 'non-disabling claudication', which would consider a patient's lifestyle and occupation. Such a subjective definition, however, would make it difficult, if not impossible, to obtain the relevant data and to interpret the results. Thus, we used the maximum walking distance to define no/mild and severe claudication. The threshold value that we used was necessarily an arbitrary one, 250 m being the upper tercile of the distribution of the maximum walking distance at baseline in patients with intermittent claudication in the Groningen-database. Some vascular surgeons would find 250 m too lenient a criterion and use lower thresholds to define severe claudication. In a sensitivity analysis we recalculated the transition probabilities in the model and the health values for no/mild and severe claudication based on a lower cut-off value (175 m, the lower tercile). The incremental CE-ratios of the revascularization strategies increased with a lower threshold value but the conclusions remained the same.

Another limitation of our analysis may be that we considered only one conservative treatment option. Exercise is generally regarded as the best conservative option. The exercise program that we considered in the current analysis is an intermediate between more intensely supervised programs and a pure home-based exercise program. Conflicting reports exist regarding the additional effect of supervision in exercise programs and further research on a larger scale is required.[66,67] There is little doubt, however, that the more intensely supervised programs are more expensive than our program. In addition to recommending exercise, many physicians would advise their patients to change their smoking habits. Cigarette smoking has been shown to increase the incidence of intermittent claudication[68], and smoking cessation may reduce the incidence of adverse events once intermittent claudication has developed.[7,69] In many exercise programs, including ours, patients are motivated to stop smoking, and thus the effects of

exercise and smoking cessation may overlap. We therefore chose not to include smoking cessation as a separate option. Of the drugs that have been marketed for intermittent claudication, pentoxifylline has probably been studied most widely but a meta-analysis of 12 randomized trials could not provide conclusive evidence of its effectiveness.[7] Finally, we did not include platelet-aggregation inhibitors as a separate treatment option but rather considered this to be adjuvant therapy, the main benefit being the reduction of coronary and cerebrovascular events, which was not the focus of the current analysis.

Finally, we found that in the setting of coronary artery disease, revascularization for claudication is not cost-effective. We did not, however, model the option of coronary revascularization prior to peripheral revascularization because this really is a different question than we set out to address and beyond the scope of this paper. However, we did consider the presence of coronary artery disease and found that the benefit of the interventional strategies compared with the conservative strategies due to the increased procedural risk in patients with cardiac ischemia was significantly reduced, especially for the strategies that include bypass surgery.

In conclusion, the results suggest that, on average, the small gain in effectiveness achieved with bypass surgery for intermittent claudication does not justify the additional costs. Angioplasty as alternative to exercise when feasible was more effective than exercise alone and the cost-effectiveness ratio was within the generally accepted range.

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APPENDIX

Model Structure

Transitions were modeled back and forth between no/mild and severe claudication and between claudication and critical ischemia. We assumed that exercise does not reduce the risk of critical ischemia[50], that critical ischemia would not improve without revascularization, and that critical ischemia in a revascularized limb would only develop after loss of patency. Patients who developed critical ischemia were assumed to undergo a revascularization procedure unless the maximum number of procedures had been reached in which case an amputation would follow. Amputation in patients with critical ischemia and progression from below-knee to above-knee amputation were also modelled.

Patency, symptom severity, and other details of the disease history were tracked for each limb separately. Comparing the results of limb-based and patient-based reporting of patency for bifurcation grafts, we found no evidence suggesting that patency in one limb depends on patency in the contralateral limb.[26] Therefore, we assumed independence of patency and failure in the two limbs. Patient characteristics, however, affected symptom severity of both limbs, which provided an indirect association between events in the two limbs.[39,41] Implantation of a bifurcation graft for unilateral symptoms was assumed not to affect the development of contralateral symptoms, an assumption that was examined in a sensitivity analysis. Exercise was assumed not to affect the development of contralateral symptoms and in a sensitivity analysis we tested whether assuming a preventive effect of exercise (ranging from 0-100%) would substantially change the results.

The degree of clinical detail incorporated in our decision model exceeded the capacity of standard decision analysis software. Therefore, a C++ based programming language (Fast Decision Language) was developed to construct the model. At the initial stage, a simpler version of the model was built in both Fast Decision Language and DATA™ and results were compared, for debugging purposes. Extensive sensitivity analyses were performed to check for inconsistencies in the model.

Exercise program

Estimates of the transition probabilities between health states associated with exercise were obtained from the Groningen-database and adjusted for age, duration of the symptoms, ABI, presence of angina, and compliance.[51] Based on 3-year follow-up in Groningen we assumed that the rate of discontinuing the exercises was constant over time. Although no survival benefit following exercise programs for intermittent claudication has been demonstrated[52], in a sensitivity analysis we tested whether a small survival benefit (i.e., a 20% reduction in mortality) among participants of the exercise program would substantially affect the results.

Revascularization

Patency estimates were obtained from three published meta-analyses[26,27,34] and adjusted for presenting symptoms (claudication vs. critical ischemia), and where applicable for lesion type (stenosis vs. occlusion), level of the distal anastomosis (above knee vs. below knee) and graft material (autologous vein vs. PTFE). For iliac PTA, we used data from studies where PTA was combined with stent placement, assuming that a stent would be placed if angioplasty alone yielded sub-optimal results.[14] We assumed that patients would not undergo multiple revascularization procedures at different arterial levels simultaneously but the model does allow for new procedures in the same limb at a different (usually infrainguinal) arterial level during follow-up. Following multiple procedures in one limb, we assumed that the procedure that was performed last would determine the overall probability of graft or PTA failure.

Transition probabilities between health states following revascularization were obtained from the Rotterdam-database, adjusted for covariates and the effects of anticoagulant medication. In addition, we incorporated the effect of failure on changes in maximum walking distance, using a drop in ABI of more than 0.15 relative to its post-revascularization value as a patency-criterion.[39,40] Estimates of the rate of development of contralateral symptoms were obtained from the Boston-database.[36]

Costs

The main cost of the exercise program is the opportunity cost of the time invested by the patient.[20] A questionnaire indicated that participants in Groningen spend, on average, 6.4 hours per week exercising. Theoretically, the value of patient time depends on how much the patient enjoys or dislikes the activity.[20,50] In the base-case analysis we used the 1995 US average hourly wage rate ($11.35, source: Bureau of Labour Statistics) as the value of patient time for all disease-related activities. For in-hospital vascular procedures, the value of patient time was estimated as the average length of stay in days (from the Boston-database) multiplied by 7.5 times the hourly wage rate. We also included transportation costs based on an average distance from the home-address to the hospital of 49 km. Estimates of the hospital-costs for each of the revascularization procedures were obtained from the Boston-database[46] adjusted for age, sex, presenting symptoms, and history of coronary artery disease. More detailed information on the cost estimation can be found in the article by Jansen et al.[46] The extra costs incurred by systemic complications or procedural mortality were also obtained from these data. We found that local complications had minimal effect on the total hospital costs. We assumed that the extra long-term medical costs for patients with a systemic complication would equal the yearly medical costs for survivors of a myocardial infarction.[48] Myocardial infarction is the most important major complication associated with invasive treatment of PAD.[70] The long-term costs for systemic complications were varied over a wide range to explore the effect of major complications other than myocardial infarction.

All the data used in the decision model are presented in Tables A and B. Table A presents the rates and probabilities and Table B the health values and costs.

Table A – Rates and probabilities*

Variable	Base-case Value	Range*	Source
Mortality			
Mortality rate ratio for PAD	3.14	2.74-3.54	3, 22-25
Revascularization procedures			
Aortic bifurcation grafts, high risk†	0.044	0.032-0.055	26
Aortic bifurcation grafts, low risk	0.007	0.005-0.009	26
Iliac PTA with selective stenting, high risk†	0.013	0-0.037	27
Iliac PTA with selective stenting, low risk	0.001	0-0.029	27
Femoro-popliteal or –infrapopliteal bypass,high risk†	0.047	0.008-0.127	28
Femoro-popliteal or –infrapopliteal bypass,low risk	0.008	0.001-0.022	28
Femoral or popliteal PTA, high risk†	0.025	0-0.264	28
Femoral or popliteal PTA, low risk	0.002	0-0.021	28
Diagnostic angiography	0.00033	0.00029-0.00162	29, 30
Amputation			
Age < 75	0.098	0.077-0.119	31
Age ≥ 75	0.147	0.113-0.181	31
Systemic complications			
Revascularization procedures			
Aortic bifurcation grafts	0.083	0.063-0.102	26
Iliac PTA with selective stenting	0.013	0-0.035	27
Femoro-popliteal or –infrapopliteal bypass	0.085	0.027-0.130	28
Femoral or popliteal PTA	0.013	0.002-0.110	28
Diagnostic angiography	0.017	0.010-0.025	32
Amputation	0.380	0.377-0.383	33
2-year patency in patients with claudication / ischemia‡			
Aortic bifurcation grafts	0.95/0.93	-	26
Iliac PTA with selective stenting§			
Stenosis	0.84/0.76	-	27
Occlusion	0.67/0.60	-	27
Femoropopliteal or femoroinfrapopliteal bypass‖			
Autologous vein	0.89/0.80	-	34
PTFE, above-knee anastomosis	0.86/0.68	-	34
PTFE, below-knee anastomosis	0.80/0.56	-	34
Femoral or popliteal PTA			
Stenosis	0.75/0.56	-	34
Occlusion	0.46/0.21	-	34

* Presented figures are probabilities, unless stated otherwise. Ranges represent 95% confidence intervals, except for the mortality rate ratio for PAD, where the range is defined by the lowest and highest average from different subsets of studies (i.e., population- vs. hospital based studies).

† High risk: (age>65 & critical ischemia) / history of coronary artery disease. The relative risk for high risk patients was obtained from Hunink et al., and assumed to be the same for suprainguinal vs. infrainguinal procedures.[28, 37]

‡ The model incorporates time-dependent graft failure rates, the 2-year patency estimates are presented as examples. The listed revascularization procedures together represented approximately 85% of all procedures performed for PAD at the Brigham and Women's hospital during a recent five-year period.

§ Patency estimates for iliac PTA with selective stenting have been shown to equal those for iliac PTA with primary stenting.[14]

‖ The patency rates for femoroinfrapopliteal bypasses were assumed equal to those of femoropopliteal bypasses with a below-knee anastomosis.[38]

Table A – Continued

Variable	Base-case Value	Range*	Source
Arterial level: probability of suprainguinal disease			
First intervention¶	0.56	0.12-0.85	Boston-database
Second or later intervention, previously suprainguinal disease	0.31	0.13-0.49	Boston-database
Second or later intervention, previously infrainguinal disease	0.17	0.09-0.25	Boston-database
*Lesions suitable for PTA**, claudication / ischemia*			
Suprainguinal disease, first intervention	0.51/0.27	0.43-0.59/0.19-0.35	Boston-database
Suprainguinal disease, second or later intervention	0.33/0.19	0.03-0.65/0-0.38	Boston-database
Infrainguinal disease, first intervention	0.18/0.07	0.11-0.25/0.04-0.10	Boston-database
Infrainguinal disease, second or later intervention	0.23/0.06	0.07-0.39/0-0.12	Boston-database
Critical ischemia and amputation			
Annual incidence rate of critical ischemia (natural history)			
Age < 65††	0.017	0-0.039	3, 5, 22, 35
Age ≥ 65	0.036	0-0.075	3, 5, 22, 35
5-week probability of critical ischemia following graft failure‡‡			
Pre-treatment symptoms: claudication	0.062	0-0.014	Boston-database
Pre-treatment symptoms: critical ischemia	0.242	0.14-0.36	Boston-database
Proportion of above-knee amputations among amputations for PAD	0.080	0.030-0.130	Boston-database
Annual incidence rate progression below- to above-knee amputation	0.015	0-0.070	Boston-database
Severe vs. no/mild intermittent claudication §§			
Relative risk of severe claudication after stopping exercise	5.81	1.8-18.5	Groningen-database
Relative risk of severe claudication after graft failure	1.36	0.96-1.92	Rotterdam-database
Contralateral symptoms (mean annual rate)||||	0.149	-	36

* Presented figures are probabilities, unless stated otherwise. Ranges represent 95% confidence intervals, except for the mortality rate ratio for PAD, where the range is defined by the lowest and highest average from different subsets of studies (i.e., population- vs. hospital based studies).

¶ The model incorporates a logistic regression function with age, sex, and presenting symptoms (claudication vs. ischemia) as independent variables. The presented base-case value assumes a 60-year old male patient with intermittent claudication.

** Lesions were considered suitable for PTA if there was one focal stenosis between 50-99% above the knee joint.

†† Relative risk for age ≥ 65 obtained from Bloor.[3]

‡‡ Graft or PTA failure was defined as a drop in ankle-brachial index of more than 0.15, compared to early post-revascularization values.[39, 40]

§§ In addition to incorporating the presented relative risks, the model adjusts the probabilities of transition from no/mild to severe claudication and vice versa for age, duration, ABI, and presence of angina pectoris, using autoregressive logistic regression.[39, 40]

|||| Includes both intermittent claudication and critical ischemia. In patients with previous unilateral ischemia, 67% of the contralateral symptoms are critical ischemia, compared to 10% in patients with previous unilateral claudication.[36]

Table B – Health values and costs

Variable	Base-case Value	Range	Source
Health values			
Above knee amputation*	0.20	(0.00-0.40)	42
Below knee amputation*	0.61	(0.41-0.81)	42
Critical ischemia*	0.35	(0.15-0.55)	42
Severe claudication†	0.71	0.67-0.75	43
No/mild claudication†	0.79	0.75-0.83	43
Systemic complication‡	0.72	0.60-0.90	44
Angina pectoris	0.90	(0.60-1.00)	44
Costs			
Exercise			
Patient time (total costs per year) §	$3,780	$800-$8,000	Groningen-database
Follow-up visit‖	$380	-	ACR
Diagnostic angiography	$680	-	ACR
Amputation			
Above knee¶	$14,420	-	Medicare data
Below knee¶	$7,790	-	Medicare data
Long-term care patients with above knee amputation (per year)	$31,920	$20,000-$40,000	45
Revascularization procedures**			
Aortic bifurcation bypass	$23,490	$21,000-$26,000	46
Iliac PTA with selective stenting††	$7,550	$5,000-$10,000	46, 47
Femoropopliteal or –infrapopliteal bypass	$16,490	$14,000-$19,000	46
Femoral / popliteal PTA	$4,170	$1,200-$7,000	46
Follow-up visit‖	$410	-	ACR
Systemic complications			
Short-term costs	$9,770	$6,500-$13,000	46
Annual long-term costs	$10,780	$5,000-$15,000	48
Mortality from revascularization procedures	$11,620	$3,600-$20,000	46

ACR: obtained from the American College of Radiology.
Ranges represent 95% confidence intervals, except those between brackets, where, in the absence of sufficient information to construct 95% confidence intervals, relatively large arbitrary ranges were chosen.
*Time Trade-off values.
†Time Trade-off values based on responses on the EuroQol-questionnaire.[49]
‡Average Time Trade-off value among survivors of a myocardial infarction, used as a proxy for the effect on quality of life of a systemic complication.[44]
§On average 6.4 hours/week (source: Groningen-database). We used the 1995 US average hourly wage rate ($11.35, source: Bureau of Labour Statistics) to value patient time.
‖Includes the costs of an office visit, non-invasive tests, patient time, and transportation costs.
¶Average 1995 Medicare reimbursement for Diagnostic Related Group 113 and 114.
**The model incorporates a linear regression function with age, sex, history of coronary artery disease, and presenting symptoms (claudication vs. ischemia) as independent variables. The presented estimates assume a 60-year old male patient with intermittent claudication, without a history of coronary artery disease.
††Assumes that in 43% of the cases a stent is placed.[14]

4

PRE-TREATMENT IMAGING WORK-UP FOR PATIENTS WITH INTERMITTENT CLAUDICATION: A COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Context: For the pre-treatment work-up of patients with intermittent claudication non-invasive imaging modalities and intra-arterial digital subtraction angiography (DSA) are available and the optimal imaging strategy is unknown.
Objective: To determine the societal cost-effectiveness of pre-treatment imaging work-up for patients with claudication.
Design: A cost-effectiveness analysis using a decision-analytic model that considered test characteristics such as sensitivity, complications induced by the test, the implications of missing lesions, and/or the consequences of overtreating patients. Data on the imaging modalities were obtained from the literature.
Setting and patients: Hypothetical cohort of 60-year old male patients without a history of coronary artery disease that presented with severe claudication to undergo pre-treatment imaging work-up.
Interventions: Magnetic resonance (MR) angiography, duplex ultrasound (US), DSA, and a no diagnostic work-up strategy. In a sensitivity analysis DSA and angioplasty were modeled as a combined procedure performed in one session.
Main outcome measures: Quality adjusted life years (QALYs), lifetime costs ($), and incremental cost-effectiveness (CE) ratios.
Results: The range in effectiveness and lifetime costs across different diagnostic work-up strategies was small (largest difference in effectiveness 0.025 and in lifetime costs $1,800). If treatment was limited to angioplasty in patients with suitable lesions then MR angiography had an incremental CE ratio of $35,000/QALY compared with no diagnostic work-up and DSA had an incremental CE ratio of $471,000/QALY compared with MR angiography. If treatment options included both angioplasty and bypass surgery, then DSA had an incremental CE ratio of $179,000/QALY compared with no diagnostic work-up and MR angiography and duplex US were inferior by dominance. When it was assumed that DSA was immediately followed by angioplasty in the same session, the effectiveness for the strategy DSA increased with 0.0007 QALYs and the lifetime costs decreased with $217.
Conclusions: The differences in costs and effectiveness across diagnostic imaging strategies for patients with intermittent claudication are small and MR angiography or duplex US can replace DSA without substantial loss in effectiveness and with a small cost reduction. Combining a diagnostic DSA and angioplasty in one session yields a minimal gain in effectiveness and a small cost-reduction.

INTRODUCTION

The pre-treatment work-up for patients with intermittent claudication consists of selecting the most appropriate intervention for each patient and varies by institution. Some centers advocate the use of duplex ultrasound (US) as the initial triaging modality followed in many cases by intraarterial digital subtraction angiography (DSA), whereas others advocate the use of magnetic resonance (MR) angiography as the only imaging modality. So far, most studies on the pre-treatment imaging work-up of peripheral arterial disease (PAD) have focused on the diagnostic accuracy of these tests. For the detection of significant stenoses duplex US has a fairly good accuracy compared with DSA whereas MR angiography is nearly as accurate as DSA.[1] Currently, angioplasty procedures and sometimes even bypass surgery are often planned on the basis of the findings of duplex US.[2-4] Likewise, the results of MR angiography for planning invasive treatment are also promising.[5,6] Intraarterial DSA, on the other hand, is considered to be the reference ("gold") standard and is still often used despite the fact that it has a small risk of morbidity and mortality[7,8] and is fairly expensive. The question arises which imaging work-up strategy is preferred.

To determine which test(s) are preferred in clinical practice we need to take into account not only the diagnostic accuracy of each test, but also the related effects of diagnostic imaging tests on the treatment plan, long-term prognosis, quality of life, and costs. Although ideally one would like to perform a clinical study to address all these issues, such a study is complicated and time-consuming. Alternatively, a cost-effectiveness analysis using a decision-analytic approach can shed light on the trade-offs involved. A model integrates all relevant effects and costs and has the ability to compare numerous diagnostic strategies. The purpose of this study was to assess the cost-effectiveness of MR angiography, duplex US, and intraarterial DSA for the pre-treatment imaging work-up of patients with lifestyle limiting intermittent claudication using a decision-analytic approach.

METHODS

Decision model

A previously developed decision-analytic model[9] that evaluated treatment and follow-up in patients with intermittent claudication was extended with an additional model on the imaging work-up to assess which work-up is most appropriate for the patient. Three different work-up strategies were considered: [1] MR angiography in all patients; [2] duplex US in all patients; and [3] intraarterial DSA in all patients. A reference strategy consisting of exercise therapy without imaging work-up was also considered.

The information obtained from the imaging work-up was used to make

treatment decisions. Figure 1 represents a simplified outline of the model. The test results indicated whether the lesion was located suprainguinal or infrainguinal and which treatment (angioplasty with selective stent placement, bypass surgery, or supervised exercise) was preferable. Intraarterial DSA was considered to be the reference standard and yields all information necessary to make the correct treatment decision. A treatment decision cannot always be made based on the MR angiography or duplex US results and, therefore, we assumed that additional work-up with DSA was performed if the test yielded technically inadequate results (e.g. bowel gas for duplex US), no treatment plan could be determined on the basis of the test result, no lesion was localized, or the test could not be performed (e.g., contraindication, like claustrophobia or having a pacemaker for MR angiography).

False test outcomes MR angiography and duplex US could induce false test results which could lead to treatment of an incorrect location and/or inappropriate treatment. For example, a patient with a suprainguinal lesion suitable for angioplasty could be diagnosed with MR angiography as having a lesion not suitable for angioplasty. Because of the limited data reported in the literature the following assumptions were made for the implications of false test results.

For angioplasty we assumed that the preceding diagnostic DSA as a part of an angioplasty procedure would detect incorrectly located lesions and/or a lesion incorrectly referred for angioplasty. For depicting incorrectly located lesions we assumed that in 10% of the cases another angioplasty session would be necessary on another day (e.g., because of contrast overload or incorrect puncture for the angioplasty procedure). The costs of a planned angioplasty procedure that had to be stopped after the DSA were assumed to be equal to a DSA plus an additional amount of money for inefficient use of personnel, equipment, and room time.

When bypass surgery was performed on a non-suitable lesion it was assumed that post-operative success rates would be lower. For patients in whom bypass surgery was performed at the wrong location because of a false test result, we assumed that a repeat DSA would be performed for persistent symptoms, followed by repeat surgery.

Treatment The treatment options for lifestyle limiting intermittent claudication included: percutaneous transluminal angioplasty with stent placement if necessary, bypass surgery, and supervised exercise. Because there seems to be disagreement on whether the presence of claudication justifies the use of bypass surgery we modeled two different treatment scenarios. In the first scenario treatment was limited to angioplasty only and patients with lesions not suitable for angioplasty entered a supervised exercise program (minimally invasive treatment scenario). In the second scenario an angioplasty was performed if feasible and otherwise bypass surgery (more invasive treatment scenario). For the strategy with no diagnostic work-up all patients entered a supervised exercise program and only if patients developed critical limb ischemia was invasive treatment performed.

Patients with recurrent lifestyle limiting claudication (defined as maximum

walking distance less than 250 m), graft failure, or development of symptoms in the contralateral limb received further treatment. Critical limb ischemia (defined as rest pain, ulcer, or gangrene) was always treated invasively and, if necessary, an amputation was performed.

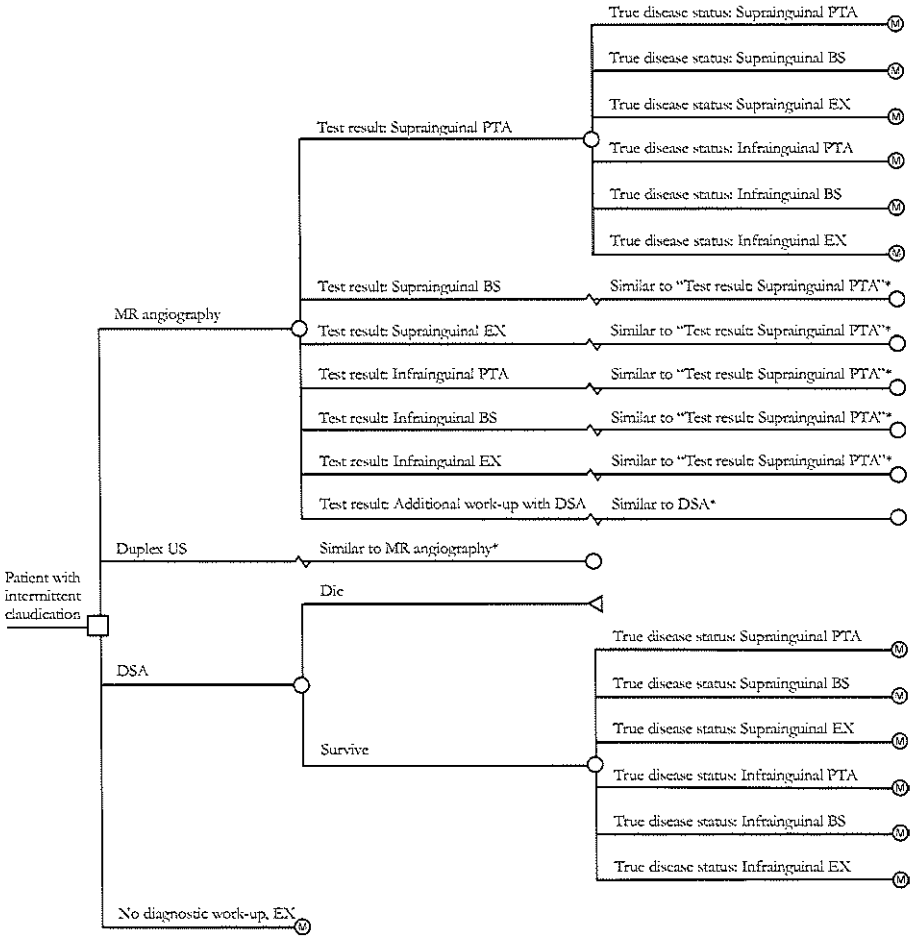

Figure 1 – Schematic representation of the structure of the decision model. Patients who undergo diagnostic work-up will be treated according to the diagnostic test result. In the Markov mo del treatment of patients and lifetime follow-up is modeled. Test results are considered true if the test result and true disease status are the same whereas test results are considered false if the test result and true disease status are discrepant. Patie nts who do not undergo diagnostic work-up enter a supervised exercise program.
MR = magnetic resonance; US = ultrasound; DSA = digital subtraction angiography; PTA = percutaneous transluminal angioplasty with selective stent placement; BS = bypass surgery; EX = supervised exercise program; (M) = Markov model
* The structure of the subsequent subtree is similar to a structure used elsewhere in the tree.

Data sources

Test characteristics Table 1 presents the data on gadolinium-enhanced MR angiography and color-guided duplex US that were incorporated in the model.[1,4-6,10,11] To our knowledge no major side effects due to MR angiography or duplex US have been reported. DSA, on the other hand, has a small risk of morbidity and mortality. The probability of systemic complications due to DSA was 0.029 (range 0.017 – 0.052)[8] and the mortality risk was 3.3*10-4 (range 2.9 – 16.2*10-4).[7,12]

Table 1 – Test characteristics of MR angiography and duplex US

	MR angiography			Duplex US		
Variable	Base-case value	Range*	Source†	Base-case value	Range*	Source†
Sensitivity > 50% stenosis‡	0.96	0.91 - 0.97	1	0.90	0.89 – 0.90	1
Specificity > 50% stenosis	0.96	0.94 – 0.98	1	0.95	0.93 – 0.96	1
Probability of uninterpretable test result§	0.07	0.05 – 0.10	Personal communication 2000, dr. Ho, Radiologist‖	0.11	0.0 – 0.23	10
Probability of indeterminate test result¶	0	-	5, 6	0.089	0.036 – 0.14	4
Probability that test result suggests angioplasty given that lesion is suitable for angioplasty**	0.79	0.87	5††, 6‡‡	0.60	0.93	11§§, 4‖‖
Probability that test result suggests angioplasty given that lesion is suitable for bypass surgery**	0.03	0.065	5, 6	0.08	0.10	11, 4
Probability that test result suggests angioplasty given that lesion is not suitable for invasive treatment**	0	0.065	5, 6	0.09	0.24	11, 4
Probability that test result suggests bypass surgery given that lesion is suitable for bypass surgery**	0.97	0.87	5, 6	0.87	0.90	11, 4
Probability that test result suggests bypass surgery given that lesion is suitable for angioplasty**	0.14	0.065	5, 6	0.36	0.07	11, 4
Probability that test result suggests bypass surgery given that lesion is not suitable for invasive treatment**	0	0.065	5, 6	0.09	0.29	11, 4

* Range or alternative numbers were used for sensitivity analysis.

† Numbers correspond to references.

‡ Sensitivity was calculated based on the specificity using a summary receiver operating characteristics regression equation available from a meta-analysis.[1]

§ An uninterpretable test result was defined as a technical inadequate test result (e.g., bowel gas for duplex US) or the test could not be performed (e.g., claustrophobia for MR angiography).

‖ Including 5% of patients that had a contraindication for MR angiography.

¶ An indeterminate test result was defined as a technically adequate test result on which no treatment plan could be determined.

** We assumed for both MR angiography and duplex US that the probabilities for assesing the treatment option were independent of location.

†† Probabilities were estimated from a cross-tabulation of treatment plans based on MR angiography and DSA. Because only the margin totals of the cross-tabulation were known it was assumed that the highest proportion of possible agreement between MR angiography and DSA was achieved based on these totals. Criteria for suitability of lesions for angioplasty were iliac artery stenoses and occlusions less than 20 mm in length.

‡‡ Treatment plans based on DSA were compared with treatment plans based on DSA with additional MR angiography. We assumed that the proportion of discrepant treatment plans was equally divided over the other two categories. No criteria for suitability of lesions for angioplasty were reported.

§§ Study was performed with grey-scale duplex US and included the complete spectrum of PAD patients In all patients treatment plans based on duplex US and DSA were compared. No criteria for suitability of lesions for angioplasty were reported.

‖‖ In only 64 out of 112 patients treatment plans of duplex US and DSA were compared. No criteria for suitability of lesions for angioplasty were reported.

The angioplasty procedure always includes an obligatory DSA preceding the procedure. For the baseline analysis, we assumed that a DSA for the diagnostic work-up of PAD and a subsequent angioplasty would be scheduled on different days meaning that information obtained from the DSA would first be discussed by the vascular surgeon and radiologist before proceeding with treatment. In a sensitivity analysis we explored the effect of performing DSA and angioplasty during one procedure. Note that the definite choice of treatment is unknown prior to DSA.

Treatment and follow-up Probabilities for location of disease and suitability for treatment were available from a Vascular Registry.[9] There were more suprainguinal than infrainguinal lesions and a higher proportion of suprainguinal lesions was suitable for angioplasty compared with infrainguinal lesions (Table 2).[9,13] Of all patients undergoing diagnostic work-up for PAD we assumed that 95% of the patients would be eligible for invasive treatment after the work-up. Patency rates were available from published meta-analyses.[14-16] Probabilities and rates are presented in Table 2.[9,13-18]

Health-related quality of life Quality adjusted life years (QALYs) were calculated as the sum of health values for each state multiplied by the time spent in those health states. Health-related quality of life was expressed as health values ranging from 0 (dead) to 1 (full health). The health values used are presented in Table 3.[19-22]

Table 2 – True disease status and patency rates for patients with intermittent claudication

Variable	Base-case value	Range*	Source†
True disease status			
Probability of suprainguinal disease	0.56	0.12-0.85	9
Probability that a suprainguinal lesion is suitable for angioplasty‡	0.51	0.43-0.59, 0.74	9, 13
Probability that a infrainguinal lesions is suitable for angioplasty‡	0.18	0.11-0.25, 0.50	9, 13
Probability that lesions are suitable for invasive treatment	0.95	0.85	9, 6
Annual rate of progression of invasively untreated disease‖	0.20	-	17
Annual rate of changing diseased location¶	0.15	-	18
Two-year patency			
Aortic bifurcation bypass surgery	0.95	-	15
Angioplasty of suprainguinal lesions			
Stenosis	0.84	-	16
Occlusion	0.67	-	16
Autologous vein	0.89	-	14
PTFE, above-knee anastomosis	0.86	-	14
PTFE, below-knee anastomosis	0.80	-	14
Angioplasty of infrainguinal lesions			
Stenosis	0.75	-	14
Occlusion	0.46	-	14

PTFE: polytetrafluoroethylene

* Range or alternative numbers were used for sensitivity analysis.

† Numbers correspond to references.

‡ A lesion was considered suitable for angioplasty if there was one focal stenosis between 50-99% above the knee joint.

§ In the Markov model, analyzing treatment and follow-up, it was assumed that 5% of the lesions was not suitable for invasive treatment.

‖ For patients with lesions suitable for angioplasty who incorrectly participated in the supervised exercise program it was assumed that the proportion of lesions suitable for angioplasty decreased over time, and, consequently the proportion of lesions suitable for bypass surgery increased, which equaled the rate of progression of disease.

¶ For patients that entered the supervised exercise program it was assumed that the predominant disease location could change over time as long as the patient was not treated invasively, and it was assumed that the rate of changing diseased location equaled the rate of developing symptoms in the contralateral limb.

Costs Costs were divided into medical costs including costs of diagnostic tests, treatment and follow-up, and non-medical costs including transportation costs and patient-time spent on diagnostic testing, interventions, and follow-up visits. All costs were converted to 1998 US dollars by using the Consumer Price Index (United States Bureau of Labor Statistics Data). We used Medicare reimbursement rates, which include both technical and professional fees, for the costs of MR angiography, duplex US, and DSA (Table 3). Extra costs for inefficient use of personnel, equipment, and housing in the case of an incorrectly scheduled angioplasty procedure were available from a cost-effectiveness analysis.[23] The costs for invasive treatment were available from a cost-identification analysis in patients with PAD[24], except for the costs of angioplasty with selective stent placement for suprainguinal disease[25].

Cost-effectiveness analyses

The principal outcomes in the model were QALYs and lifetime costs and both were discounted at an annual rate of 3%.[26] QALYs and lifetime costs for downstream treatment and follow-up of all possible diagnostic outcomes were calculated in the Markov model with first order Monte Carlo simulations of100,000 patients and combined with the costs and effectiveness of the pre-treatment work-up. The time period between pre-treatment work-up and subsequent treatment was assumed to be negligible in comparison to the patients' life expectancy.

Table 3 – Health-related quality of life and costs

Variable	Base-case Value	Range*	Source†
Health values			
Severe intermittent claudication‡	0.71	0.67-0.75	19
Mild intermittent claudication‡	0.79	0.75-0.83	19
Critical limb ischemia‡	0.35	0.15-0.55	20
History of angina pectoris‖	0.90	0.60-1.00	21
Systemic long-term complications after interventions‡‖	0.72	0.60-0.90	22
Costs (US $ 1998)			
MR angiography	574	287 – 861¶	Medicare
Duplex US	243	121 – 365¶	Medicare
Conventional angiography	1,183	1,822**	Medicare
Mortality from vascular interventions	12,758	3,950 – 21,960	24
Complications DSA	7,393	4,100 – 10,690	24
Extra costs for planned but not performed angioplasty††	316	158 – 474	23
Aortic bifurcation bypass surgery	25,790	23,300 –28,300	24
Suprainguinal angioplasty with selective stent placement	8,290	5,600 –11,000	24, 25
Infrainguinal bypass surgery	18,110	15,800 – 20,400	24
Infrainguinal angioplasty	4,480	1,600 – 7,500	24
One year supervised exercise‡‡	4,150	880 –9,500	9

* Range or alternative numbers were used for sensitivity analysis.
† Numbers correspond to references
‡ Health values were EuroQol responses from participants in an exercise program transformed to Time Tradeoff values.
‡ Values were based on Time Trade-off.
‖ These health values were incorporated by assuming a simple multiplicative relation.
¶ Ranges in costs represent 50% and 150% of baseline estimate.
** Inclusive costs of overnight stay in the hospital.
†† Extra costs for one hour of inefficient use of personnel, equipment, and room time were counted if an angioplasty was planned, but not performed. The costs of the planned but not performed angioplasty equaled the costs of an angiography plus the extra costs for inefficient use.
‡‡ Main source of costs was patient time spent on walking.

To determine cost-effectiveness of alternative diagnostic strategies we used incremental cost-effectiveness (CE) ratios. The strategies were ordered according to increasing effectiveness, and (extended) dominated strategies were eliminated. A strategy was considered to be dominated by another strategy if the latter yielded more QALYs at lower costs. A strategy was considered to be extended dominated if another strategy yielded more QALYs and had a lower incremental CE-ratio. Incremental CE ratios were then calculated as the difference in average lifetime costs divided by the difference in average QALYs for one particular strategy compared to the next best strategy.[27] The model was programmed in DATA™ (Decision Analysis by TreeAge, version 3.5.6, Treeage Software Inc., Williamstown, MA, USA).

Base-case analysis The base-case analysis evaluated a cohort of 60-year-old men with a one-year history of severe unilateral claudication, with an initial ankle-brachial index (systolic ankle blood pressure divided by systolic brachial blood pressure) of 0.70, and no history of coronary artery disease. The analysis was done separately for the scenario when angioplasty was the only treatment option (minimally invasive treatment scenario) as well as when both angioplasty and bypass surgery were available (more invasive treatment scenario).

In an additional analysis two other patient cohorts were 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). For patients with a history of coronary artery disease we assumed that the more invasive treatment scenario was not possible, since these patients have high complication rates following bypass surgery.

Sensitivity analysis In one-way sensitivity analyses we varied parameters over a range of plausible values (Table 1). Extensive sensitivity analyses for the treatment and follow-up model were previously performed[9] and our sensitivity analysis therefore focused on diagnostic parameters. We evaluated some of our base-case assumptions and, also, varied the threshold walking distance from 250 m to 175 m (probabilities and health values were adjusted accordingly). Only the most influential and clinically relevant sensitivity analyses were reported in detail.

We also explored the cost-effectiveness of two additional diagnostic strategies for the more invasive treatment scenario. The first strategy was MR angiography in all patients followed by DSA in those requiring bypass surgery in order to plan the operation. The second strategy was duplex US with DSA for planning bypass surgery.

RESULTS

Base-case analysis

Considering the minimally invasive treatment scenario (Table 4) for the

base-case analysis (60-year old men without a history of coronary artery disease), no diagnostic work-up yielded the lowest effectiveness and costs. The incremental CE ratio for MR angiography yielded $35,000/QALY compared with no diagnostic work-up. DSA was the most effective strategy and the incremental CE ratio was $471,000/QALY compared with MR angiography. Under the more invasive treatment scenario (Table 4) DSA was the most effective strategy with an incremental CE ratio of $179,000/QALY compared with no diagnostic work-up. MR angiography and duplex US were both dominated by DSA.

For 40-year-old men the results were quite similar, although the incremental CE ratios decreased. For 70-year-old men with a history of coronary artery disease, only the minimally invasive treatment scenario was considered and MR angiography had an incremental CE ratio of $95,000/QALY. Figure 2 presents the preferred strategy depending on society's willingness-to-pay for the gain in one QALY for the alternative cohorts. For example, for the base-case considering the more invasive treatment scenario (Figure 2B) no diagnostic work-up was preferred for values of society's willingness-to-pay below $179,000/QALY. Above that value DSA was preferred.

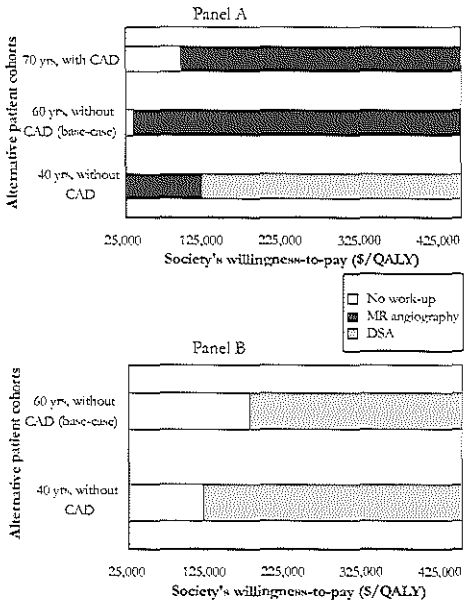

Figure 2 – Preferred strategies for alternative patient cohorts. Panel A represents the minimally invasive treatment scenario and panel B represents the more invasive treatment scenario. The x-axis represents the range in society's willingness-to-pay ($25,000 to $450,000/QALY) and the y-axis represents the different patient cohorts considered. The horizontal bars represent the pre-treatment strategies that are preferred for the indicated society's willingness-to-pay values.
CAD: history of coronary artery disease

Table 4 – Quality adjusted life years, costs, and incremental CE ratios for the base-case analysis

	Minimally invasive treatment scenario			More invasive treatment scenario		
	QALY	Cost ($)	Increm. CE ratios[†]	QALY	Cost ($)	Increm. CE ratios[†]
No diagnostic work-up	6.0606	18,912	-	6.0606	18,912	-
Duplex US	6.1465	22,042	D	6.2002	50,178	D
MR angiography	6.1487	21,959	35,000	6.2136	48,980	D
DSA	6.1498	22,497	471,000	6.2254	48,411	179,000

QALY: Quality adjusted life years
Numbers of incremental CE ratios could be slightly different from calculating based on the numbers in the table because of rounding.
[*] Strategies were ordered on increasing effectiveness (QALYs).
[†] Increm. CE ratios = incremental cost-effectiveness ratios, D = dominated. Incremental CE ratios were calculated compared to the next best strategy after excluding dominated strategies.

Sensitivity analysis

The results were not sensitive to changes in the diagnostic test characteristics, except that using the alternative values for the treatment recommendations by duplex US[4] (Table 2), changed the results in favor of duplex US under the minimally invasive treatment scenario. Duplex US was now the optimal strategy (6.1503 QALY and $21,928) and had an incremental CE ratio of $34,000/QALY.

In a sensitivity analysis we assumed that angioplasty could immediat ely follow DSA (Fig 3) and found that for DSA the QALYs increased by 0.0007 and the costs decreased by $217 but only the incremental CE ratio for DSA under the minimally invasive treatment scenario changed to $195,000/QALY. Also, when we broadened the criteria of suitability for angioplasty for patients with intermittent claudication (0.74 for suprainguinal lesions and 0.50 for infrainguinal lesions, Table 2) the results changed in favor of DSA (Fig 3). Effectiveness and costs for DSA were 6.2449 QALYs and $24,640 for the minimally invasive treatment scenario and 6.3024 QALYs and $40,714 for the more invasive treatment scenario.

By defining severe intermittent claudication as a walking distance less than 175 m (base-case analysis 250 m) the effectiveness increased and the costs decreased. For both the minimally invasive treatment scenario and the more invasive treatment scenario, the incremental CE ratio of DSA increased ($968,000/QALY and $233,000/QALY, respectively).

Finally, we explored the cost-effectiveness of both MR angiography (6.2253 QALYs and $48,587) and duplex US (6.2257 QALYs and $48,374) in combination with DSA for planning bypass surgery for the more invasive treatment scenario and these strategies were similar to DSA. The strategy duplex US with DSA for planning bypass surgery was the optimal strategy with an incremental CE ratio of $179,000/ QALY compared with the no diagnostic work-up strategy.

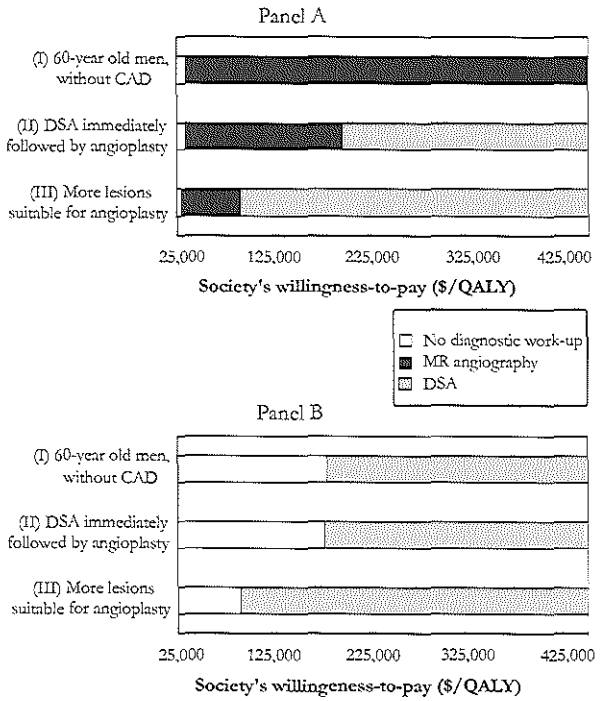

Figure 3 – Most influential and clinically relevant sensitivity analyses. Panel A represents the sensitivity analyses for the minimally invasive treatment scenario and panel B represents the sensitivity analyses for the more invasive treatment scenario. The x-axis represents the range in society's willingness-to-pay ($25,000 to $450,000/QALY) and the y-axis represents the different sensitivity analyses performed. The horizontal bars represent the pre-treatment strategies that are preferred for the indicated society's willingness-to-pay values.
(I) Results of the base case analysis; (II) For a sensitivity analysis we assumed that a DSA for the pre-treatment work-up would immediately be followed by an angioplasty procedure in 90% of the patients; (III) We assumed that more patients with intermittent claudication had lesions suitable for angioplasty (0.74 for suprainguinal and 0.50 for infrainguinal lesions, Table 2).
CAD: history of coronary artery disease; BS: planning bypass surgery.

COMMENTS

We found that differences in costs and effectiveness between the various diagnostic imaging strategies for patients with intermittent claudication were small. Differences between the strategies arise from the differences in costs of the tests, risks of the tests, and the proportion and consequences of false test results, all of which seem important at the time of testing. However, what may seem a large difference at the time of testing becomes relatively small when considering long

term overall outcomes such as lifetime costs and quality adjusted life expectancy. Furthermore, the results were to some extent dependent on the treatment options considered. When treatment was limited to angioplasty MR angiography, duplex US, and DSA yielded similar costs and effectiveness whereas if both angioplasty and bypass surgery were considered as treatment options DSA yielded slightly lower costs and higher effectiveness compared to the other strategies. The reason that the optimal diagnostic strategy depended on the available treatment options can be explained by considering that the consequences of a false diagnostic test result were more influential if the treatment scenario included bypass surgery than if only angioplasty was considered. Also, bypass surgery was more expensive than angioplasty resulting in higher incremental CE ratios for the more invasive treatment scenario.

We found two other studies[28,29] that analyzed the cost-effectiveness of the pre-treatment work-up for PAD. In one study[29] duplex US and DSA were compared and it was concluded that duplex US was not a cost-effective alternative because of its low sensitivity which was confirmed by the results of our study. The other study[28] reported that MR angiography alone or in combination with selective use of DSA might be a cost-effective alternative compared with DSA. Both the inflow and outflow assessment were evaluated in that analysis which was comparable to our analysis in which we evaluated the localization of the lesion and the assessment of the treatment option. Three key differences in their analysis in comparison to ours were that patients with limb-threatening PAD were considered instead of intermittent claudication, they did not consider angioplasty as a possible treatment option, and MR angiography was performed without gadolinium-enhancement.

Rather than performing a clinical trial, we developed a decision model and retrieved data from various literature sources. The use of such secondary data has limitations in that data are not always fully applicable to the question under study. For instance, much of the radiological literature on the diagnostic work-up of PAD has focused on the diagnostic performance of the imaging modalities for arterial segments, whereas in our analysis we estimated the lifetime costs and quality adjusted life expectancy for patients. Using various modeling strategies we were able to integrate the per segment diagnostic performance data to a more meaningful patient level. Also, many studies have been published on treatment recommendations according to MR angiography and duplex US but most of them do not give sufficient detail for use in a decision model. The data for duplex US on treatment recommendations were based on an older study[11] in which no color-guidance was used, implying that the diagnostic performance of duplex US is probably better than our baseline estimate. By using data from a more recent study[4] in the sensitivity analysis, the results of strategies including duplex US improved. Besides, criteria for the suitability of lesions for angioplasty were reported in only one[5] of the quoted studies[4,6,11] and therefore we were unable to

compare the criteria.

Another limitation of decision analysis is that assumptions have to be made to keep the model tractable. We had to make assumptions about outcomes following false test results because not all the consequences are known. In our model all false test results entailed a decrease in quality adjusted life expectancy and/or an increase in costs. Another assumption that may be questionable is that DSA was assumed to be the reference standard. Earlier studies reported[30,31] that MR angiography detected more patent runoff vessels than DSA, which may be important for assessing the feasibility of bypass surgery and the optimal distal anastomosis. Also the definition of severe intermittent claudication (walking distance less than 250 m) may be arbitrary. We found that using a more stringent cutoff value (175 m) did not change the conclusions.

In our base-case analysis we assumed that a DSA for the pre-treatment work-up of PAD and a subsequent angioplasty would be scheduled as separate sessions. In clinical practice, however, diagnostic DSA and angioplasty may be planned as one procedure, even though the definite choice of treatment is unknown prior to the procedure. If the lesion is not suitable for angioplasty, the procedure will be terminated after performing the diagnostic DSA and, depending on the flexibility of the work process the angiography room may remain unused. This implies inefficient use of personnel, equipment, and room time, thereby increasing costs. The advantages of combining it in one procedure are that the patient is only exposed once to the risks of a percutaneous procedure and it is cost saving due to more efficient use of room time, personnel, and other resources. In a sensitivity analysis we assumed that 10% of the patients needed a second session for an angioplasty. The cost-savings of performing the procedures in one session outweighed the cost-increase of inefficient use of personnel, equipment, and room time and there was a slight increase in effectiveness suggesting that if a diagnostic DSA and an angioplasty can be planned as one procedure this is preferred over initial non-invasive imaging.

The incremental CE ratios in our baseline analysis ranged from $35,000 to $471,000/QALY. Society's willingness-to-pay for health care interventions is unknown and depends on many aspects like for instance the health care system and economic situation in a country. In the literature a wide range of estimates for society's willingness-to-pay have been published. A study that determined estimates for society's willingness-to-pay by converting value-of-life estimates available from various fields to dollars per QALY demonstrated a range of $25,000 to $450,000/QALY (1998 US dollars, rounded).[32] However, in the medical literature the generally reported range varies between $10,000 and $100,000 per QALY.[33]

In the current analysis we evaluated MR angiography, duplex US, and DSA, three imaging modalities that are currently widely used for the diagnostic work-up of PAD. However, not every center has all three modalities at its disposition. The

development of new radiological techniques is ongoing and multidetector spiral CT angiography might be a new alternative for the work-up of PAD.[34-36] It is often used for the diagnostic work-up of abdominal aortic aneurysms and has been shown to have an excellent diagnostic accuracy with relatively low costs ($300, 1997).[37] The currently developed decision model may in the future be useful in comparing CT angiography with the existing imaging modalities as more information becomes available regarding sensitivity and specificity and the effect on the treatment plan, prognosis, quality of life, and costs.

Although we attempted to incorporate all the relevant costs and effects of the diagnostic imaging work-up for patients with intermittent claudication in this cost-effectiveness analysis, this analysis has limitations, as discussed, and presents only one way of looking at the problem. A decision analysis does not make a clinical study superfluous. In fact, we consider the current study a prelude to, rather than a substitution for, a clinical study. Since the differences in costs and effectiveness across diagnostic imaging strategies were small our results suggest that a clinical study should focus on the decision making process and workflow in clinical practice. An appropriate design for such a comparison would be a pragmatic randomized controlled trial in which patients are randomized between available diagnostic imaging and the outcome measures focus on the clinical decision-making process.[38]

In conclusion, the differences across diagnostic imaging strategies for patients with intermittent claudication are small. This implies that a MR angiography or duplex US can replace DSA without substantial loss of effectiveness and a small cost-reduction, especially if minimally invasive treatment options are considered. Furthermore, planning an angioplasty procedure in conjunction with a diagnostic DSA yields a minimal gain in effectiveness and a small cost-reduction.

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5

COST-EFFECTIVENESS OF DIAGNOSTIC IMAGING WORK-UP AND TREATMENT FOR PATIENTS WITH INTERMITTENT CLAUDICATION IN THE NETHERLANDS

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ABSTRACT

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. Diagnostic work-up options included magnetic resonance (MR) angiography, 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 diagnostic imaging work-up and treatment options. A conservative strategy with no diagnostic 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 the same treatment options was small (largest difference: 0.0252 QALYs and €451). MR angiography in combination with angioplasty (6.1487 QALYs and €8,556) 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 MR angiography in combination with angioplasty.

Conclusion The results suggest that the diagnostic imaging work-up with non-invasive imaging modalities can replace DSA for the work-up of patients with intermittent claudication. Management strategies including angioplasty are cost-effective in the Netherlands and strategies with bypass surgery are more effective but against a very high cost.

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 (MR) angiography, and duplex ultrasound (US). DSA is considered to be the reference ("gold") standard but involves small risks[2,3] and is expensive compared with non-invasive tests. MR angiography is nearly as accurate as DSA but has contra-indications such as claustrophobia and the presence of a pacemaker whereas duplex US 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 graft failure rate 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 diagnostic 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 analysis 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[13] and treatment strategies[14]. The model consisted of a Markov Monte Carlo model that was embedded in a larger decision-analytic model. 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 MR angiography, color-guided duplex US, and intraarterial DSA. DSA was the reference standard in our analysis and we assumed that MR angiography and duplex US 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, percutaneous transluminal angioplasty with selective stent placement (PTA), or bypass surgery (BS). Patients that entered a supervised exercise program 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. Of all patients, 95% had lesions suitable for invasive treatment and the remainder of the patients entered a supervised exercise program. Lesions were considered suitable for angioplasty if there was one focal stenosis between 50-99% above the knee joint. Bypass surgery may be considered if angioplasty was not feasible. 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. 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) MR angiography in all patients with angioplasty for patients with suitable lesions otherwise supervised exercise ["MRA+PTA/EX"]; (2) MR angiography in all patients with angioplasty for patients with suitable lesions otherwise bypass surgery ["MRA+PTA/BS/EX"]; (3) duplex US in all patients with angioplasty for patients with suitable lesions otherwise supervised exercise ["DUS+PTA/EX"]; (4) duplex US in all patients with angioplasty for patients with suitable lesions otherwise bypass surgery ["DUS+PTA/BS/EX"]; (5) DSA in all patients with angioplasty for patients with suitable lesions otherwise supervised exercise ["DSA+PTA/EX"]; (6) DSA in all patients with angioplasty for patients with suitable lesions otherwise bypass surgery ["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.

Data sources

Costs The cost calculations were performed according to the Dutch guidelines for cost calculations in health care[15] 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.[16] 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).[15] Costs for complications of invasive treatments and costs for follow-up after amputation of the limb were based on literature data.[17,18] 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 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 (Appendix, Table A).[2,3,19] For gadolinium-enhanced MR angiography and color-guided duplex US 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 MR angiography and duplex US to detect a stenosis of more than 50% were available from a meta-analysis (Appendix, Table A).[4] Also the test characteristics of MR angiography and duplex US to assess the treatment option (angioplasty vs bypass surgery vs lesions not suitable for invasive treatment) were available from the literature.[20-23] Data on equivocal MR angiography and duplex US results were available from the literature.[4,20,21,23,24]

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, femoro-popliteal bypass surgery, and femoro-infrapopliteal bypass surgery. Most lesions being treated invasively for the first time were located suprainguinally and more suprainguinal lesions were suitable for angioplasty than infrainguinal lesions.[14,25] Risk of mortality and systemic complications for vascular interventions were available from the literature.[5,6,26-28] For patency estimates we used published meta-analyses[5-7] and in the model a time-dependent graft failure rate was used. In Table B (Appendix) 2-year patency estimates are shown as an illustration. During follow-up patients could develop critical limb ischemia and/or symptoms in the contralateral limb for which incidence were available from the literature.[14,29-33] Also age and gender adjusted estimates for the natural mortality rate and the excess mortality due to PAD were incorporated in the model.[30,31,34-36]

Health-related quality of life The life expectancy of patients was adjusted with the quality of life. Mostly, health-related quality of life is measured on a scale from 0 (death) to 1 (perfect health). For intermittent claudication the health values were available from patients that participated in a supervised exercise program and the obtained responses to the EuroQol were transformed to time tradeoff values.[37]

For patients with critical limb ischemia or an amputation time tradeoff values were used from the literature.[38] Health values for systemic complications and angina pectoris were incorporated by using a simple multiplicative relation.[39] Actual values are presented in Table C in the Appendix.

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

Variable	Baseline value (Alternative values)	Source	United States costs (1998 $)§§
Interventions			
MR angiography	494	UHM	574
Duplex US	184	UHM	243
Intraarterial DSA*	1,062 (605)	UHM	1,183‖‖
Planned angioplasty and stopped after angiography†	357	UHM	316
Angioplasty for suprainguinal lesions	1,934	UHM	8,290
Angioplasty for infrainguinal lesions	1,655	UHM	4,580
Bypass surgery for suprainguinal lesions	10,179	UHM	25,788
Bypass surgery for infrainguinal lesions	5,452	UHM	18,108
Amputation above the knee	9,817	UHM	15,830
Amputation below the knee	9,379	UHM	8,550
Supervised exercise program, time costs per year	1,267	14	4,147
Complications			
DSA‡	666	Assumption	7,393
Systemic complications§	6,894	17	10,723
Mortality from vascular interventions‖	2,286	Assumption	12,758
Follow-up			
Long-term systemic complications¶	1,781	17	11,832
Follow-up visit including office visit, duplex US and ABI measurement	298	UHM	392
Follow-up after amputation of the limb			
First year**	45,225	18‡‡	¶¶
Subsequent years††	11,079	18‡‡	¶¶

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 (2 patients returned home after a couple of hours 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 dying from vascular procedures were assumed to equal the costs of two days of admission at an intensive care unit.

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

** 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[18] 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.

‖‖ In the United States a DSA is usually performed as an outpatient procedure.

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

Cost-effectiveness analysis

Our primary outcome measures were quality-adjusted life years (QALYs) and lifetime costs (both discounted at 3%)[40] and management strategies were ordered by increasing QALYs. 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.

The baseline analysis evaluated a 60-year-old cohort of 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, USA). 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.[14]

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 ("Notest+EX") strategy was the least effective and least costly (6.0606 QALYs and €6,793). The strategy "MRA+PTA/EX" had an incremental CE ratio of €20,000/QALY compared with the conservative strategy and the strategy "DSA+PTA/BS/EX" had an incremental CE ratio of €131,000/QALY compared with "MRA+PTA/EX". All other management strategies were inferior by (extended) dominance (Table 2). 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.

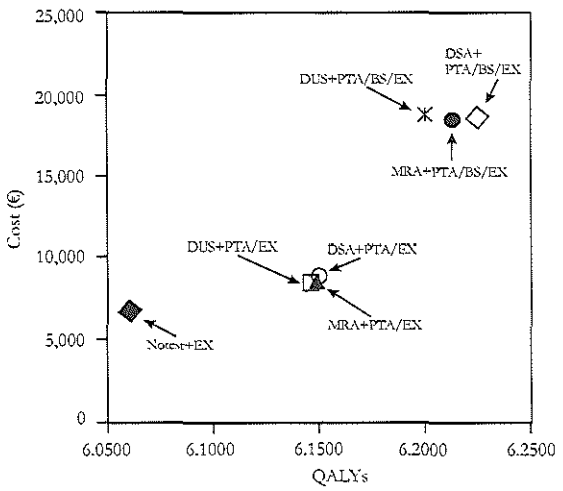

Figure 1 – Quality adjusted life years (QALYs) vs. lifetime costs for the base-case analysis

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 "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 MR angiography. 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 MR angiography to €544 and to €115,000/QALY if the costs of MR angiography were assumed to be 150% that of baseline (€741). The results were not sensitive for lower costs of MR angiography: the incremental CE ratio decreased to €17,000/QALY if MR angiography cost €247. Using alternative estimates for the treatment recommendations made by duplex US (Table A, Appendix), "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 B Appendix). 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: €1,197 to €1,243) but decreased for management strategies with both angioplasty and bypass surgery (range of decrease: €1,739 to €2,072). The incremental CE ratios of "MRA+PTA/EX" and "DSA+PTA/BS/EX" slightly decreased 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 the first imaging modality ("DSA+PTA/EX" and "DSA+PTA/BS/EX", respectively). On the other hand, the incremental CE ratios and the 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".

Table 2 – 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	6,793	-
DUS+PTA/EX†	6.1465	8,546	ED
MRA+PTA/EX†	6.1487	8,566	20,138
DSA+PTA/EX†	6.1498	8,997	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 = 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.

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 included also 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 MR angiography or duplex US was small. Apparently, the diagnostic work-up had minor influence on the cost-effectiveness.

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. 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 team and the workflow allow it that a diagnostic DSA can be planned 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.

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[13] but can be questioned since some studies reported that MR angiography yielded better results in the detection of patent runoff vessels than DSA.[41,42]

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.[13] The incremental CE ratio for MR angiography 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 MR angiography with angioplasty as

treatment option could be calculated from the figures presented in that article and 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.[43] 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)[44] is considered acceptable whereas lung transplantation[45] 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.

The development of new techniques for the diagnostic imaging work-up and treatment for patients with PAD is ongoing. Potential new imaging modalities are multi-detector computed tomography angiography[46-48], MR angiography with blood pool agents[49], or DSA with carbon dioxide[50]. These new imaging modalities would be cost-effective compared with established imaging modalities like MR angiography and DSA if the costs would be low and the diagnostic accuracy reasonable.[51] Endovascular devices are currently being developed to combine the advantages of both percutaneous interventions (low risk) and bypass surgery (higher patency rates). For suprainguinal disease angioplasty with selective stent placement has already been implemented in clinical practice, as considered in our analysis.[52] Endovascular devices for infrainguinal disease are under development and preliminary results show 1-year primary patency rates of 63%[53] and 79%[54]. With those reported patency rates a new device could potentially be cost-effective compared with angioplasty or bypass surgery.[55]

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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APPENDIX

Table A, B, and C contain the data-sources used for the cost-effectiveness analysis.

Table A – Test characteristics of imaging modalities

Variable	Base-case (range or alternative value)*	Source
MR angiography		
Sensitivity (stenosis ≥ 50%)	0.98 (0.96 - 0.99)	4
Additional work-up with DSA for equivocal MR angiography results	0.09 (0.06 – 0.14)	4, 20, 21
Probability that MR angiography result suggests angioplasty given that lesion is suitable for angioplasty	0.79 (0.87)	20, 21
Probability that MR angiography result suggests angioplasty given that lesion is suitable for bypass surgery	0.03 (0.065)	20, 21
Probability that MR angiography result suggests angioplasty given that lesion is not suitable for invasive treatment	0 (0.065)	20, 21
Probability that MR angiography result suggests bypass surgery given that lesion is suitable for bypass surgery	0.97 (0.87)	20, 21
Probability that MR angiography result suggests bypass surgery given that lesion is suitable for angioplasty	0.14 (0.65)	20, 21
Probability that MR angiography result suggests bypass surgery given that lesion is not suitable for invasive treatment	0 (0.065)	20, 21
Duplex US		
Sensitivity (stenosis ≥ 50%))	0.88 (0.84 –0.91)	4
Additional work-up with DSA for equivocal duplex US results	0.23 (0.08 – 0.37)	4, 23, 24
Probability that duplex US result suggests angioplasty given that lesion is suitable for angioplasty	0.60 (0.93)	22, 23
Probability that duplex US result suggests angioplasty given that lesion is suitable for bypass surgery	0.08 (0.10)	22, 23
Probability that duplex US result suggests angioplasty given that lesion is not suitable for invasive treatment	0.09 (0.24)	22, 23
Probability that duplex US result suggests bypass surgery given that lesion is suitable for bypass surgery	0.87 (0.90)	22, 23
Probability that duplex US result suggests bypass surgery given that lesion is suitable for angioplasty	0.36 (0.07)	22, 23
Probability that duplex US result suggests bypass surgery given that lesion is not suitable for invasive treatment	0.09 (0.29)	22, 23
DSA		
Major complications	0.03 (0.02 – 0.05)	2
Mortality	$3.3*10^{-4}$ ($2.9 – 16.2*10^{-4}$)	3, 19

* Presented values are probabilities.

Table B – 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)	30, 32, 34-36
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)	26
Infrainguinal angioplasty	0.025 (0 – 0.264) / 0.002 (0 – 0.021)	26
Amputation, Age < 75 / Age ≥ 75	0.098 (0.077 –0.119) / 0.147 (0.113 – 0.181)	27
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)	26
Infrainguinal angioplasty	0.013 (0.002 – 0.110)	26
Amputation	0.38 (0.377 – 0.383)	28
2-year patency in patients with intermittent claudication		
Aortic bifurcation grafts	0.95	6
Supminguinal 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)	14
For subsequent interventions with previously suprainguinal disease	0.31 (0.13 – 0.49)	14
For subsequent interventions with previously infrainguinal disease	0.17 (0.09 – 0.25)	14
Suitability for angioplasty, claudication		
Suprainguinal disease, first intervention	0.51 (0.74)	14, 25
Suprainguinal disease, subsequent interventions	0.33 (0.74)	14, 25
Infrainguinal disease, first intervention	0.18 (0.50)	14, 25
Infrainguinal disease, subsequent interventions	0.23 (0.50)	14, 25
Critical limb ischemia		
Annual incidence rate, Age < 65 / Age ≥65	0.017 (0 – 0.039) / 0.036 (0 – 0.075)	30-33
Five-week probability following graft failure: pre-treatment symptoms, claudication / critical limb ischemia	0.062 (0 – 0.014) / 0.242 (0.14 – 0.36)	14
Amputation		
Proportion of above knee amputations	0.08 (0.03 – 0.13)	14
Annual incidence rate of progression below-knee to above-knee amputation	0.015 (0 – 0.07)	14
Severe vs mild intermittent claudication		
Relative risk of severe intermittent claudication after stopping exercise	5.81 (1.8 – 18.5)	14
Relative risk of severe intermittent claudication after graft failure	1.36 (0.96 – 1.92	14
Contralateral symptoms		
Mean annual rate	0.149	29

PFTE: 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

Table C – Health-related quality of life values

Variable	Base-case (range)	Source
Asymptomatic or mild intermittent claudication	0.79 (0.75 – 0.83)	37
Severe intermittent claudication	0.71 (0.67 – 0.75)	37
Critical limb ischemia	0.35 (0.15 – 0.55)	38
Above knee amputation	0.20 (0.00 – 0.40)	38
Below knee amputation	0.61 (0.41 – 0.81)	38
Systemic complications	0.72 (0.60 – 0.90)	39
Angina pectoris	0.90 (0.60 – 1.00)	39

6

TARGETS FOR A NEW DIAGNOSTIC IMAGING MODALITY IN THE WORK-UP OF PATIENTS WITH INTERMITTENT CLAUDICATION

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ABSTRACT

Background The development of new imaging modalities in the work-up of peripheral arterial disease is ongoing and the cost-effectiveness of these new modalities cannot yet be determined since parameters such as sensitivity and costs are unknown in the early development of new modalities.

Purpose To determine target values for a new imaging modality in the work-up of patients with intermittent claudication that would make a new modality cost-effective compared with magnetic resonance (MR) angiography.

Methods A decision model was used to compare the (societal) cost-effectiveness of a new imaging modality compared with MR angiography. Main outcome measures were quality adjusted life years (QALYs) and lifetime costs. By threshold analysis for a given willingness-to-pay per QALY, target values for costs, sensitivity, and the proportion requiring additional work-up with intraarterial digital subtraction angiography for equivocal results of a new modality were determined. The base case evaluated 60-year-old men with severe intermittent claudication and assumed a cost-effectiveness threshold of $100,000/QALY. Results were presented for the situation in which invasive treatment was limited to angioplasty and for the situation in which both angioplasty and bypass surgery were available for complaints of intermittent claudication.

Results If treatment was limited to angioplasty a new imaging modality would be cost-effective if the costs were $300 and sensitivity was 85% even if up to 35% of patients needed additional work-up. When both angioplasty and bypass surgery were considered as treatment options a new imaging modality would be cost-effective if the costs were $300, 20% of patients required additional work-up, and the sensitivity was above 94%.

Conclusion The target values for a new imaging modality for patients with intermittent claudication are probably attainable for imaging modalities under development.

INTRODUCTION

The development of new diagnostic imaging modalities for the evaluation of peripheral arterial disease (PAD) is ongoing. Intraarterial digital subtraction angiography (DSA) has traditionally been used as the sole pre-interventional imaging modality. It is still considered as the gold standard and has a small risk of mortality.[1,2] In the 1980s duplex ultrasound was introduced into clinical practice.[3,4] The addition of color-guidance to this non-invasive modality improved the diagnostic accuracy[5] and US became a useful diagnostic tool that potentially could replace part of the DSAs performed.[6] In the early 1990s magnetic resonance (MR) angiography was developed for the work-up of PAD.[7-9] It is minimally invasive and, with gadolinium-enhancement it is highly accurate.[10-12] MR angiography can be used as the sole imaging modality in planning treatment for PAD.[13-15]

Computed tomography (CT) angiography has been recently developed as a potential diagnostic imaging modality for PAD. The preliminary results of studies evaluating CT angiography are promising.[16-18] Also other alternatives like MR angiography with blood pool agents[19], MR angiography[20] or DSA with carbon dioxide as contrast media[21], or duplex ultrasound with contrast media[22] have been suggested as new imaging modalities for PAD.

The future role of any of these new imaging modalities is currently only speculative. To determine if a new modality could potentially be cost-effective compared with current practice, the diagnostic accuracy, costs, and complications associated with the modality should be known. In the early development of new technologies these parameters are generally unknown and it is difficult to predict what the exact values for these parameters will be. However, because these values are known for the currently used modalities it is possible to calculate what target values a new modality should meet to be cost-effective compared with the current diagnostic work-up.[23-25] Calculations of this kind could not only focus the development of new modalities in the diagnostic work-up of PAD but also the development of new technologies in health care in general.

The purpose of our study was to set targets for a new imaging modality in the work-up of patients with intermittent claudication to be cost-effective compared with MR angiography.

MATERIALS AND METHODS

Decision model

For the current study we used a decision-analytic model that was developed to evaluate the (societal) cost-effectiveness of diagnostic imaging strategies for the work-up of patients with intermittent claudication.[26] In the model patients presented with severe unilateral intermittent claudication (maximum walking

distance less than 250 m) and all patients had at least one significant stenosis (diameter reduction of more than 50%). Diagnostic work-up with MR angiography consisted of localizing the lesion (suprainguinal vs infrainguinal) and determining the treatment plan (percutaneous angioplasty vs bypass surgery vs. supervised exercise program). MR angiography could yield equivocal results and in that case an intraarterial DSA was performed. Results were defined as equivocal if the test result was technically inadequate, if the test did not enable formulation of a treatment plan, or the modality could not be performed because of a contra-indication (e.g., claustrophobic patient). A DSA was also performed if no significant lesion was localized. Furthermore, it was recognized that MR angiography may yield incorrect information and, as a result, patients could be treated incorrectly. For percutaneous treatment we assumed that the DSA performed just prior to the procedure would detect such incorrect MR angiography results. If the percutaneous intervention procedure were then stopped, the costs equaled the costs of a DSA plus some extra costs for inefficient use of personnel, housing, and equipment. For bypass surgery we assumed that the incorrect MR angiography result would not be detected unless the incorrect arterial segment was bypassed in which case the patient would still have persistent symptoms and would return to the hospital for DSA followed by repeat intervention.

To reflect clinical practice where bypass surgery is not always considered for complaints of intermittent claudication, two treatment scenarios were evaluated. In the first scenario percutaneous treatment was performed in those patients who had suitable lesions otherwise patients entered a supervised exercise program (minimally invasive treatment scenario). Under the minimally invasive treatment scenario the use of bypass surgery was limited to patients with critical limb ischemia in which angioplasty was not feasible. In the second scenario bypass surgery was performed in those patients who did not have lesions suitable for angioplasty (more invasive treatment scenario). It was assumed that 95% of patients had lesions suitable for invasive treatment, the remainder of patients entered a supervised exercise program.

Data sources

Diagnostic test characteristics The sensitivity for MR angiography with respect to the detection of significant stenoses was available from a meta-analysis.[12] Probabilities for treatment recommendations by MR angiography were derived from the literature.[15] The test characteristics for MR angiography were available from studies that compared MR angiography with DSA as the reference standard.[12,15,27] We incorporated the risks of morbidity and mortality associated with DSA[1,2] and assumed that MR angiography did not involve any risks. A diagnostic DSA was planned in such a way that an angioplasty could immediately follow if a patient had a suitable lesion. The test characteristics of MR angiography

and DSA are presented in Table 1.

Table 1 – Test characteristics for MR angiography and intraarterial DSA*

Parameters	MR angiography		DSA	
	Value	Source	Value	Source
Sensitivity for stenosis > 50%	0.96	12	1	Assumption
Probability that modality depicts angioplasty given that lesion is suitable for angioplasty	0.79	15	1	Assumption
Probability that modality depicts angioplasty given that lesion is suitable for bypass surgery	0.03	15	0	Assumption
Probability that modality depicts angioplasty given that lesion is not suitable for invasive treatment	0	15	0	Assumption
Probability that modality depicts bypass surgery given that lesion is suitable for bypass surgery	0.97	15	1	Assumption
Probability that modality depicts bypass surgery given that lesion is suitable for angioplasty	0.14	15	0	Assumption
Probability that modality depicts bypass surgery given that lesion is not suitable for invasive treatment	0	15	0	Assumption
Morbidity	0	Assumption	0.03	2
Mortality	0	Assumption	$3.3*10^{-4}$	1
Additional diagnostic work-up required	0.07†	12, 15, 27	0	Assumption

* Presented values are probabilities.
† Additional work-up with DSA was required if the modality yielded a technically inadequate result, no treatment plan could be determined on the basis of the test result, or the modality could not be performed because of a contra-indication.

Treatment and follow-up Data on treatment and follow-up were derived from a Monte Carlo Markov model in which 100,000 patients were simulated for each possible diagnostic outcome in the diagnostic model.[26] The Markov model allowed for treatment of recurrent symptoms and symptoms involving the contralateral limb. Lesions were predominantly located suprainguinal or infrainguinal (56% vs 44%, respectively), and 51% of the suprainguinal lesions were suitable for percutaneous treatment vs. 18% of the infrainguinal lesions.[28] Treatment for suprainguinal lesions consisted of angioplasty with selective stent placement and aortic bifurcation surgery. Treatment for infrainguinal lesions consisted of angioplasty, and femoropopliteal or femoro-infrapopliteal bypass surgery. Patency rates were available from published meta-analyses.[29-31] The annual incidence rate of critical limb ischemia was 0.017 for patients younger than 65 years[32] and 0.036 for patients of 65 years and older.[32-35] An amputation of the limb was performed if treatment for critical limb ischemia failed and three invasive interventions had already been performed on the diseased limb.

Costs Medicare reimbursement rates were used for the costs of MR angiography and DSA and yielded estimates of $574 and $1,183, respectively. Costs for treatment were available from a cost-accounting study that was performed to assess the costs of revascularization procedures for PAD[36] and yielded $25,790 for aortic bifurcation surgery, $8,290 for suprainguinal angioplasty, $18,110 for infrainguinal bypass surgery, and $4,480 for an infrainguinal

angioplasty. The costs of a below knee amputation and above knee amputation were $8,550 and $15,830, respectively (Medicare reimbursement rates). The costs of a supervised exercise program yielded $4,417 per year and consisted mainly of patient time spent on walking and also costs for control visits in the hospital were included. Extra costs for inefficient use of personnel, housing, and equipment in the case of a planned but not performed angioplasty were estimated to be $316.[37] All costs were converted to 1998 US dollars by using the Consumer Price Index (United States Bureau of Labor Statistics Data).

Health-related quality of life Health values for patients with intermittent claudication were available from a study among participants of an exercise program in the Netherlands.[38] These were derived from responses to the EuroQol-5D transformed to time tradeoff values. The values were 0.79 and 0.71 for patients with no/mild claudication and severe claudication, respectively. For patients with critical limb ischemia the utility was 0.35.[39] Patients with a below knee amputation had a value of 0.61 whereas patients with an above knee amputation had value of 0.20.[39] The health values for critical limb ischemia and amputation were based on time tradeoff estimates.

Determination of thresholds

Cost-effectiveness analysis was used to determine if a new modality would be cost-effective compared with MR angiography. The lifetime costs and quality-adjusted life years (QALYs) were calculated (discount rate 3%)[40] and a strategy was considered to be cost-effective if the additional cost per QALY did not exceed society's willingness-to-pay. For the analyses we varied the cost-effectiveness threshold from $50,000 to $250,000 per QALY gained and we used a threshold of $100,000 per QALY gained for the baseline analysis.

For the calculation of the target values we used net health benefits (NHB).[41] For each strategy the NHB was calculated using the following formula: QALYs – lifetime costs/society's willingness-to-pay for the gain of one additional QALY. By applying our criteria of being cost-effective, the strategy with the highest NHB was the most cost-effective strategy. In essence, the use of NHB is equivalent to the use of incremental cost-effectiveness ratios except that society's willingness-to-pay is incorporated explicitly whereas using incremental cost-effectiveness ratios society's willingness-to-pay is considered after the results are obtained. Strategies that yielded similar NHB were considered equivalent in terms of cost-effectiveness.

Based on the analysis, we determined what combinations of costs of the modality, sensitivity, and proportion of patients requiring additional work-up with DSA would be required for the new modality to be cost-effective compared with MR angiography. To determine these thresholds for a new imaging modality we had to make assumptions on the risks involved and the treatment recommendations by the new modality. For the risk of mortality and morbidity of a new modality we assumed that it equaled the risks that are associated with the use

of low-osmolality contrast media ($9.0*10^{-6}$ and $3.1*10^{-4}$, respectively).[42] Furthermore, the probabilities for treatment recommendations by a new imaging modality were assumed to be the same as for MR angiography (Table 1). For a sensitivity analyses we assumed that the probabilities for the treatment recommendations by a new modality were the same as for duplex ultrasound or DSA.[43]

Analyses The base-case analysis evaluated cohorts of 60-year-old men with symptoms of severe unilateral claudication for one year, an ankle-brachial index of 0.70, and no history of coronary artery disease. Target values for a new imaging modality were determined for both the minimally and more invasive treatment scenario. Two other patient cohorts were considered: 40-year-old men (other characteristics similar to the base-case), and 70-year-old men with a history of coronary artery disease (other characteristics similar to the base-case). For patients with a history of coronary artery disease it was assumed that bypass surgery could only be performed if the patient developed critical limb ischemia. In a sensitivity analysis the target criteria for a new imaging modality were determined for which it would be cost-effective compared with DSA.

RESULTS

Minimally invasive treatment scenario

Using a societal willingness-to-pay of $100,000 per QALY, a new imaging modality was equivalent in terms of cost-effectiveness with MR angiography if the cost of the modality was $420, the sensitivity was 90%, and 20% of the patients required additional work-up. Under these conditions the strategy with the new imaging modality yielded 6.1490 QALYs at a cost of $21,965 whereas MR angiography yielded 6.1487 QALYs at a cost of $21,942.

Figure 1 presents the target values for cost and sensitivity of a new modality that would make it cost-effective compared with MR angiography. For example, if the cost of a new modality would be $300 or less and the sensitivity at least 85% then the new imaging modality would be cost-effective compared with MR angiography even if up to 35% of patients need additional work-up after undergoing the new modality. If the proportion of patients requiring additional work-up with DSA decreases, a higher cost for the new modality is acceptable.

More invasive treatment scenario

The new imaging modality was equivalent in terms of cost-effectiveness with MR angiography if the costs were $673, sensitivity was 95%, and 20% of the patients required an additional DSA. Under these conditions the strategy with a new imaging modality yielded 6.2151 QALYs at a cost of $49,102 and the MR angiography strategy yielded 6.2137 QALYs at a cost of $48,965. The target values

for the costs and sensitivity of a new imaging modality are presented in Figure 2. If, for example, a new modality cost only $300 and 20% of patients require an additional DSA then the new modality would still need to have a sensitivity of 94% or more to be cost-effective compared with MR angiography.

Figure 1

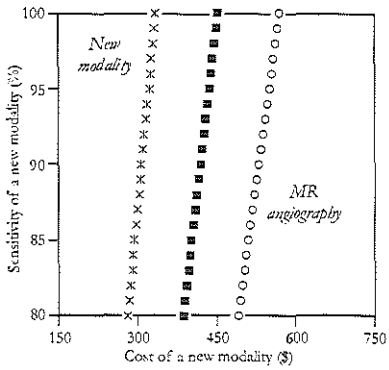
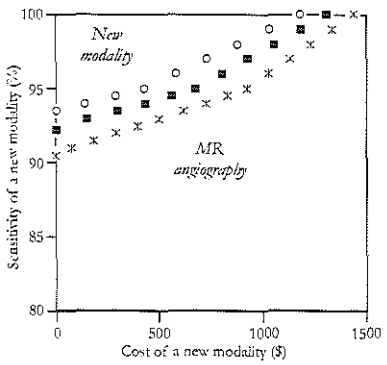


Figure 2



Figures 1 and 2 – Target values for costs and sensitivity of a new imaging modality for the minimally invasive treatment scenario (left panel) and for the more invasive treatment scenario (right panel) with a threshold for society's willingness-to-pay of $100,000 per QALY gained. Lines represent combinations of costs and sensitivity that would make a new modality cost-effective compared with MR angiography depending on the proportion of patients that would require additional work-up: 35% (*), 20% (■) and 5% (O). A new modality would be cost-effective compared to MR angiography if the combination of costs and sensitivity of a new modality would fall to the left of the line. If, however, the combination of costs and sensitivity of a new modality would fall to the right of the line then MR angiography would be more cost-effective.

Sensitivity analysis

The target values for a new imaging modality did not change substantially if society's willingness-to-pay was varied (Table 2). For 40-year-old men the target criterion for the cost of a new imaging modality was more lenient whereas the target criterion for 70-year-old men with a history of coronary artery disease was stricter (only the minimally invasive treatment scenario was considered). If it was assumed that the capabilities of a new imaging modality in determining the treatment plan were the same as duplex ultrasound then the target values for a new imaging modality were more strict (minimally invasive treatment scenario) or a new imaging modality would not be cost-effective compared with MR angiography (more invasive treatment scenario). Assuming that a new imaging modality would have the same capabilities in planning treatment as DSA made the target criteria more lenient (Table 2).

In a sensitivity analysis we compared a new imaging modality with DSA (Table 2). For the minimally invasive treatment scenario we found that the target criterion for the cost of a new modality was more lenient. For the more invasive

treatment scenario a new modality would not be cost-effective compared with DSA under the assumptions we made, even not if the sensitivity were 100% and no patients required additional work-up with DSA.

Table 2 – Combinations of target values for a new imaging modality to be cost-effective compared with MR angiography for a threshold of society's willingness-to-pay of $100,000 per QALY gained

	Minimally invasive Treatment scenario			More invasive Treatment scenario		
	Cost ($)	Sensitivity (%)	Additional work-up (%)	Cost ($)	Sensitivity (%)	Additional work-up (%)
Base-case, 60-year-old man with history of CAD	420 551	90 95	20 5	673 729	95 97	20 5
WTP ($/QALY)						
50,000	409	90	20	604	95	20
250,000	454	90	20	877	95	20
40-year old man	495	90	20	836	95	20
70-year old man with history of CAD	367	90	20	NA	NA	NA
Treatment recommendations of new imaging modality similar to duplex ultrasound	0	95	5	NC	NC	NC
Treatment recommendations of new imaging modality similar to DSA	825	90	20	2,357	95	20
New imaging modality compared with DSA	584	90	20	NC	NC	NC

CAD: coronary artery disease
WTP: society's willingness-to-pay for the gain in one QALY
NA: not applicable; for patients with a history of coronary artery disease bypass surgery was not considered.
NC: not cost-effective; under the assumptions we made for a new imaging modality a new modality would not be cost-effective, even not when it was assumed that there were no costs involved, sensitivity was 100% and no additional DSAs for equivocal test result were required.

DISCUSSION

In the current study we present target values for a hypothetical new imaging modality in the pre-treatment work-up of patients with intermittent claudication. When we compared a new imaging modality to MR angiography as the current work-up the target values found seemed reasonable to achieve. Compared with DSA the target values for a new imaging modality would be attainable if angioplasty was considered as the only treatment option. Under the assumptions that we made for a new imaging modality (small risks involved and could give incorrect treatment recommendations), DSA would always be more cost-effective than a new imaging modality if both angioplasty and bypass surgery were considered as treatment options. For the development of new imaging modalities, it is important that the new modality has a reasonably low cost and a reasonable to high sensitivity.

Our study was limited by the fact that we used various data sources and made a number of assumptions to keep the model tractable. These limitations are inherent to decision models and cost-effectiveness analyses. For instance, in our model we considered DSA as the reference ("gold") standard, a precedent well established in the literature on the diagnostic work-up of PAD.[12] This implies that new imaging modalities that are potentially better than DSA could not be evaluated with the current model.

Another limitation of the study was that we did not consider regional health care circumstances such as expertise of the radiologists and availability of equipment. In an earlier study it was found that the differences in quality-adjusted life expectancy and lifetime costs between the diagnostic imaging modalities were small[26] and a new imaging modality that would meet the target values would be in the same range. To determine the cost-effectiveness of a new imaging modality that fulfills the target criteria assessed in the current study it may be better to compare the imaging modality with the currently used work-up in a pragmatic empirical setting. Such a comparison could be made with a randomized controlled trial in which patients were randomized between the new imaging modality and the currently used work-up[44] and followed for a certain time. Possible outcome measures would be the quality of life of the patients, costs induced by the imaging work-up including supplementary imaging and treatment, confidence of the physician in the test result, and patients' and/or physicians' preferences for the imaging modalities. This suggested study design can also take into account local expertise, physicians' preferences, and availability of equipment.

Furthermore, it may have been a limitation that we assumed that society's willingness-to-pay (i.e., an amount of money that society is willing to pay for one additional QALY) could be defined. The amount society is willing to pay depends on many variables such as the characteristics of the health care system and the general economy, as well as the decision context. The actual value must remain hypothetical. The range of incremental cost-effectiveness ratios for generally accepted interventions varies between $10,000 to $100,000 per QALY gained.[45] Recently, an attempt was made to estimate society's willingness-to-pay based on converting estimates of value-of-life available from various fields to dollars per QALY gained and a range from $25,000 to $428,000 per QALY (1997 US dollars) was found.[46] In our base-case analysis we used $100,000 per QALY as an estimate for society's willingness-to-pay and the results did not substantially change by varying society's willingness-to-pay ($50,000 to $250,000 per QALY gained).

Currently, several new imaging techniques have been suggested for the work-up of PAD.[16-22] MR angiography with blood pool agents showed a sensitivity of approximately 80% and the costs of the performance of MR angiography with blood pool agents are probably higher than with gadolinium-enhancement since blood pool agents are more expensive than gadolinium. A disadvantage of blood pool agents is that the venous system may overlap on the image, which will limit

the interpretation and require additional work-up. In the current analysis a risk of morbidity and mortality for a new imaging modality was incorporated. To our knowledge no serious adverse events have been reported for the use of blood pool agents, implying that if MR angiography with blood pool agents was considered as the new imaging modality the target values would be slightly more lenient than presented in our results.

Another potentially new imaging modality is multi-detector CT angiography which is simple and fast and is quickly becoming widely available. Preliminary results show that the diagnostic accuracy is high[16-18] with a sensitivity around our estimated target value. The cost of a contrast-enhanced CT angiography was estimated to be $237 (1997, US dollar)[47], which was below the target cost. The ability of CT angiography to image the calcified vessel wall has a disadvantage in that it may interfere with accurate depiction and, thereby, increase the additional work-up. On the other hand, contraindications for CT angiography are rare. A low-osmolality contrast medium is generally used for the performance of CT angiography and a small risk due to use of contrast media was incorporated in our analysis. Long-term risks of radiation were not considered in this analysis but the risk of a one-time exposure is low and the life expectancy of most patients with PAD is shorter than the time required to develop long-term harmful effects of radiation.

In conclusion, the target criteria for a new imaging modality in the diagnostic work-up of patients with intermittent claudication to be cost-effective compared with MR angiography are attainable. Further assessment of the role of new imaging modalities with fairly good preliminary results can be done by performing a pragmatic randomized controlled trial in which the new imaging modality is compared with the current diagnostic imaging work-up.

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7

PATIENT PREFERENCES FOR MR ANGIOGRAPHY, DUPLEX US, AND DSA IN THE WORK-UP OF PERIPHERAL ARTERIAL DISEASE

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ABSTRACT

Purpose: To measure patient preferences for magnetic resonance (MR) angiography, duplex ultrasound (US), and intra-arterial digital subtraction angiography (DSA) for the diagnostic work-up of peripheral arterial disease (PAD).
Materials and methods: Ninety-nine patients who underwent MR angiography, duplex US, and (in 39 cases) DSA were interviewed to assess their preferences for these modalities. A rating scale ranging from 0 (not bothersome at all) to 10 (extremely bothersome) was used. Patients were asked about their willingness-to-pay (Euros, €) and willingness to give up free time for undergoing an "ideal" modality to avoid one of the existing modalities. Means were compared with a pair-wise Wilcoxon signed-rank test.
Results: The average rating scale scores for MR angiography (1.6, $P < .001$) and duplex US (1.7, $P < .001$) were significantly lower than the average score for DSA (4.1). The average willingness-to-pay and willingness to give up time to avoid MR angiography (€12.5 [$P = .03$] and 11.1 hours [$P = .03$], respectively) and duplex US (€11.7 [$P = .02$] and 11.0 hours [$P = .01$], respectively) were significantly lower than that to avoid DSA (€43.9 and 26.1 hours, respectively). No significant differences were found between MR angiography and duplex US.
Conclusion The results suggest that patients prefer MR angiography and duplex US over DSA and that there is no clear preference between MR angiography and duplex US for the diagnostic work-up of PAD.

INTRODUCTION

Currently used imaging modalities for the pre-treatment work-up of peripheral arterial disease (PAD) are magnetic resonance (MR) angiography, duplex ultrasound (US), and intra arterial digital subtraction angiography (DSA) often in combination with percutaneous treatment. The decision as to which imaging modality or combination of imaging modalities to use in clinical practice usually depends on the diagnostic performance, the complications, and the costs of the diagnostic procedures. In a cost-effectiveness analysis, taking these aspects into account, we found that differences in quality adjusted life expectancy and lifetime costs between various pre-treatment work-up strategies for patients with intermittent claudication were small.[1] In this study, however, the amount of discomfort associated with particular imaging modalities experienced by the patient was not taken into account. It may be possible that the level of discomfort between modalities differs and therefore patients' preferences for a particular modality may be a decisive factor. For example, the preference for an imaging modality might be influenced by discomfort such as the confined space for MR angiography, the pressure on the abdomen for duplex US, and the time the patient is confined to bed after a DSA procedure. Moreover, earlier work by Swan et al[2,3] showed that patients experienced more discomfort due to DSA than due to MR angiography.

To incorporate patient preferences for imaging modalities in a cost-effectiveness analysis, these preferences should be measured as either a utility or a cost. A utility is a numerical value measured on a scale from 0 (death) to 1 (full health), which reflects the patient's preference for a certain health state.[4] Commonly used techniques are the visual analogue scale, time tradeoff, and standard gamble. These techniques, however, are mostly applied for the measurement of chronic health states. Discomfort caused by imaging modalities is typically temporary resulting in a short-term change in health state and traditional methods fail to measure these preferences since these assume that health states remain constant over time.

Another way to measure patient preferences is to place a monetary value on gains and losses in utilities, so called contingent valuation.[5,6] The method involves a technique which assesses the willingness-to-pay (WTP) of patients for a certain intervention. WTP can serve as a monetary value for patient preferences. To obtain a time value for patient preferences for imaging modalities we suggest a method which assesses willingness to give up free time (WTGT) for a procedure.

The goal of our study was to assess patient preferences for MR angiography, duplex US, and DSA for the diagnostic work-up of PAD by using a rating scale to assess a 'utility', a WTP technique to assess a monetary value, and a WTGT to assess a time value.

METHODS

Clinical study

One hundred seventeen patients included in an ongoing clinical study on the diagnostic work-up for PAD[7] and recruited between May 1999 and November 2000 were asked to participate in the ancillary patient preference study. Both the clinical and the patient preference study were approved by the institutional review board. Patients were included if they had complaints of intermittent claudication for which they were referred by their vascular surgeon to undergo a duplex US of the arteries of the lower extremity and excluded if they had a contra-indication for MR angiography or did not give informed consent. MR angiography was planned on average 4.2 days before or after the duplex US (range from 11 days before to 21 days after duplex US). If one of these modalities or both indicated the presence of a hemodynamically significant stenosis (diameter reduction > 50%) the patient was referred for a DSA. If based on the MR angiography and duplex US results an intervention was not considered feasible or conservative treatment (e.g., exercise training) was considered appropriate, patients were not referred for DSA. When indicated, DSA was performed on average 55.8 days after the last non-invasive imaging modality (range 11 to 139 days).

Performance of imaging modalities

MR angiography was performed as an outpatient procedure. For all acquisitions a 1.5T MR system with gradient strength of 23 mT/m and rise time of 200 microseconds was used (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). Before the exam the imaging procedure was explained to the patient. Next, the patient was positioned on the scanner table and a venflon was inserted in an antecubital vein. To prevent motion artifacts, sandbags were placed lateral to the lower legs, which were fixated with Velcro straps to a footboard. The patient was instructed to lie still during imaging and the breathhold procedure was practiced (two times a breathhold of about 25 seconds during the procedure). A three-station localizer was obtained for which the patient was placed with feet first in the MR bore and 2-D time-of-flight (TOF) localizer scans were acquired. Subsequently, the table was moved to make upper leg and pelvic scans and, depending on the length of the patient, their head would either stay out of the bore or would be at the edge of the bore. On the basis of the TOF scout scans, one series of 3-D scans without contrast material and one series during administration of contrast material (35 ml gadolinium DPTA, Magnevist, Schering, Berlin, Germany) were made. Patients reported that MR angiography lasted on average 45 minutes which includes changing clothes.

Duplex US with color-guidance (Aloka 2000 or 5000 ultrasonographic scanner, Aloka, Tokyo, Japan) was performed as an outpatient procedure from the infrarenal aorta down to the common femoral arteries. In addition, the femoro-

popliteal arteries were imaged if the vascular surgeon suspected infrainguinal lesions. Patients were placed in a supine position on the table and ultrasound gel was applied to the abdomen. Imaging was done by experienced ultrasound technologists. A convex transducer of 5 MHz was used for the pelvic arteries whereas a 7.5 MHz linear transducer was used for the femoral-popliteal arteries. A 3.5 MHz transducer was used in obese patients and in the presence of bowel gas. Patients were instructed to fast at least 8 hours before the exam. Patients reported that the duplex US procedure lasted on average 67 minutes which includes changing of clothes.

Intra arterial DSA was performed as an inpatient procedure and routine blood tests were done the day before. Extremely anxious patients were premedicated with 50 mg pethidine (intramuscular injection) and 0.25 mg atropine (subcutaneous injection) half an hour before the procedure. The procedures were performed with a Philips Integris V5000 angiography suite (Philips Medical Systems, Best, The Netherlands). The procedure was explained to the patient and he/she was instructed to lie as still as possible. After shaving the groin and applying local anaesthesia, a small incision was made through the skin and a sheath was placed into the common femoral artery through which a catheter was advanced into the aorta and placed proximal to the renal arteries. Contrast medium was injected with a flowrate ranging from 4 to 12 ml/sec for a total of 50 –175 ml Iohexol (Omnipaque, Nycomed Amersham, Eindhoven, The Netherlands, 300 mg I/mL). Eleven DSA procedures were done for a diagnostic work-up only whereas 28 were immediately followed by percutaneous treatment (angioplasty with or without stent placement). At the end of the procedure, after removing all catheters, the physician applied manual pressure to the groin for about 10 minutes to obtain hemostasis. Patients reported that the DSA procedure took, on average, 107 minutes (76 min without and 120 min with subsequent treatment). 72% (28/39) of all patients were admitted for two days whereas 8% (3/39) stayed for only one day.

The interviews

A total of 99 patients completed the interviews. Eighteen patients included in the clinical study were not interviewed due to communication problems between the institutions (n=12), refusal to participate (n=5), or because the telephone interview was impossible due to a hearing problem (n=1). One patient missed his appointment for duplex US and could not answer the questions on duplex US. Furthermore, due to unclear phrasing of some questions we had to rephrase a section of the questionnaire (i.e., the WTGT questions) while the study was ongoing and therefore responses to this part of the questionnaire were not available in eleven patients.

Patients were interviewed by telephone after receiving a questionnaire by mail and were instructed to read the questionnaire in advance. The interviews were performed after the MR angiography and duplex US had taken place. A second

telephone interview was performed in those patients who underwent a DSA. Forty-four of the 99 (44%) patients underwent a DSA. Among these 44 patients we were unable to perform the interview regarding the DSA procedure due to logistical reasons (n=3), because of a stroke (n=1), and because of refusal to participate (n=1).

Although four trained interviewers performed the interviews, the majority, 75.4% (104/138), were performed by one investigator (KV). The duration of the first interview was about 20 minutes, the second about 10 minutes. Four patients answered the questionnaire by postal mail and one patient answered the questionnaire by a proxy-respondent. On average the interviews took place 10.1 days after MR angiography, 10.8 days after duplex US, and 27.4 days after DSA.

Patient preference measures

Patient preferences for the imaging tests were measured with rating scales, willingness-to-pay (WTP) questions, and willingness to give up free time (WTGT) questions (Appendix). In addition, we asked patients if they experienced certain discomfort associated with the imaging modalities. These questions were asked in a closed format (i.e., yes versus no response) and in an open format. Also, in the questionnaire, a short description of each modality, to serve as a reminder, was given and read aloud to each patient during the interview before questions regarding the modalities were asked (Appendix). Since no standard instruments were available for measuring patient preferences for diagnostic tests we used WTP and WTGT techniques with some adjustments for the context.

On the rating scales patients were asked to assign a value to each modality between 0 (not bothersome at all) and 10 (extremely bothersome) that corresponded to their experience of the modality. Before starting the WTP and WTGT questions, patients were asked which imaging modality (MR angiography or duplex US) they would choose if they were to return to the hospital in two years time with the same complaints.

WTP and WTGT questions were introduced with a hypothetical scenario in which the patient has to return to the hospital with the same complaints two years later. First, patients were asked the maximum amount they would be willing to pay to undergo MR angiography instead of duplex US if duplex US were covered by health insurance but MR angiography were not covered. In addition, they were asked the maximum amount they would be willing to pay to undergo duplex US if the reverse situation were to apply. The interviewer repeated the responses if a patient gave inconsistent answers (i.e., patients who answered that they were willing to pay for both MR angiography and duplex US) and patients were given the opportunity to change their initial response, which only occurred in a few cases.

In a second scenario, patients were asked to consider the choice between the modalities they were familiar with (respectively, MR angiography, duplex US, or

DSA) and an imaginary modality, the "Arterial scan". The "Arterial scan" was described as an 'ideal' modality without any discomforts (such as noise or pain) and that the diagnostic information was comparable with the existing modality. Patients were asked how much they were willing to pay and how much free time they were willing to give up to avoid one of the existing imaging modalities. Patients were told that the time they were willing to give up had to be spent in a hospital bed. Patients that had undergone percutaneous treatment were asked to imagine that the "Arterial Scan" also included an immediate treatment.

As an elicitation method for WTP questions we used an array of possible answers (payment card) with four different ranges (€5 – €455, €5 – €227, €11 – €455, and €11 – €227) which were randomly assigned. The original amounts were in Dutch Guilders and converted to Euros (1 Euro (€) = 2.20 Dutch Guilders = 0.92 US dollar, Dutch Bureau of Statistics 2000). The different ranges were used to determine whether the presented values influence the responses of the patients. The array of answers for the WTGT ranged from 30 minutes to two days. Patients were allowed to give responses outside the range (e.g., zero for patients who would not be willing to pay or give up free time).

In addition, some general questions were asked concerning income, education, duration of the procedures, if the patient knew the test results at the time of the interview, and whether the questions were clear. To get a general sense of the patients' current health-related quality of life, patients were asked to fill out an EuroQol-5D once, before the MR angiography procedure was performed. The EuroQol is a self-administered questionnaire consisting of five questions covering the following health dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.[8] Each question has three alternatives which correspond roughly to "no problems", "some problems", and "extreme problems". On the basis of these five questions, 243 different health states can be formed. For each patient a single index value for the EuroQol-5D was calculated based on a published generalized least-squares regression model.[9] A value of 0 corresponds to dead, a value of 1 corresponds to full health, and values lower than 0 correspond to health states that are valued worse than dead. To place the responses on the EuroQol-5D in perspective: 29.3% of the general population aged between 60 to 69 years had some or extreme problems with mobility[10] and a patient reporting only some problems with mobility had a utility of 0.85.[9]

Data analysis

Patient preferences for the modalities were assessed by calculating descriptive statistics for the rating scale, WTP, and WTGT (i.e., mean and standard deviation (SD)). To demonstrate the distribution of responses box and whisker plots were made. Mean values were compared by using a pair-wise Wilcoxon signed-rank test for MR angiography versus duplex US, MR angiography versus DSA, and duplex US versus DSA.

In a linear regression analysis the influence of determinants on the rating scale was assessed. Also the influence of determinants on the WTP and WTGT was determined in the subgroup of patients that were willing to pay or willing to give up time for the "Arterial scan". We assessed the influence of the responses on the questions with a closed format (yes vs no) for MR angiography, duplex us, and DSA. Also, the following determinants were examined: age (years, continuous), gender (male vs female), health-related quality of life (euroqol-5D, continuous), level of education (high vs intermediate vs low), monthly net income (≤ €1364: low vs €1364-2273: intermediate vs ≥ €2273: high), MR angiography and/or duplex us results were known at the time of the interview (yes vs no), angioplasty followed DSA immediately (yes vs no), order of MR angiography and duplex us (first MR angiography vs first duplex us), range of array used for WTP questions (€5 – €455 vs €5 – €227 vs €11 – €455 vs €11 – €227), interviewer (first author vs other), were the questions clear (yes vs other), and the time between the imaging modality and the interview (days, continuous). Because we included about 20 determinants (including all dummy variables) the level of significance for the regression analysis was shifted to $P \leq .003$. Only significant and borderline significant ($.003 < P < .05$)

Table 1 – Patient characteristics (N = 99)

Age in years: mean (SD), range	63 (9), 42 – 79
Gender: N (%) male patients	65 (66)
Fontaine classification: N (%)	
IIA (intermittent claudication, walking distance ≥ 100 m)	66 (65)
IIB (intermittent claudication, walking distance < 100 m)	26 (26)
III (critical limb ischemia)	5 (5)
No intermittent claudication or critical limb ischemia	3 (3)
Net monthly income, N (%)	
Low (< €1364)	42 (42)
Intermediate (€1364 – €2273)	31 (31)
High (> €2273)	8 (8)
Not willing to answer / missing	18 (18)
Education, N (%)	
Low (primary school / Lower vocational education)	46 (47)
Intermediate (Lower general secondary education/ Intermediate vocational training)	36 (36)
High (Higher general education/ Pre-university education/ Higher vocational education/ University)	17 (17)
*EuroQol-5D**	
Utility: mean (SD)	0.62 (0.24)
Some mobility problems in daily life, N (%)	94 (97)
Interviews concerning DSA, N (%)	39 (38)
For diagnostic work-up of PAD without subsequent treatment	11 (28)†
With subsequent percutaneous treatment	28 (72)†
Patients that knew test result at time of interview, N (%)	
MR angiography	36 (36)
Duplex US	55 (56)
MR angiography was performed before duplex US, N (%)	48 (49)
Questions were clear according to the patient, N (%)	
MR angiography and duplex US interview	90 (91)
DSA interview	35 (90)†

SD: standard deviation
PAD: peripheral arterial disease
* Four patients did not fill in the EuroQol-5D or handed in a partly filled in questionnaire.
† As percentage of patients that were interviewed on DSA.

results were reported. All analyses were performed with SPSS for windows (release 9.0.0; SPSS, Chicago, IL).

In subgroup analyses, we assessed if patient preferences were similar in the subgroup of patients that underwent an additional DSA versus those that underwent only MR angiography and duplex US. Furthermore, we analyzed whether patient preferences were similar for patients who underwent DSA without percutaneous intervention vs. patients who underwent DSA combined with percutaneous intervention. Also, we tested whether patient preferences changed if patients with inconsistent responses to the WTP questions (i.e., willing to pay for both MR angiography and duplex US in the direct comparison) were excluded from the analyses.

Since we had no prior knowledge of how the tests would be evaluated by the patients we were unable to perform a formal sample size calculation prior to the study. However, to be able to compare the results of our study with a previous study of Swan et al[2], we decided that the group that underwent DSA in our study would need to be at least the same in size as in their study. In addition, we anticipated that at least one third of the total group of patients would need to undergo DSA.

Results

Patient population

The mean age of the patient group was 63 years and 65 out of 99 patients (66%) were male. The mean health-related quality of life score, as measured with the EuroQol-5D, was 0.62 and 94 out of 97 patients (97%) reported that they had some problems with mobility in daily life. Other patient characteristics are presented in Table 1.

Patients' experiences of the imaging modalities

Table 2 shows the responses to the specific discomfort questions for each imaging modality. The most frequently reported problems were the sound of the MR scanner despite wearing headphones (21/99, 21%), fasting for duplex US (32/98, 32%), pain during DSA (19/39, 49%), and the time confined to bed after the DSA procedure (19/39, 49%). For MR angiography 4 out of 99 patients (4%) reported that they had pain during the procedure whereas 18 out of 98 patients (18%) reported pain during duplex US. In response to an open-ended question, discomfort was reported due to the periods of breathhold during the MR angiography (n=6), the long duration of the duplex US examination (n=4), the insertion of the catheter for the DSA procedure (n=5), and the injection of contrast media during the DSA (n=6).

When patients were asked to consider the choice between MR angiography

and duplex US upon returning to the hospital in two years with the same complaints, 49% (48/98) reported that they had no preference, 41% (40/98) reported that they would choose MR angiography, and 9% (9/98) reported that they would choose duplex US. One (1%) patient reported that he would prefer to undergo both imaging modalities, even after the interviewer explained that this was not an option, because he presumed that undergoing both modalities improved diagnostic accuracy.

Table 2 – Experienced discomfort on MR angiography, duplex US, and DSA

Closed format questions (yes versus no response)	Yes responses, N (%)
MR angiography (N = 99)	
Did you have any pain during magnetic resonance angiography (MRA)?	4 (4)
Did you feel anxious during magnetic resonance angiography (MRA)?	8 (8)
Did you feel enclosed during magnetic resonance angiography (MRA)?	13 (13)
Did the sound (noise) during magnetic resonance angiography (MRA) bother you?	21 (21)
Duplex US (N = 98)	
Did you have any pain during the ultrasound test?	18 (18)
Did you feel anxious during the ultrasound test?	1 (1)
Was it a problem for you that you had to fast for the ultrasound test?	32 (32)
DSA (N=39)	
Did you have any pain during the angiography?	19 (49)
Did you feel anxious during the angiography?	6 (15)
You were admitted to the hospital for the DSA for a day or overnight.	
Was your stay in the hospital unpleasant for you?	4 (10)
After the angiography you had to lie still in bed for several hours to allow the wound in the artery in your groin to heal. Was this unpleasant for you?	19 (49)

Rating scale On a scale from 0 (not bothersome at all) to 10 (extremely bothersome), patients valued MR angiography as 1.6 (SD 2.1), duplex US as 1.7 (SD 2.2), and DSA as 4.1 (SD 3.2) (Fig 1-A). For MR angiography and duplex US the rating scale scores were not significantly different ($P = .53$), but the rating scale score of DSA was significantly higher than that of MR angiography ($P < .001$) as well as that of duplex US ($P < .001$).

Willingness-to-pay (WTP) In the direct comparison of MR angiography with duplex US we found that 40% (39/98) of the patients would be willing to pay for MR angiography and 21% (20/98) would be willing to pay for duplex US. The average WTP for MR angiography and duplex US among patients that were willing to pay was €51.2 (SD €58.2) and €43.9 (SD €55.7), respectively. Including all patients, the average WTPs decreased (Table 3). Of all patients, 16% (16/98) were willing to pay for both MR angiography and duplex US which were considered inconsistent responses. Furthermore, 20 out of 98 patients (20%) were not willing to pay any amount for any test.

The proportion of patients willing to pay to undergo the hypothetical "Arterial scan" instead of MR angiography (26%; 26/99) or duplex US (31%; 30/98) was less than the proportion that were willing to pay to undergo the "Arterial scan" instead of DSA (59%; 23/39). Furthermore, they were willing to

pay less to undergo the "Arterial scan" instead of MR angiography (€47.6; SD €60.3) or duplex US (€38.3; SD €43.8) than to undergo the "Arterial scan" instead of DSA (€74.5; SD €77.7). Including all patients, the average WTP decreased (Fig 1-B, Table 3). The average WTP among all patients to avoid MR angiography and duplex US were not significantly different (P = .43) whereas the average WTP to avoid DSA was higher than that of MR angiography (P = .03) and duplex US (P = .02).

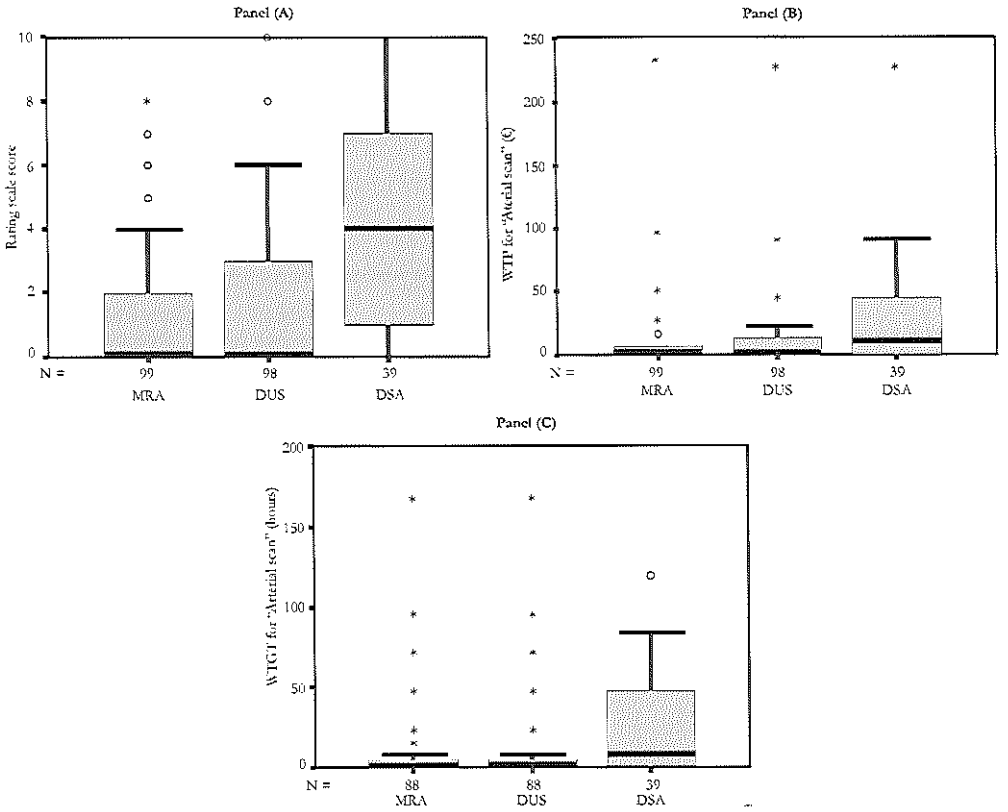

Figure 1 – Box and whisker plots for the rating scale score (A), willingness-to-pay (WTP) (B), and willingness to give up free time (WTGT) (C). The lower and upper line of the box correspond with the first and third quartiles, respectively. The bold line in the middle of the box is the median. The vertical line with 'whiskers' represents values less than 1.5 times the interquartile range from the first and third quartiles. Outliers (O) are defined as more than 1.5 times the interquartile range outside the box and extremes (*) are defined as more than 3 times the interquartile range outside the box. Panel (A) represents the box plots of the rating scale score for MR angiography, duplex US, and DSA with 0 for "not bothersome at all" and 10 for "extremely bothe rsome". Panel (B) represents the box plots of the WTP (€) for the "Arterial scan" instead of MR angiography, duplex US, or DSA. Panel (C) represents the box plots of the WTGT (hours) for the "Arterial scan" instead of MR angiography, duplex US, or DSA. All plots could be interpreted as the higher the box was located the more patients experienced discomfort due to the imaging modality. Relatively more patients experienced discomfort due to DSA than due to MR angiography and duplex US. WTP = willingness-to-pay; WTGT = willingness to give up free time; MRA= magnetic resonance angiography; DUS = duplex ultrasound.

Willingness to give up free time (WTGT) The proportion of patients willing to give up free time to undergo the "Arterial scan" instead of MR angiography (52%; 46/88) or duplex US (51%; 45/88) was less than the proportion that were willing to give up free time to undergo the "Arterial scan" instead of DSA (82%; 32/39). Furthermore, they were willing to give up less free time to undergo the "Arterial scan" instead of MR angiography (21.2 hours; SD 34.2 hours) or duplex US (21.5 hours; SD 34.5 hours) than that they were willing to give up free time to undergo the "Arterial scan" instead of DSA (31.8 hours; SD 30.2 hours). The average WTGT decreased if all patients were included (Fig 1-C, Table 3). The average WTGT among all patients to avoid MR angiography and duplex US were not significantly different (P = .61) whereas the average WTGT to avoid DSA was significantly higher than to avoid MR angiography (P = .03) or duplex US (P = .01).

Table 3 – Responses on WTP and WTGT questions

Question (unit)	Patients willing to give up money or time, Average (SD, N)	All patients, Average (SD, N)	Patients with consistent responses*, Average (SD, N)
WTP for MR angiography instead of duplex US (€)	51.2 (58.2, 39)	20.4 (44.3, 98)	16.4 (40.7, 82)
WTP for duplex US instead of MR angiography (€)	43.9 (55.7, 20)	9.0 (30.4, 98)	4.1 (26.9, 82)
WTP for "Arterial scan" instead of MR angiography (€)	47.6 (60.3, 26)	12.5 (37.1, 99)	8.4 (29.7, 83)
WTP for "Arterial scan" instead of duplex US (€)	38.3 (43.8, 30)	11.7 (29.8, 98)	7.0 (16.9, 82)
WTP for "Arterial scan" instead of DSA (€)	74.5 (77.7, 23)	43.9 (69.8, 39)	44.6 (75.0, 33)
WTGT for "Arterial scan" instead of MR angiography (hours)	21.2 (34.2, 46)	11.1 (26.8, 88)	9.7 (26.1, 73)
WTGT for "Arterial scan" instead of duplex US (hours)	21.5 (34.5, 45)	11.0 (26.8, 88)	8.9 (25.7, 73)
WTGT for "Arterial scan" instead of DSA (hours)	31.8 (30.2, 32)	26.1 (29.9, 39)	26.3 (31.6, 33)

WTP: willingness-to-pay
WTGT: willingness to give up free time
SD: standard deviation
N: number of patients; the number of patients differed per question.
* Patients with inconsistent responses were excluded. Responses of patients were considered inconsistent if they were willing to pay to undergo MR angiography instead of duplex US and for duplex US instead of MR angiography.

Influence of determinants on rating scale, WTP, and WTGT

The closed format questions correlated well with the rating scale score: patients assigned higher scores if they reported that they experienced discomfort due to the imaging modality (Table 4). Patients with a high income were willing to

pay more to avoid DSA than patients with a low income (regression coefficient 186.1, P = .001). This result was not found for the WTP to avoid MR angiography and duplex US. Patients that filled out the WTP questions with the payment card ranging from €5 to €227 were willing to pay more to avoid MR angiography than patients that filled out questionnaires with payment cards with higher ranges. A similar effect was found for duplex US but not all regression coefficients reached significance. Overall, no significant effect was found if the averages of the four ranges of payment cards were compared. Gender, current health-related quality of life, and level of education had a minor influence of borderline significance in some cases (Table 4). All the other examined determinants (not tabulated) had no influence on the preference measures.

Table 4 – Regression coefficients for determinants that had an influence on the rating scale score, WTP, or WTGT. Regression coefficients in bold were (borderline) significantly different from zero.

Determinants		MR angiography			Duplex US			DSA		
		RS	WTP	WTGT	RS	WTP	WTGT	RS	WTP	WTGT
Closed format questions on discomfort										
Pain (yes vs no)		**2.26†**	-44.8	-21.4	**1.77***	-13.8	2.1	**4.06***	52.9	12.5
Anxious (yes vs no)		**4.00***	42.1	1.7	**4.38†**	-	-20.6	**3.00†**	-38.6	15.3
Noise MRA (yes vs no)		**1.99***	-35.3	-11.8	NA	NA	NA	NA	NA	NA
Feeling enclosed MRA (yes vs no)		**3.32***	18.1	-2.9	NA	NA	NA	NA	NA	NA
Patient characteristics										
Gender (male vs female)		0.12	-43.6	-19.7	0.21	-16.3	**-26.8†**	-1.93	18.4	-4.4
Health-related quality of life (EuroQol-5D)		0.28	32.2	-27.5	-0.60	17.8	-24.7	1.33	92.5	**46.2†**
Level of education:	Intermediate vs low	0.70	8.0	1.9	0.76	-12.4	6.6	**2.55†**	31.5	5.8
	High vs low	-0.03	7.8	24.0	0.22	10.1	25.1	0.80	72.7	-9.0
Monthly net income:	Intermediate vs low	0.47	-1.3	21.4	0.04	-0.5	15.7	-0.26	37.7	4.0
	High vs low	1.36	-10.0	-5.3	1.03	15.4	-10.6	0.60	**186.1***	-24.4
	Missing vs low	0.97	20.0	21.2	-0.15	33.9	24.5	-1.26	5.8	17.9
Clinical and interview study characteristics										
Range of WTP§:	€5 - €455 vs €5 - €227		**-73.0†**			**-47.7†**			-52.2	
	€11 - €227 vs €5 - €227	NA	**-70.8†**	NA	NA	-41.9	NA	NA	12.8	NA
	€11 – €455 vs €5 - €227		**-71.7†**			-36.0			29.5	

Presented values are regression coefficients available from a linear regression analysis
RS: rating scale
WTP: willingness-to-pay
WTGT: willingness to give up free time
MRA: magnetic resonance angiography
DUS: duplex ultrasound
NA: not applicable
* P < .003
† .003 < P < .05
§ No significant differences were found between the different versions for MR angiography, duplex US, and DSA

Subgroup analyses

The patient preferences for imaging modalities were not significantly different between the subgroup of patients that underwent a DSA compared with the subgroup of patients that underwent MR angiography and duplex US only. Furthermore, we found no differences in the rating scale scores and responses to

specific discomfort questions for DSA between patients who underwent a diagnostic DSA without percutaneous intervention vs. those who underwent a diagnostic DSA combined with percutaneous intervention. Of the patients who underwent diagnostic DSA without percutaneous intervention, 73% (8/11) were willing to pay whereas 54% (15/28) of the patients who underwent DSA with percutaneous intervention were willing to pay to avoid the DSA. All patients (11/11) who underwent a diagnostic DSA without percutaneous intervention were willing to give up time compared with 75% (21/28) of the patients who underwent DSA with percutaneous intervention. No differences were found in the average WTP and WTGT responses for patients who underwent diagnostic DSA with vs. without percutaneous intervention (results not shown). In another subgroup analysis we excluded all patients with inconsistent responses and found that the average WTP and WTGT responses decreased (Table 3) compared with the analysis in which all patients were considered.

Discussion

We found that patients were both willing to pay less and willing to give up less free time to avoid MR angiography and duplex US compared with avoiding DSA. This was consistent with the results of the rating scale score for which patients responded that they experienced the MR angiography and duplex US as less bothersome than the DSA. It was also consistent with earlier studies which found that patients experienced less discomfort due to MR angiography than due to DSA.[2, 3]

The direct comparison of MR angiography and duplex US showed that half of the patients had no preference for either of the modalities whereas among the other patients more preferred MR angiography over duplex US. Also, patients were willing to pay more to undergo MR angiography instead of duplex US than to undergo duplex US instead of MR angiography and less patients reported pain due to MR angiography than due to duplex US. In the indirect comparison with a hypothetical modality and in the rating scale score, however, we did not find a significant preference for MR angiography over duplex US. This suggests that there is a slight preference for MR angiography over duplex US but that the preference is not as distinct as the preference for the non-invasive modalities over DSA.

For DSA, patients indicated that the pain and time confined to bed after the procedure were especially uncomfortable. Prior to the study we had expected that patients undergoing a percutaneous intervention during the same procedure as the diagnostic DSA would experience more discomfort due to inflation of the balloon, a larger sheath size, and the longer duration of the procedure than patients undergoing a diagnostic DSA without an intervention. This preference was neither

consistent nor significant but we could have missed a small effect because of the limited number of DSAs performed.

The major limitations of our questionnaire were that some of the questions required cognitive abilities and a certain amount of imagination on the part of the patient. In spite of the difficulty of the questions, we did not find that patients with a lower education had more trouble responding. Furthermore, there was no consistent relationship between level of education and the preference measures.

Another limitation was that no direct comparison of DSA with either MR angiography or duplex US could be made because DSA took place, on average, eight weeks after the last non-invasive modality and was performed in only about 40% of the patients. We thought that sending a questionnaire after more than two months to patients who did not undergo a DSA would decrease the overall response rate. Furthermore, we thought that a patient's recollection of their experience eight weeks after MR angiography or duplex US would be less reliable. Therefore, we chose to interview patients twice: a first interview following MR angiography and duplex US, and a second interview if they underwent a DSA. This necessitated an indirect comparison between the three modalities by using a hypothetical imaging modality.

Also the use of WTP questions to assess patient preferences has limitations. First, about 20% of patients were not willing to pay for any test no matter how small the amount. These patients were resistant to paying for health care interventions out of their own pocket. This could be due to the Dutch health insurance system where more than 98% (Dutch Central Bureau of Statistics, 1985-1999) of the population is insured and, compared with other countries, the premium is high while out-of-pocket expenses are low.[11] Second, some patients (ranging from 7% to 25% per question) were unwilling to pay because they preferred the modality which was covered by health insurance over the modality that they had to pay for. With our assumption that their response was zero we may have slightly overestimated the average WTP. Third, some patients responded that they would always like to pay if it involved their health irrespective of which tests were reimbursed by their health insurance and irrespective of which test they preferred. Apparently, these patients did not understand the questions. In spite of the explanation and feedback given during the interview, 16% of all patients gave inconsistent responses.

The usefulness of a questionnaire in practice depends on the feasibility, reliability, and validity of the questionnaire. The feasibility of our questionnaire differed per instrument. The rating scale score and specific questions on experienced discomfort were fairly straightforward and easy to complete for patients. The WTP and WTGT questions, on the other hand, were not always understood, sometimes led to inconsistent responses, and some patients were resistant to the WTP questions. Because we found a good correlation between the responses to the straightforward questions (rating scale score, specific questions)

and the more difficult questions (WTP, WTGT), we would suggest that measuring patient preferences for diagnostic modalities could be done with a rating scale and some specific questions on discomfort.

The test-retest reliability was not assessed because short-term noxious effects are not always remembered to the same degree if measured directly following the effect vs. being measured with a time delay[12] whereas measuring test-retest reliability requires that the same effect should be measured twice with an intervening time delay. To test the validity of the questionnaire requires measuring the true preference of the patient for an imaging modality. Patient preferences are, however, by definition subjective and no matter how you measure these preferences, no objective reference standard ("gold standard") measurement of preference exists. Thus, we checked only the face validity based on the internal consistency of the responses to the questions.

Patient preferences for diagnostic modalities should theoretically be included in a cost-effectiveness analysis from the societal perspective, which includes all costs and effects relevant to society.[13] Including patient preferences for diagnostic modalities becomes especially relevant if the differences in all other costs and effectiveness across different work-up strategies are small or if the experienced discomfort is extremely high.

Including patient preferences in a cost-effectiveness analysis would imply incorporating one of the three quantitative preference measures. The rating scale score should be adjusted for the duration the patient experienced discomfort due to the diagnostic modality and then included in the calculation of the effectiveness. To use the WTP estimate we would need to assume that the amount of money the patient is willing to pay to avoid the imaging modality represents the monetary cost corresponding to the discomfort the patient experienced. Because patient discomfort is an indirect "cost" to society, this monetary cost would need to be added to the cost of the modality. To use the WTGT estimate we would need to assume that the amount of free time the patient is willing to give up to avoid the imaging modality represents the experienced discomfort in an effectiveness measure. The preferences determined with the WTGT can therefore be subtracted from the effectiveness estimate possibly with an adjustment.

For clinical practice non-invasive imaging modalities, like MR angiography and duplex US, should be considered for the diagnostic work-up of PAD to avoid DSA where possible to prevent unnecessary discomfort for the patient. In the decision to use non-invasive modalities instead of an invasive modality one should take into account that DSA is still considered the reference ("gold") standard but that it has a small risk of mortality and morbidity, and is expensive. Moreover, planning a diagnostic DSA in conjunction with percutaneous intervention would avoid unnecessary discomfort.

In conclusion, the results suggest that patients prefer MR angiography and duplex US over DSA for the diagnostic work-up of PAD and that there is no clear

preference between MR angiography and duplex US.

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APPENDIX

The appendix contains the translated questionnaire used in this study.

DESCRIPTION OF MODALITIES

Magnetic resonance angiography (MRA) During the scan you were lying on a table, which was moved into a tunnel. Contrast agent was injected into your arm. You heard a rattling noise. You were given headphones to prevent discomfort from the noise.

Duplex ultrasound For the ultrasound test, gel was applied to your abdomen and/or leg. The laboratory assistant moved a microphone over your abdomen and/or leg to measure the speed of the blood flow in the arteries in your abdomen and/or legs. You heard sound pulses during the procedure.

X-ray Angiography During X-ray angiography a contrast agent was administered through a catheter into the artery in your groin and your pelvis and leg were x-rayed. After the test pressure was applied to the wound in your groin for 10 to 20 minutes. In order to allow the wound in your groin to heal, you had to lie still for a few hours.
During x-ray angiography you may have undergone treatment. A small balloon was inflated (angioplasty) to remove the obstruction in the arteries in your abdomen and/or leg. A small metal tube (stent) may have been placed in an artery to keep the arteries in your abdomen or leg open.

PART 1

A. Rating scale
If you were asked to indicate how bothersome the magnetic resonance angiography (MRA) was for you on a scale from 0 (not bothersome at all) to 10 (extremely bothersome), how many points would you give? ..... points

Similar questions were asked for duplex US and DSA.

B. Direct comparison of MR angiography and duplex US
Imagine that in two years time you visit your specialist for the same complaints for which you were examined this time. There are two tests to examine the arteries in your legs, namely magnetic resonance angiography (MRA) and ultrasound. Before a decision can be made about further treatment you have to undergo a test. Together with your specialist you have to choose between MRA and ultrasound. Which test would you prefer?

- ❑ Magnetic resonance angiography (MRA)
- ❑ Ultrasound
- ❑ No preference
- ❑ Other, namely:

Part 1 also included the open and closed format questions on specific discomfort due to the imaging modalities (See Table 2).

PART 2

A. Direct comparison of MR angiography and duplex US (WTP)

Scenario
Imagine that in two years time you visit your specialist for the same complaints for which you were examined this time. The specialist explains to you that there are two tests for examining the arteries in your abdomen and legs, namely magnetic resonance angiography (MRA) and ultrasound. Before a decision can be made about further treatment you have to undergo a test. Together with your specialist you have to choose between MRA and ultrasound.

Question
Imagine that your health insurance does not cover magnetic resonance angiography (MRA). Ultrasound, on the other hand, is covered. If you choose magnetic resonance angiography (MRA) you will have to pay for it out of your own pocket (not tax deductible).
What is the maximum amount (in Dutch guilders) that you would be willing to pay to have the magnetic resonance angiography (MRA) instead of the ultrasound?
Please circle the maximum amount you would be willing to pay or enter an amount lower than DFL 10 in the first box or an amount higher than DFL 1000 in the last box.

DFL	DFL 10	DFL 25	DFL 50	DFL 100	DFL 200	DFL 500	DFL 1000	DFL .....

If you are not willing to pay any amount (you entered DFL 0 in the first box) please give the reason for this.
Please, read all the answers carefully before answering the question.

- ❑ No, I am not willing to pay any amount for any test.
- ❑ No, I am not willing to pay a certain amount, because I have no preference for either test.
- ❑ No, I am not willing to pay a certain amount because I prefer ultrasound
- ❑ Do not know
- ❑ Other, namely:

For the reverse question the following text was changed:

Imagine that your health insurance does not cover duplex ultrasound. Magnetic resonance angiography (MRA), on the other hand, is covered.

The remainder of the question and answers were changed accordingly.

B. Indirect comparison with "Arterial scan" (WTP)

Scenario
Imagine that in two years time you visit your specialist for the same complaints for which you were examined this time. The specialist explains to you that there are two options for examining the arteries in your abdomen and legs. The first option is one of two existing tests, either magnetic resonance angiography (MRA) or ultrasound. The second option is a different test, which we will call the "Arterial scan". The "Arterial scan" does not really exist, but you should think of it as a test that causes no discomfort like pain or noise. Before a decision can be made about further treatment you have to undergo a test. Together with your specialist you have to choose between the two options (one of the existing tests or the "Arterial scan").

Question
Imagine that you can have magnetic resonance angiography (MRA) and that you have full health insurance coverage for MRA. Imagine now that you can also undergo the "Arterial scan". The "Arterial scan" is not painful, there is no discomfort, and no health risks. The test will give the same information as the MRA, but you do not have to undergo the MRA. However, you have no health insurance coverage for the "Arterial scan". So, if you choose to undergo the "Arterial scan", you will have to pay for it out of your own pocket (not tax deductible).

What is the maximum amount (in Dutch guilders) that you would be willing to pay to have the "Arterial scan" instead of magnetic resonance angiography (MRA)?
Please circle the maximum amount you would be willing to pay or enter an amount lower than DFL 10 in the first box or an amount higher than DFL 1000 in the last box.

DFL	DFL 10	DFL 25	DFL 50	DFL 100	DFL 200	DFL 500	DFL 1000	DFL .....

If you are not willing to pay any amount (you entered DFL 0 in the first box) please give the reason for this.

Please, read all the answers carefully before answering the question.

- ❑ No, I am not willing to pay a certain amount for any test.
- ❑ No, I am not willing to pay a certain amount, because I have no preference for either test.
- ❑ No, I am not willing to pay a certain amount because I prefer MRA.
- ❑ Do not know
- ❑ Other, namely:

A similar question was asked for duplex US. For DSA the text of the scenario was changed into that x-ray angiography was now the first option. The following text was added for DSA:

Imagine that x-ray angiography is performed in the same way as you experienced. If you had treatment following x-ray angiography, you should imagine that the "Arterial scan" is also followed by additional treatment.

C. Indirect comparison with "Arterial scan" (WTGT)

Same scenario as in part 2.B

Question

Imagine that you can have magnetic resonance angiography (MRA) to examine the arteries in your abdomen and/or legs. Imagine that you can also undergo the "Arterial scan". The "Arterial scan" is not painful and there are no health risks. The test will give the same information as the MRA, but you do not have to undergo the MRA. You can have magnetic resonance angiography (MRA) or the "Arterial scan" free of charge, they will not cost you any money, but they will take up some of your time. You have to undergo magnetic resonance angiography (MRA) or the "Arterial scan" in your own free time. You should think of free time as time that you do not use for paid work. For instance free time would be time for: reading a book, making phone calls, doing volunteer work, visiting someone, sleeping, doing sports, cleaning the house or going to a movie.

Imagine next that the "Arterial scan" takes up additional time for recovery. This means that after the "Arterial scan" you will spend some time in a bed in a hospital ward. Just like the time for the "Arterial scan" itself, the time needed for recovery will be your own free time. The question you are asked to answer is if you are willing to give up additional free time (time for recovery in a hospital bed) so that you can have the "Arterial scan" instead of magnetic resonance angiography (MRA)?

How much additional time are you willing to spend in order to have the "Arterial scan" instead of magnetic resonance angiography (MRA)?
Circle the maximum number of minutes, hours or days you would be willing to spend or enter a number of minutes lower than 30 in the first box or a number of days higher than 2 in the last box.

.... minutes	30 minutes	1 hours	4 hours	8 hours	16 hours	24 hours	2 days	.... days

If you are not willing to spend any time (you entered 0 minutes in the first box) please give the reason for this?
Please read all the answers carefully before answering the question.

- ❑ No, I am not willing to spend any additional time to have the "Arterial scan" because I prefer magnetic resonance angiography (MRA).
- ❑ No, I am not willing to spend any time because I have no preference for either test.
- ❑ Do not know
- ❑ Other, namely:

Similar questions were asked for duplex US and DSA (see part 2.B).

8

DUPLEX SCAN SURVEILLANCE DURING THE FIRST YEAR AFTER INFRAINGUINAL AUTOLOGOUS VEIN BYPASS GRAFTING SURGERY: COSTS AND CLINICAL OUTCOMES COMPARED WITH OTHER SURVEILLANCE PROGRAMS?

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ABSTRACT

Purpose: In this study we assessed the costs and clinical outcomes of duplex scan surveillance during the first year after infrainguinal autologous vein bypass grafting surgery and compared duplex scan surveillance, ankle-brachial index surveillance, and clinical follow-up.

Methods: In a clinical study, 293 patients (mean age, 70.1; 58.7% men) with peripheral arterial disease were observed in a duplex scan surveillance program fter infrainguinal autologous vein bypass grafting surgery. Costs were calculated from the health care perspective for surveillance and subsequent interventions from 30 days to one year post-operatively. All costs are presented in 1995 US dollars per patient. In a simulation model, we estimated the costs and amputations of duplex scan surveillance, ankle-brachial index surveillance, and clinical follow-up conditional on the indication for surgery. The main outcome measure was the incremental cost per major amputation per patient avoided during the first post-operative year.

Results: Duplex scan surveillance was the least expensive ($2823) and resulted in the least major amputations (17 per 1000 patients examined) compared with ankle-brachial index surveillance ($5411 and 77 amputations per 1000 patients) and clinical follow-up ($5072 and 77 amputations per 1000 patients). In patients treated for critical limb ischemia, duplex scan surveillance was the least expensive ($2974) and resulted in the fewest major amputations (19 per 1000 patients). Under all surveillance programs, 13 major amputations per 1000 patients treated for intermittent claudication were performed and clinical follow-up had the lowest costs ($1577). In a sensitivity analysis that assumed that duplex scan surveillance could have avoided six major amputations per 1000 patients treated for intermittent claudication compared with the other programs, duplex scan surveillance had an incremental cost of $80708 per major amputation per patient avoided compared with clinical follow-up.

Conclusions: Duplex scan surveillance is highly effective for patients treated for critical limb ischemia, leading to a reduction of major amputations and consequently to a reduction in costs compared to other surveillance programs. In patients treated for intermittent claudication the evidence supporting duplex scan surveillance is less firm, but if duplex can avoid six major amputations per 1000 patients examined, the incremental costs are justified.

INTRODUCTION

Early occlusions of infrainguinal autologous vein bypass grafts are mostly caused by thrombosis occurring during the first few weeks postoperatively whereas late occlusions are mostly caused by stenotic lesions.[1] Unfortunately, these late occlusions have been found to occur in 20% to 30% of the vein grafts in the first postoperative year.[1-5] Vein graft surveillance is increasingly being used as a means of identifying failing grafts during the first postoperative year.[6-8] Currently, surveillance programs usually consist of clinical follow-up with measurement of the ankle-brachial index (ABI) or color-guided duplex scan examination of the bypass graft. The best criterion for detecting a graft stenosis in a surveillance program is the peak systolic velocity (PSV) ratio available from duplex scan examination, whereas the addition of ABI to the PSV ratio does not increase the area under the receiver operating characteristic curve, implying that the diagnostic performance will not improve.[9]

An overall gain in long-term patency of grafts undergoing duplex scan surveillance has been demonstrated in a randomized trial.[10] It is, however, unclear whether the gain in effects (ie avoiding an amputation) justifies the expense of such a program. The TransAtlantic Inter-Society Consensus Working group advised further research on this issue.[11] Early repair of stenosed grafts is a relatively simple and inexpensive procedure compared with an amputation of the limb after a failed graft because of a uncorrected high-grade stenosis. Amputation clearly has a major impact on the health-related quality of life of the patient[12,13] and involves high costs for hospitalization and rehabilitation.[14,15] The costs of duplex scan surveillance may be justified if there is an overall gain in effects, which could also lead to an overall cost-reduction of the follow-up of these patients.

The objective of our study was to assess the costs and clinical outcomes of duplex scan surveillance during the first year following infrainguinal autologous vein bypass grafting surgery and to compare duplex scan surveillance, ABI surveillance, and clinical follow-up.

METHODS

Clinical study

In a prospective multi-center study, 293 patients with peripheral arterial disease underwent infrainguinal autologous vein bypass grafting surgery and were observed in a duplex scan surveillance program. The three participating centers were Catharina Hospital, Eindhoven (176 grafts), Sint Antonius Hospital, Nieuwegein (56 grafts), and the University Hospital Maastricht (61 grafts). Between June 1993 and September 1995, 340 patients underwent bypass surgery, but 47 patients did not meet the inclusion criteria of the study because of death within 30

days after surgery (n=6), irreversible graft occlusion within 30 days after surgery (n=20), amputation within 30 days after surgery (n=7), or no duplex scan surveillance being performed (n=14). Follow-up ended in September 1996, and only one graft per patient was considered. The clinical study was approved by the Institutional Review Board and all patients gave informed consent.

The duplex scan surveillance program started between 4 and 6 weeks after the initial bypass grafting procedure with a colorflow duplex ultrasound examination of the graft and its adjacent inflow and outflow tracts. Subsequently, colorflow duplex ultrasound scanning was performed at 3, 6, 9, and 12 months after the procedure. Additionally, an ABI in rest and during reactive hyperemia were performed at the same time points as duplex scan examination. An intra-arterial digital subtraction angiography (DSA) (Catharina Hospital and Sint Antonius Hospital) or an intravenous DSA (University Hospital Maastricht) was indicated when one of these was present: (1) symptoms of intermittent claudication or rest pain; (2) a drop in ankle-brachial of more than 0.15; (3) visualization of more than 30% stenosis on duplex; (4) PSV-ratio more than 2.0; (5) PSV-graft less than 45 cm/sec; (6) end diastolic velocity more than 20 cm/sec (suggests the presence of a stenosis more than 70%[16]). Surgical revascularization or angioplasty was indicated if a stenosis ≥ 70% was present and a 50% - 70% stenosis was followed with another colorflow duplex scan examination 6 weeks later as a means of detecting progression of disease. Only in the absence of progression of the lesion was the 3-month surveillance program resumed until 1 year after the first detection of the lesion. Bypass grafts with less than 50% stenosis were considered normal grafts. Angioplasty was indicated when the stenosis was no longer than 1 cm and located distal to the anastomosis or in the middle of the graft; otherwise, surgical revascularization was performed.

Colorflow duplex scanning was performed with an Acuson 128 XP/ 10 (Acuson, Mountain view, California, USA) (Catharina Hospital), a Hewlett Packard Sonos 2000 (Sint Antonius Hospital) and a Hewlett Packard Sonos 1000 (Hewlett Packard, Palo Alto, California, USA) (University Hospital Maastricht), all using a 7.5-MHz transducer except for deep located vein grafts for which a 5.0 MHz transducer was used. The settings of the duplex scan machines used in this study were similar. The systolic ankle blood pressure was measured twice with the patient lying supine with a 15-cm wide blood pressure cuff, and the systolic brachial blood pressure was measured at both arms. To determine the ABI, the mean of the two ankle pressures was divided by the highest of the brachial pressures. ABI during reactive hyperemia was measured after 50-mm Hg suprasystolic thigh cuff inflation during a 3-minute period.

More detailed information on the clinical study and surveillance results can be found in the articles by Idu et al.[9,17,18]

Cost data

Costs were estimated from the cost accounting system of the Catharina Hospital. In addition, for duplex ultrasound scanning examination, ABI, and DSA, a detailed microcosting analysis of personnel and capacity was performed both in the Catharina Hospital and the University Hospital Maastricht. All costs were calculated from the health care perspective and included personnel (including social security and overtime), equipment, disposables, hospitalization, and overhead. Overhead costs consisted of a percentage of the total costs for general administration and the board of directors; an amount per square m for use of the building, security service, inventory and energy; an amount for general personnel costs, special regulations and personnel services weighted by the number of working hours; and an amount for personnel administration weighted by the number of employees.

Table 1 – Costs of interventions for graft failures and procedures performed in a surveillance program, 1995 US dollars ($)

Intervention	Costs	
Duplex scan examination	91	
ABI	37	
DSA	271	(868)*
Outpatient visit	15	
Angioplasty	2920	
Secondary reconstruction	3886	
Thrombolysis†	8052	
Minor amputation	4652	
Major amputation	48,324	
Procedure and hospital costs	9162	
Rehabilitation	39,162	
Nursing home for 2 months	13,478	
Home care for 1 month	2484	
Artificial leg	4037	
Rollator	528	
Adaptation of home	18,634	

* Inclusive 1 day of hospitalization, used in the sensitivity analysis.

† Costs of thrombolysis were available from the literature.[24]

Actual costs were calculated for duplex scan examination, ABI, DSA, outpatient visits and interventions related to peripheral arterial disease of the studied limb (Table 1). These interventions were surgical revascularization of the graft, thrombolysis, angioplasty, major amputations, and minor amputations (toe or forefoot). The hospitalization costs and procedure costs of minor amputations were assumed to be half of the costs of a major amputation, except material cost during the procedure which were assumed to be the same. Costs for rehabilitation of major amputations were estimated and costs of rehabilitation for minor amputations were assumed to be negligible. Because all major amputations were

above the knee, the rehabilitation costs were estimated for amputations above the knee only. Costs for thrombolysis were available from literature data. Costs of complications related to the performed procedures and intercurrent illness were not considered. All costs were calculated in 1995 Dutch guilders and subsequently converted to US dollars by using the mean exchange rate for 1995 (1 US dollar = 1.61 Dutch guilders) (Central Bureau of Statistics, The Netherlands).

Data analysis and simulation model

On the basis of clinical description of the Rutherford classification[19], we subdivided the patients into those treated for critical limb ischemia (n=215) and those treated for intermittent claudication (n=78). The average costs per patient for duplex scan surveillance and subsequent interventions were calculated for the period between 30 days and 1 year after surgery for the entire patient group and defined subgroups. Costs included duplex scan examinations, outpatient visits, DSAs, interventions related to peripheral arterial disease, and repeat interventions for failed interventions, if performed. Angioplasties, surgical revascularizations, and thrombolyses of the graft were included in the proportion performed in the clinical study, and on the basis of these proportions, the number of angioplasties, surgical revascularizations, and thrombolyses were estimated for ABI surveillance and clinical follow-up. The cost analysis of the duplex scan surveillance program did not include ABI measurements. Because the number of outpatient visits was not recorded, we assumed that the number of outpatient visits equaled the number of duplex examinations during the first year. Because of logistical reasons only, 12 patients had their first duplex scan examination before the official starting point of 30 days after surgery, and the costs of these duplex examinations were included.

A simulation model was developed as a means of estimating the costs and clinical outcomes of ABI surveillance and clinical follow-up without surveillance. In this model, we assumed that patients who did not undergo a reintervention or amputation during the first post-operative year in the clinical study (ie with duplex scan surveillance) had the same course in the ABI surveillance program and under clinical follow-up. In essence, this assumes that duplex scan surveillance is the most sensitive means of identifying lesions of the three programs. For patients who had an intervention in the clinical study during the first post-operative year, the number of amputations, angioplasties, surgical revascularizations, and thrombolyses of the graft for clinical follow-up were estimated by use of probabilities available from literature data.[6] On the basis of the data extracted from the study by Bergamini et al.[6] we calculated relative risks for duplex scan surveillance versus clinical follow-up for major amputations performed and interventions performed. The probabilities under clinical follow-up were calculated by multiplying the probability under duplex scan surveillance by the relative risk (Table 2). For patients who had an intervention in the clinical study during the first post-operative year, we assumed for ABI surveillance that a drop of more than

0.20 in ABI compared with the preceding ABI would lead to the same medical advice and intervention as when duplex scan surveillance was performed. If a drop of 0.20 or less in ABI was noted compared with the preceding ABI, we assumed that the course would be the same as having clinical follow-up. A scheme of the simulation model is presented in Fig 1.

Table 2 – Outcome of clinical follow-up of infrainguinal graft failures without a surveillance program

Outcome	Probabilities (range)* Critical limb ischemia		Intermittent Claudication	
Baseline analysis				
Interventions: surgical revascularization, thrombolyses and angioplasties	0.59	(0.44 to 0.89)	0.67	(0.50 to 1.0)
Major amputations	0.30	(0.21)†	0.05‡	(0.11)
Minor amputations	0.34§‡	(0.17 to 0.91)	0‡	
Sensitivity analysis‖				
No further surgery	0.21		0.62	
Interventions: surgical revascularization, thrombolyses and angioplasties	0.31		0.31	
Primary amputation	0.31		0.05	
Intervention followed by amputation	0.13		0.02	
Died before further treatment	0.04		0	

* Numbers are based on the relative risk calculated from the paper by Bergamini et al.[6] and the numbers between brackets were used for the sensitivity analysis.
† The probability used for the baseline analysis was based on the 1-year limb salvage rate available from Bergamini et al.[6] In the sensitivity analysis we used the probability based on the annual amputation rate calculated from the 5-year limb salvage rate.
‡ We assumed that the relative risk for minor amputations was 2.0 for patients treated for critical limb ischemia, with a range from 1.0 to 5.38 (baseline relative risk major amputations).
§ No major amputations were performed for patients treated for intermittent claudication in the study by Bergamini et al.[6] and therefore we assumed that the relative risk was 1.0 and we doubled the risk in a sensitivity analysis.
‖ Numbers are based on the probabilities available from the paper by Brewster et al.[20]

The follow-up scheme of the ABI surveillance was the same as the follow-up scheme of the duplex scan surveillance during the first post-operative year. For clinical follow-up, we assumed that patients had, on average, four outpatient visits during the first year, and patients who died or underwent a major amputation during the first year had, on average, two outpatient visits. The numbers of DSAs performed under duplex scan surveillance equaled the number of DSAs on indication performed in the clinical study. For ABI surveillance and clinical follow-up, we estimated the number of DSAs that would have been performed among the studied patients had they not been examined with duplex but instead examined with, respectively, ABI surveillance or clinical follow-up. For ABI surveillance, we estimated the number of DSAs performed based on the assumption that a DSA would have been performed if a drop of more than 0.20 in ABI occurred in the first postoperative year. For clinical follow-up we estimated the number of DSAs

performed based on the assumption that a DSA would have been performed when the patient had symptoms of intermittent claudication or critical limb ischemia during the first postoperative year.

Costs and clinical outcomes were compared across the different surveillance programs, and we calculated incremental costs per major amputation avoided during the first postoperative year compared with the next best program for all programs that were not inferior by (extended) dominance. A program was inferior by dominance when another program was more effective and less costly, and a program was inferior by extended dominance when another program was more effective and had a lower incremental cost-effectiveness ratio. Effectiveness was defined in this study as the number of major amputations avoided per 1000 patients during the first postoperative year. The fewer major amputations that were performed under a certain program, the more effective the program was deemed to be. Incremental cost-effectiveness ratios were expressed as additional dollars per major amputation per patient avoided.

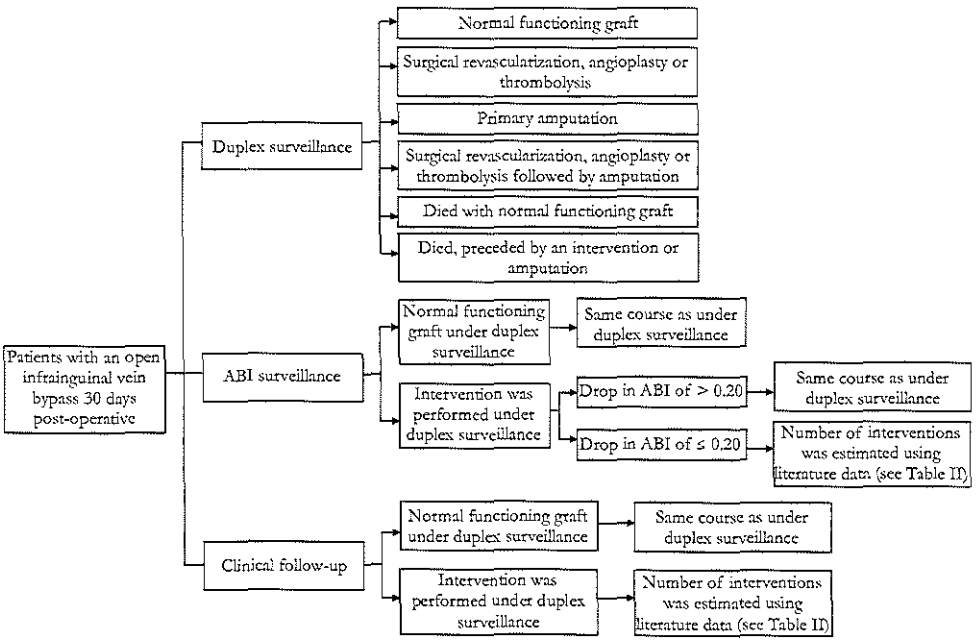

Figure 1 – Scheme of the simulation model. In the simulation model, patients will enter duplex scan surveillance, ABI surveillance and clinical follow-up. Data for duplex scan surveillance were available from the clinical study. Results for ABI surveillance and clinical follow-up were partly based on literature data.

For a sensitivity analysis probabilities extracted from the article by Brewster et al.[20] were used to run the simulation model. Also in a one-way sensitivity

analysis we explored the effect of (1) assuming DSA would be performed as an inpatient procedure (Table 1), (2) assuming that a large proportion of revisions could be planned solely based on the findings on duplex ultrasound (number of performed DSA's was reduced by 50%) (3) varying the costs between 50% and 150% of the baseline cost estimates (Table 1), (4) using other values for the relative risks (Table 2), (5) using different cutoff values of the ABI for ABI surveillance (0.15 and 0.25), (6) assuming a higher proportion of thrombolysis under ABI surveillance and clinical follow-up (half of the interventions were thrombolyses), (7) assuming that half of the additional major amputations under ABI surveillance and clinical follow-up were below-knee amputations and therefore less costly (50% of the baseline rehabilitation costs), (8) assuming that duplex scan surveillance could have avoided 6 major amputations per 1000 patients treated for intermittent claudication compared to the other surveillance programs, and (9) varying the number of outpatient visits with clinical follow-up (ranging from 3 to 5 clinical visits per patient in surveillance).

RESULTS

Clinical study

More than half of the study population was male (58.7%), and the mean age was 70.1 years. Critical limb ischemia was the presenting symptom in most patients (73.4%). More detailed information on patient characteristics can be found in Table 3. The overall 1-year primary patency rate was 0.64 (SE, 0.03) and the overall 1-year primary assisted patency rate was 0.87 (SE, 0.02). For patients treated for critical limb ischemia, these numbers were 0.63 (SE, 0.03) and 0.86 (SE, 0.02), respectively. For patients treated for intermittent claudication, these numbers were 0.66 (SE, 0.05) and 0.88 (SE, 0.04), respectively. More information on patency rates can be found in the article by Idu et al.[9] The average costs per patient during

Table 3 – Patient characteristics (n=293)

Age (y): mean (range)	70.1 (33 to 97)
Sex (% male)	58.7
Treatment indications: % (n)	
Critical limb ischemia	73.4 (215)
Tissue loss	37.2 (109)
Rest pain	36.2 (106)
Intermittent claudication	26.6 (78)
Diabetes mellitus (%)	39.9
Hypertension (%)	31.7
History of smoking (%)	69.6
History of other vascular disease (%)	49.8

the first post-operative year were $2823 (SE, $417). These costs were $2974 (SE, $504) for patients treated for critical limb ischemia and $2404 (SE, $724) for patients treated for intermittent claudication. Four (1.9%) patients treated for critical limb ischemia needed a major amputation above the knee, compared with one (1.3%) patient treated for intermittent claudication (Table 4).

In total, 79 (27.0%) patients had 1 or more interventions (34 angioplasties, 67 surgical revascularizations, and 3 thrombolyses). Angioplasty was the first intervention for 30 patients, and 8 needed 1 or more repeat interventions. Surgical revascularization was the first intervention for 47 patients and 13 needed one or more repeat interventions. Two patients had a thrombolysis, one of whom needed a repeat thrombolysis, and the other patient had a repeat surgical revascularization. Of the 104 interventions 61 (58.7%) were based on duplex criteria only, 1 (1.0%) was based on a drop in ABI only, 1 (1.0%) was based on symptoms only, 11 (10.6%) were based on both duplex scanning and a drop in ABI, and 3 (2.9%) were based on the combination of duplex, drop in ABI, and symptoms. For one intervention, the data regarding the surveillance criteria were missing.

Table 4 – Observed costs of the duplex scan surveillance program, resource use and including induced costs during 1-year follow-up.

Treatment indication	No. of interventional procedures*	No. of patients	Max no. of interventions per patient	Mean cost per patient†	SE
Critical limb ischemia (n=215)					
Major amputation	4	4	1‡	899	446
Minor amputation	12	12	1	260	73
Angiography	103	76	5	130	14
Duplex examination	735	215	6	311	8
Outpatient visit§	735	215	6	51	1
Angioplasty	28	26	2	380	72
Surgical revascularization	46	40	3	831	128
Thrombolysis	3	2	2	112	83
			Total	2974	504
Intermittent claudication (n=78)					
Major amputation	1	1	1‡	620	620
Minor amputation	0	0	0	0	-
Angiography	31	22	3	108	22
Duplex examination	299	78	6	349	11
Outpatient visit§	299	78	6	58	2
Angioplasty	6	6	1	225	89
Surgical revascularization	21	14	3	1046	281
Thrombolysis	0	0	0	0	-
			Total	2404	724

* Interventional procedures that consisted of treatment of multiple stenoses simultaneously were counted as one procedure. For the patency data, the severest lesion was considered. For the costs data the total costs of the procedure were considered.
† Costs are 1995 US dollars.
‡ Only one limb per patient was considered, and thus, the maximum number of amputations per patient was one.
§ Based on the assumption that number of outpatient visits equals number of duplex examinations.

Fourteen patients were excluded from the study population because they did not have duplex scan surveillance. Between 30 days postoperatively and 1 year follow-up, three of these patients died. Four major amputations above the knee were performed, six interventions to salvage the graft and seven DSAs were performed. The average costs for these patients were $16134 (SE, $7189).

Simulation model

In the total study population of 293 patients, 134 DSAs were performed under the duplex scan surveillance program, 130 DSAs would have been performed under the ABI surveillance program and 51 DSAs would have been performed under clinical follow-up. For the entire patient population duplex scan surveillance was the least expensive ($2823) and resulted in the least major amputations (17 per 1000 patients examined), compared with ankle-brachial index surveillance ($5411 and 77 major amputations per 1000 patients) and clinical follow-up ($5072 and 77 major amputations per 1000 patients). For patients treated for critical limb ischemia, duplex scan surveillance was the superior surveillance program, resulting in the fewest amputations performed (19 per 1000 patients) and the lowest costs ($2974) per patient (Fig 2,A). Both ABI surveillance and clinical follow-up were inferior by dominance for patients treated for critical limb ischemia. For patients treated for intermittent claudication, under all programs, 13 major amputations per 1000 patients were performed and clinical

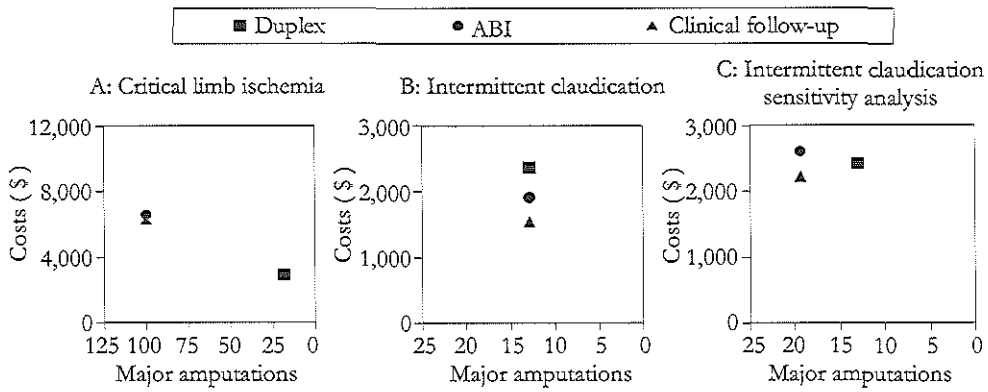

Figure 2 – Cost-effectiveness plots. For patients treated for tissue loss (A), for patients treated for intermittent claudication (B), and for patients treated for intermittent claudication assuming that duplex scan surveillance could have avoided six major amputations per 1000 patients compared with the other surveillance programs (sensitivity analysis; C). In all panels, the y-axis represents the average costs per patient with surveillance during the first postoperative year in 1995 US dollars. The x-axis represents the number of major amputations per 1000 patients during the first postoperative year and is inverted to be consistent with the usual presentation of cost-effectiveness plots (ie effectiveness increases to the right).

follow-up was the least expensive ($1577; Fig 2,B). The mean costs, the number of major amputations per 1000 patients and incremental cost-effectiveness ratios for the different treatment indications are presented in Table 5.

Sensitivity analysis

Neither the assumptions made in the simulation model nor the parameters used in the simulation model influenced the results found for the total group of patients or for patients treated for critical limb ischemia In each situation, duplex scan surveillance prevented substantially more amputations than other surveillance programs leading to lower overall costs. When a different cutoff (0.15) for a drop in ABI was used, 60 major amputations per 1000 patients would have been performed. The costs under ABI surveillance ($4758) were lower than in the baseline analysis but duplex scan surveillance was still the optimal program for patients treated for critical limb ischemia. The explanation for the decrease in major amputations is that the measured drop in ABI was always between 0.15 and 0.20 among patients who underwent a major amputation, and thus, with the lower cutoff, many amputations could have been avoided. The results were sensitive for the relative risk of major amputations for patients treated for intermittent claudication. ABI surveillance ($1959 and 13 major amputations per 1000 patients) was now the optimal program by doubling the relative risk. Under the assumption that duplex scan surveillance could have avoided six major amputations per 1000 patients treated for intermittent claudication compared with ABI surveillance and clinical follow-up, duplex scan surveillance was cost-effective at an incremental ratio of $80,708 compared with clinical follow-up, whereas ABI surveillance was dominated (Fig 2,C). By the use of the probabilities available from the article by Brewster et al.[20] duplex scan surveillance ($2974 and 19 major amputations per 1000 patients) was the optimal program for patients treated for critical limb ischemia, compared with ABI surveillance ($4710 and 66 major amputations per 1000 patients) and clinical follow-up ($7357 and 133 major amputations per 1000 patients). For patients treated for intermittent claudication, ABI surveillance ($1439 and 9 major amputations per 1000 patients) had an incremental cost of $20936 per major amputation per patient avoided compared with clinical follow-up ($1278 and 16 major amputations per 1000 patients), and duplex scan surveillance ($2404 and 13 major amputations per 1000 patients) was dominated by ABI surveillance.

Discussion

The current study shows that duplex scan surveillance as a means of detecting failing infrainguinal autologous vein bypass grafts during the first post-operative year is justified from a cost-effectiveness point of view. In patients treated for critical limb ischemia, duplex scan surveillance leads to a reduction in

amputations and, consequently, lower overall costs than other surveillance programs. In patients treated for intermittent claudication, duplex scan surveillance was equally effective as the other programs and yielded higher costs, but if duplex scan surveillance could have avoided six major amputations per 1000 patients, it would have been cost-effective at a relatively low incremental cost per major amputation per patient avoided.

Table 5 – Mean costs and number of major amputations per 1000 patients across various surveillance programs for infrainguinal autologous vein bypass surgery including induced costs during 1-year follow-up.

	Critical limb ischemia (n=215)			Intermittent claudication (n=78)		
Surveillance program	Mean cost*	Major amputations†	Incremental Cost‡	Mean cost*	Major amputations†	Incremental cost‡
Duplex scan	2974	19	S	2404	13	D
ABI	6664	100	D	1959	13	D
Clinical follow-up	6340	100	D	1577	13	S

* Costs are 1995 US dollars ($).
† Major amputations per 1000 patients.
‡ Incremental cost per major amputation per patient avoided during the first postoperative year.
D, inferior by dominance; S, superior, meaning that the strategy is both more effective and less costly than the other strategies.

A limitation of our study is that we used a simulation model instead of a randomized controlled trial to compare the different surveillance programs.[21] At the time the study was initiated, in the early 1990s, duplex scan surveillance was increasingly being used in clinical practice, although the effectiveness of such a program had not been proven. It was not found ethically sound to withhold duplex scan surveillance from patients, because it was thought that surveillance might be effective and certainly not harmful. We, therefore, chose to simulate ABI surveillance and clinical follow-up. A simulation model, however, has limitations in that assumptions must be made. We have stated these assumptions explicitly for the reader to judge, and, moreover, we found that slightly different assumptions did not influence the results substantially. Furthermore, in the simulation model, data from the clinical study were integrated with data from the medical literature to estimate the costs and clinical outcomes for the clinical follow-up program. A bias could potentially have been introduced by differences in patient characteristics between the clinical study and the available literature data for the clinical follow-up.[6] However, comparing the mean age (70.1 years this study vs 65 years), percentage of male patients (59% in this study vs 63%), and the percentage of patients with intermittent claudication (27% in this study vs 16%), we did not find major differences between the two studies. A drawback of using the data by Bergamini et al.[6] is that their clinical follow-up included some form of surveillance with noninvasive tests, but this was limited and not based on a protocol. Follow-up

data without any kind of surveillance are only available from studies published in the early 1980s. An example of such a study is the one by Brewster et al.[20] which we used in the sensitivity analysis. The results of our analysis may be biased because clinical follow-up without any form of surveillance probably has a worse prognosis than that based on the data available from Bergamini et al.[6] The implication of this potential bias would be that duplex scan surveillance could be even more favorable than what our results suggest.

Another limitation of our study is that the results are based on a small number of amputations, with as a result, uncertainty of the estimated cost-effectiveness ratios. This limitation applies especially to patients treated for intermittent claudication in which the amputation rate during the first year was low (13 per 1000 patients). In the baseline analysis, all surveillance programs were equally effective for patients treated for intermittent claudication and clinical follow-up had the lowest overall costs. A sensitivity analysis, however, showed that duplex scan surveillance was cost-effective if six major amputations per 1000 patients treated for intermittent claudication could have been avoided compared with the other programs. Considering the sensitivity analysis and taking into account that an amputation of the limb has a major impact on the patient's life, we think that the use of duplex scan surveillance for patients treated for intermittent claudication is probably justified.

According to the recommendations of the Panel on "Cost-effectiveness in health and medicine"[22], effectiveness is ideally measured in quality adjusted life years (QALY's) to ensure comparability across health care interventions. In our study, we chose to measure the effectiveness in number of major amputations avoided during the first postoperative year. Amputation of the limb has an enormous impact on the health-related quality of life of the patient.[12,13] Thus, duplex scan surveillance (compared with other surveillance programs) increases effectiveness, whether expressed as amputations avoided or QALYs, and decreases costs by the cost-savings of avoiding amputations. Duplex scan surveillance did increase the number of graft revisions but these additional costs did not outweigh the cost-savings of avoiding amputations. Overall, duplex scan surveillance is both more effective and less costly than other surveillance programs, implying that the estimation of QALYs gained is irrelevant. For the subgroup treated for intermittent claudication, the additional cost per amputation avoided found in the sensitivity analysis was reasonable ($80,000). Because a major amputation avoided will impact health-related quality of life substantially for the rest of the patient's lifespan, this additional cost per amputation avoided translates to a low cost per QALY gained. For example, if the difference in quality of life for an amputation avoided is approximately 0.40 and a patient has 10 years of life expectancy, then an $80,000 per amputation avoided translates to $80,000 /(0.40*10) QALYs = $ 20,000 /QALY, which is well within the generally accepted range.

Furthermore, a limitation of our study is that we only explored the cost-

effectiveness of duplex scan surveillance during the first post-operative year. We thought it was justified to focus on the surveillance programs with this limited timeframe, because the most infrainguinal vein bypass failures occur within the first postoperative year.[23] Surveillance programs beyond the first postoperative year should be addressed, but are likely to be very expensive since the failure rate is so much lower. Finally, we did not address the scheme of surveillance, because this is generally dictated by what is practically feasible.

In summary, we found that duplex scan surveillance is highly effective for patients treated for critical limb ischemia, leading to a reduction of amputations and, consequently, to a reduction in costs compared with other surveillance programs. For patients treated for intermittent claudication, the evidence supporting duplex scan surveillance was less firm, but if duplex can avoid six major amputations per 1000 patients the incremental costs are justified. We conclude that duplex scan surveillance during the first year after infrainguinal autologous vein bypass grafting surgery is cost-effective.

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9

SUMMARY AND GENERAL DISCUSSION

The aim of this thesis was to evaluate the diagnostic imaging work-up for patients with intermittent claudication. Patients with intermittent claudication have cramps in their leg muscles during exercise, which will be relieved after a short period of rest. The symptoms are caused by an impaired blood flow to the muscles in the leg because of an obstruction in the arteries supplying these muscles. For the work-up of peripheral arterial disease (PAD) several imaging modalities are available and different centers advocate different strategies. There are centers that advocate the use of duplex ultrasound (US) with selective use of intraarterial digital subtraction angiography (DSA) whereas other centers advocate the sole use of magnetic resonance (MR) angiography. All imaging modalities have their advantages and disadvantages and in this thesis an evaluation of MR angiography, duplex US, and DSA in the work-up of patients with intermittent claudication was presented. In this chapter the main findings of the research project, methodological considerations, and future developments in the field of imaging technology for PAD will be discussed.

SUMMARY OF THE MAIN FINDINGS

To evaluate the diagnostic imaging work-up for patients with intermittent claudication a meta-analysis, cost-effectiveness analyses, and a study on the assessment of patients' preferences were conducted. In each of the studies a comparison was made between MR angiography, duplex US, and intraarterial DSA.

The meta-analysis (Chapter 2) dealt with the comparison of the diagnostic accuracy of MR angiography and duplex US, using DSA as the reference standard. It was found that the diagnostic accuracy of MR angiography was higher than that of duplex US, and MR angiography was nearly as accurate as DSA. Since it was assumed in the meta-analysis that the reference standard gives perfect diagnostic information, the diagnostic performance of DSA exceeds the accuracy of MR angiography and duplex US. However, only considering the diagnostic accuracy ignores the fact that DSA has a risk of morbidity and mortality and is fairly expensive. MR angiography and duplex US may not yield perfect diagnostic information compared to DSA but these non-invasive imaging modalities are without any risks and the costs are lower. Therefore, a decision-analytic model incorporating all relevant costs and effects was developed to compare the cost-effectiveness of the imaging modalities.

Three cost-effectiveness analyses for patients with intermittent claudication were presented in this thesis: conservative vs. invasive treatment strategies, diagnostic strategies in the United States and diagnostic strategies in the Netherlands. The first analysis dealt with the evaluation of treatment strategies for patients with intermittent claudication (Chapter 3). For the evaluation of diagnostic work-up it is essential to account the costs and effects of treatment and follow-up that may be induced by the test result. In a Markov Monte Carlo model all relevant

costs and effects of treatment and subsequent follow-up were considered and the results showed that treatment strategies that limited invasive treatment options to angioplasty for symptoms of intermittent claudication were cost-effective by most standards. Strategies including both angioplasty and bypass surgery were more effective but against a high cost.

The second cost-effectiveness analysis dealt with the comparison of imaging modalities for the pre-treatment work-up (Chapter 4). For this analysis two different treatment scenarios were distinguished because controversy exists as to whether the complaints of intermittent claudication justify the use of bypass surgery. Furthermore, it may be possible that the results of the cost-effectiveness for diagnostic work-up depend on the treatment options considered. We found that the differences between the three imaging modalities were small, especially if treatment options were limited to percutaneous interventions. If treatment also included bypass surgery then the differences between MR angiography and duplex US remained small but DSA dominated the other strategies by a combination of higher effectiveness and lower costs. It seems justified to say that non-invasive imaging modalities such as MR angiography and duplex US could replace DSA without a substantial loss in effectiveness and with a small cost-reduction if treatment is limited to percutaneous interventions. Single non-invasive imaging strategies may not be the optimal choice if both percutaneous interventions and bypass surgery are considered for complaints of intermittent claudication. Non-invasive imaging modalities could then be used as the initial work-up and an additional DSA would be performed if bypass surgery is considered on the basis of the non-invasive test result. In this case only a proportion of the patients will have to undergo a DSA. The combination of non-invasive imaging modalities and DSA yielded similar effectiveness and costs as performing only DSA in all patients.

The last cost-effectiveness analysis dealt with the evaluation of management strategies for patients with intermittent claudication in The Netherlands (Chapter 5). Although the absolute cost-effectiveness ratios differed between The Netherlands and the United States, the practical implications for diagnostic work-up and treatment were similar. With hindsight, this result is not surprising but prior to performing the analysis it was difficult to predict how the incremental cost-effectiveness ratios would be affected by considering Dutch costs. In general the costs of health care interventions in The Netherlands are lower than the costs in the United States. If all costs would be decreased by the same ratio then the effect on the incremental cost-effectiveness ratio would be predictable if we can assume that effectiveness is equal across countries, which is a reasonable assumption for the United States and The Netherlands. However, not all costs decreased by the same ratio and therefore the effect on the incremental cost-effectiveness ratio was not directly predictable.

The cost-effectiveness analysis did not take into account which imaging modality would be preferred by the patient. Patients' preferences may be highly

dependent on the amount of discomfort associated with the performance of the imaging modalities. The amount of discomfort experienced due to DSA is expected to be larger than due to non-invasive imaging modalities. Patients' preferences for the imaging modalities were assessed with three different measures (rating scale score, willingness-to-pay (WTP) and willingness to give up free time (WTGT)) (Chapter 7). The results showed that patients preferred non-invasive imaging modalities to DSA. Taking this last finding into account in the evaluation of diagnostic imaging modalities strengthens the conclusion that non-invasive imaging modalities could replace DSA as initial test.

In summary, the results of the meta-analysis showed that there were differences between the imaging modalities: MR angiography was better than duplex US and was nearly as accurate as DSA. The cost-effectiveness analysis in which all relevant costs and effects due to the imaging modalities were taken into account showed, however, that there were no substantial differences between the imaging modalities. In the cost-effectiveness one relevant aspect was not considered, namely the patients' preferences. These preferences were different for the imaging modalities: non-invasive modalities were preferred over DSA. Considering the results of the cost-effectiveness analysis and the patients' preferences the overall conclusion would be that non-invasive imaging modalities could replace DSA for the imaging work-up of patients with intermittent claudication and only selective use of DSA may be required if bypass surgery is considered on the basis of the non-invasive test result.

The studies discussed in chapters 2 through 5 and 7 dealt with the comparison of MR angiography, duplex US, and DSA. In these studies we considered MR angiography, duplex US, and DSA the current work-up for PAD. New developments in imaging technology for PAD are, however, ongoing. In the early development of new imaging modalities parameters like sensitivity and costs of the new imaging modality are uncertain and the cost-effectiveness of the new imaging modality cannot yet be determined. What can be helpful at an early stage of the development is the establishment of target values for a new imaging modality. In chapter 6 target values were estimated for which a new modality would be cost-effective compared with MR angiography. The target values for a new imaging modality seemed achievable and potential new imaging modalities for PAD will be discussed later on in this chapter (See Future directions).

In addition to the use of imaging modalities for the pre-treatment work-up of PAD, imaging modalities are also used for the surveillance of bypass grafts. The goal of imaging work-up in the surveillance of bypass grafts is to detect graft failures at an early stage so that the graft can be repaired and an amputation of the limb can be avoided. In a cost-effectiveness analysis we found that the use of a duplex US surveillance program justified the costs of the program (Chapter 8). At the time this study was performed (1993-1996) MR angiography was not widely available for the surveillance of PAD. Thus, including MR angiography as an

option may lead to the conclusion that MR angiography is preferable to duplex US. The use of DSA for surveillance seems unjustified since a patient without any symptoms will be exposed to the small but existing risks of DSA.

METHODOLOGICAL CONSIDERATIONS

Decision-analytic models versus clinical studies

The presented cost-effectiveness analyses in this thesis were all based on decision-analytic models, which have their advantages and disadvantages. The developed models all attempt to reflect reality but since reality is unwieldy and complex, assumptions have to be made to keep the model tractable. The most pertinent assumptions in the models were discussed in the separate studies. Another limitation of decision models is that the input data needs to be derived from various sources. In the models presented in this thesis data were available from meta-analyses, studies published in the literature, and original patient data. Where possible the data were adjusted for potential confounding factors. A clinical study comparing alternative imaging modalities is not hampered by the limitations of making assumptions and the use of secondary data. On the other hand, evaluating the cost-effectiveness of many alternative strategies in a clinical study is a cumbersome (if not impossible) task. Many diagnostic work-up strategies are conceivable and comparing all these strategies in a clinical study is not practical. Decision-analytic models have the advantage that many alternative strategies can be compared which can help focus the design and conduct of a clinical study. To assess the costs and effects of diagnostic imaging work-up strategies requires that not only the diagnostic accuracy, costs, and risks of the modality should be measured but also the impact of the test result on the treatment and follow-up. To obtain the relevant data, patients would need to be followed for a fairly long time after the imaging work-up. In addition, comparing two imaging modalities requires that each modality is performed in a group of patients and the two groups are compared. Given these considerations, decision-analytic models and clinical studies can be thought of being complementary to each other rather than being mutually exclusive alternatives.

Recently, a new design for the evaluation of diagnostic imaging technology has been suggested.[1] The design involves an empirically based pragmatic trial and deals at the same time with the development, assessment, and implementation of a new diagnostic imaging modality. For the evaluation of new imaging modalities for the work-up of PAD this would mean that the current work-up would be compared with a potential new imaging modality of which the preliminary results are promising. For example, MR angiography would be compared with multi-detector computed tomography (CT) angiography. Patients would be randomized between the two alternative strategies to prevent bias and outcome measures

should focus on the clinical decision-making process and the trend over time. Potential outcome measures could be the recruitment rate of patients for the study, the number of requested additional DSAs after the initial test, the costs of the diagnostic test, the physicians' confidence in making a treatment decision, and the patients' quality of life. Another advantage of this design is that it allows for the assessment of the local setting including the expertise of the radiologists and availability of equipment, which is cumbersome to do in a decision model.

Incremental cost-effectiveness ratios versus net health benefit

To determine the cost-effectiveness of alternative strategies incremental cost-effectiveness ratios were used in the studies presented in this thesis. The incremental cost-effectiveness ratio for a strategy is calculated as the difference in costs divided by the difference in effectiveness compared with the next best strategy after excluding (extended) dominated strategies.[2] Strategies are considered to be dominated if another strategy yields higher effectiveness against a lower cost and strategies are considered to be extended dominated if another strategy yields higher effectiveness against a lower cost per additional gain in effectiveness. Presenting the results of cost-effectiveness analyses as incremental ratios is common practice[3] and nowadays many researchers and physicians know how to interpret these results. A disadvantage of these ratios is that small differences in the costs and effectiveness across strategies do not directly show up and (extended) dominated strategies could be almost similar to the optimal strategy. Another method to determine the cost-effectiveness of alternative strategies is the use of net health benefits (NHB).[4]

NHB is a multi-attribute outcome combining costs, quality adjusted life years (QALYs) and an estimate for society's willingness-to-pay for the gain of one additional QALY (λ).[4] For each strategy the NHB can be calculated with the following formula: NHB = QALYs - costs / λ. Using the NHB, a strategy is considered cost-effective compared with another strategy if the gain in QALYs justifies the additional costs and this trade-off is considered justified if the cost per additional QALY does not exceed society's willingness-to-pay. Practically, this implies that the strategy with the highest NHB is preferred and two strategies with the same NHB are considered to be equivalent in terms of cost-effectiveness. Basically, NHBs gives the same results as the incremental cost-effectiveness ratios and it is only a matter of different presentation of the results. By using the NHB approach, the threshold of society's willingness-to-pay is explicitly considered since it is included in the outcome measure. With the use of incremental cost-effectiveness ratios the threshold for society's willingness-to-pay is also considered but after the results are obtained.

A big advantage of using the NHB approach in evaluating diagnostic imaging technology lies in the fact that the differences in outcomes across imaging strategies are generally small. Using the NHB approach small differences in costs

and effectiveness across alternative strategies are directly apparent because the strategies will have almost equal NHBs. This also applies to strategies that are inferior by (extended) dominance but have only minor differences in costs and effects compared to similar non-dominated strategies.

Patients' preferences

Cost-effectiveness analyses from the societal perspective include all costs and effects of interventions for everyone who is affected by the intervention.[3] By this definition of cost-effectiveness analysis patients' preferences for diagnostic imaging modalities should also be included. Sometimes these preferences are negligible compared to all other costs and effects induced by the test. However, patients' preferences may be a decisive factor if a test is extremely uncomfortable for patients and/or if differences in costs and effectiveness across diagnostic strategies are small.

Studies on patients' preferences for diagnostic tests are rare in the literature. Examples of studies are the assessment of patients' preferences for several screening strategies of colorectal cancer[5], assessment of preferences for additional testing in patients suspected of lung cancer[6], assessment of preferences for screening strategies for cystic fibrosis carriers[7], and the assessment of patients' preferences for MR angiography and DSA in the work-up of PAD[8,9]. Except for the latter, all studies assessed preferences for undergoing the test along with preferences for higher diagnostic accuracy. Using these preference measures in a cost-effectiveness analysis would mean that the diagnostic accuracy is double counted since the sensitivity and specificity have already been included in this analysis. The preferences determined in this thesis did not include measurements of preferences for diagnostic accuracy to avoid this double counting.

In the study presented in this thesis patients' preferences for diagnostic imaging modalities were measured in three ways: a rating scale score, a WTP technique, and a WTGT technique. Including patients' preferences for imaging modalities in a cost-effectiveness analysis would imply incorporating one of the three preference measures. Before the estimates can be incorporated in a cost-effectiveness analysis we need to consider how each measure can be incorporated and if all patients' responses are valid.

The rating scale score, measured on a scale from 0 (not bothersome) to 10 (extremely bothersome), represents the patients' experience of undergoing the modality. The score may be straightforward to include in a cost-effectiveness analysis if it is considered as a proxy measure for a utility. It can then be expressed as a disutility during the time period the patient experiences discomfort due to the test. The time period multiplied by the disutility can then be subtracted from the overall effectiveness. The rating scale score was easy to complete for patients and it seems justified that all responses were valid and could be used for the preference measure.

The second preference measure was based on a WTP technique in which the patients were asked about their willingness-to-pay and instead to undergo another imaging modality to avoid an imaging modality. Using the WTP the preference of a patient is expressed as the monetary equivalent of the disutility the patient experiences and may therefore be considered a cost that should be added to the overall costs of a diagnostic strategy. Although this seems fairly straightforward some pitfalls exist. Not all responses obtained on the WTP question are valid. First, approximately 20% of the patients were resistant to paying for health care interventions and the responses of these patients could not be used since these patients did not express a preference. Second, there were also patients that had a preference for the modality that was covered by health insurance (range 7 tot 25%). The inverse WTP (i.e., the WTP of patients for the modality covered by health insurance) was not determined and, therefore, we assumed that those patients were not willing to pay. By including these responses as an amount of zero Euros, the WTP might be slightly overestimated. Third, approximately 15% of the patients gave inconsistent responses to the WTP questions. It can be argued that the responses of these patients are not valid since, apparently, these patients did not understand the questions and presumably the responses do not reflect the patients' preferences. The question arises whether the responses obtained on the WTP questions in this study are useful since so many responses were invalid. The order of preferences for the imaging modalities based on the WTP was the same as based on the rating scale score but it is possible that the preferences of patients with valid responses are not a good representation of the preferences of the total patient population with PAD.

The third preference measure was the WTGT that reflected the patients' preferences by the hours the patient was willing to spend in a hospital bed to avoid undergoing a certain imaging modality. The inclusion of the WTGT in a cost-effectiveness analysis may not be as straightforward though. One option is to subtract the hours that a patient is willing to give up from the quality adjusted life years. Implicitly, this assumes that the patient is willing to give up a couple of hours of his/her life to avoid a certain imaging modality, which may be unrealistic. It is more realistic to assume that the patient's quality of life is reduced while restricted to the bed compared to his current health state and in a cost-effectiveness analysis the WTGT can be subtracted from the effectiveness with a quality adjustment. Similar to the WTP, also not all responses to the WTGT questions were valid. A minority of the patients (range 3 to 24%) preferred the imaging modality for which no extension of the hospital admission was required. Furthermore, in the questionnaire of the study presented in this thesis no question was included that checked if patients understood the WTGT questions. However, since the format of the WTGT questions was similar to the WTP questions it is reasonable to assume that patients who did not understand the WTP questions also did not understand the WTGT questions. In contrast to the WTP questions,

no patients were resistant about giving up time for health care interventions.

To determine the influence of patients' preferences on the costs-effectiveness of diagnostic imaging modalities all three measures should probably be considered in turn in the analyses. Since non-invasive imaging modalities were preferred over DSA one would expect that including patients' preferences would benefit the non-invasive imaging modalities compared with DSA. However, still no major differences between the diagnostic work-up strategies will be expected since the absolute differences in patients' preferences were small.

A final note on the patients' preferences should be made. In this study the preferences were measured in a patient population. Ideally, preferences that will be used in a cost-effectiveness analysis from the societal perspective should be measured among the general public.[3] The preferences of the general public may differ from the preferences of the patient population. PAD is a generalized disease and for many of the patients interviewed this was not their first visit to the hospital. Undergoing a DSA or MR angiography may be unpleasant but compared to, for example, a bypass surgery in the limb the associated discomfort is minor. So, it is possible that on average patients with PAD reported less discomfort due to the imaging modalities than the general public would. This does not necessarily imply that the order of preferences for the imaging modalities would change if we had measured the preferences in the general public.

FUTURE DIRECTIONS

The evaluation of imaging modalities for PAD in this thesis was based on the current knowledge of MR angiography, duplex US, and DSA at the time the research project was conducted. Most of the data on the imaging modalities were available from academic centers that usually have highly selected patient populations and expertise in the performance of the studied imaging modalities. Widespread use of these imaging modalities in patients with broader clinical indications might result in different diagnostic performance of these examinations and therefore generalization of the results should be made with caution. For instance, duplex US is known to be operator-dependent and the results as shown in the literature might not be achieved by every hospital. The same would apply for the results of MR angiography since the performance of contrast-enhanced MR angiography requires extensive knowledge of the MR technique. Furthermore, the development of imaging technology is ongoing and improvements in the current imaging modalities may change the results found in this research project.

New developments in the imaging technology for PAD are MR angiography with blood pool agents[10], duplex US with contrast agents[11,12], DSA with carbon dioxide[13,14] or gadolinium-enhancement[15,16], and multi-detector computed tomography (CT) angiography. [17,18] These techniques are under development and will be discussed in the next few paragraphs.

A limitation of MR angiography with gadolinium-enhancement is that the gadolinium chelates rapidly move into the extracellular spaces, which requires an optimal timing of the contrast medium bolus and fast collection of the imaging data. Blood pool agents remain longer in the intravascular lumen which can overcome these limitations. The specificity of MR angiography with the use of blood pool agents was high (range 97 to 100%) but because of the venous overlap the sensitivity was only moderate (range 71 to 86%).[10] The costs of a MR angiography examination with blood pool agents would probably be higher than MR angiography with gadolinium-enhancement since blood pool agents are more expensive than gadolinium. The combination of the low sensitivity and the relatively high costs would probably make MR angiography with blood pool agents not cost-effective compared with the current MR angiography technique.

Important pitfalls of duplex US are the operator-dependency and technical failure of some of the US examinations. The use of contrast agents for duplex US might overcome these limitations partially.[12] Preliminary results in a selected group of patients with a diagnosis of carotid artery occlusion based on a color-guided duplex US showed that duplex US with contrast agents had a perfect correlation with carotid DSA.[19] For the lower extremities a pilot study suggested that the diagnostic accuracy of duplex US increases slightly if contrast agents are used.[11] In this pilot study duplex US with and without contrast agents was compared to intravascular ultrasound as reference standard which makes a comparison with the diagnostic accuracy of duplex US found in the meta-analysis questionable. Potentially, the use of duplex US with contrast agents may be cost-effective compared with MR angiography if the diagnostic accuracy of US will improve significantly and if the overall costs of duplex US with contrast agents are fairly comparable to duplex US without contrast agents.

Intraarterial DSA with the use of iodinated contrast media are considered to be the reference ("gold") standard which is substantiated by the extensive literature on diagnostic imaging modalities for PAD that reported on DSA as the reference standard. The use of iodinated contrast media is not without problems mainly due to the allergic reactions and renal toxicity that it can cause. To overcome these problems, carbon dioxide has been suggested as an alternative. A disadvantage of the use of carbon dioxide is that the patient can experience uncomfortable sensations like smarting pains and nausea. The detection of arterial stenosis using carbon dioxide was almost as accurate as with iodinated contrast media but the radiologists were more certain about their decisions based on the images with iodinated contrast media.[13,14] In summary, DSA with carbon dioxide as contrast medium has probably lower costs due to the use of an inexpensive contrast medium, lower diagnostic accuracy, and more discomfort for the patients compared with DSA using iodinated contrast media but the differences are minor. It is questionable if the cost-reduction outweighs the decrease in diagnostic accuracy and the increase in discomfort for the patient.

Another alternative for patients with contra-indications for iodinated contrast media may be gadolinium chelates. Two studies reported that DSA using gadolinium as a contrast medium could produce useful images in patients with contra-indications for iodinated contrast media but the image quality was inferior to images based on iodinated contrast media.[15,16]

A potential new imaging modality for the work-up of PAD is multi-detector CT angiography which is simple and fast, and will be widely available in the near future. Preliminary results were available and showed that the sensitivity ranged from 83 to 97% and specificity was above 94%.[17,18] Information on the costs of a contrast-enhanced CT angiography was available and these were estimated to be $237 (1997 US dollars).[20] CT angiography has the ability to image the arterial wall which has the advantage of showing atherosclerotic plaque and the disadvantage that, when the wall is heavily calcified, this interferes with accurate depiction of arterial stenoses. Multi-detector CT angiography may be cost-effective compared with MR angiography and, based on the preliminary results, CT angiography would meet the targets for a new imaging modality that were estimated.

New developments are not only seen in the introduction of new imaging technology but also in the use of established imaging modalities for other indications. Recently, MR angiography has been introduced for the surveillance of bypass grafts. This imaging modality seems to be accurate in the detection of failing bypass grafts in most cases.[21,22] It is, however, possible that MR angiography will overestimate the stenosis[21] which may result in an unnecessary repair of the bypass graft if the MR angiography result is not verified by a DSA. Furthermore, although the presence of intravascular stents or metallic clips is no contra-indication for MR angiography these metal parts may cause artifacts on the image and, thereby, hamper the interpretation of the image.[22]

The implementation of a MR angiography surveillance program would yield higher costs for the performance of the imaging modalities compared with a duplex US surveillance program. Overall the costs of the MR angiography surveillance program might be lower than a duplex US surveillance program if due to a possibly higher diagnostic accuracy of MR angiography more amputations of the limb would be avoided. The literature on the diagnostic accuracy of MR angiography for detecting failing bypass grafts is still limited. However, the diagnostic accuracy of MR angiography for the pre-treatment work-up for PAD was higher than that of duplex US and it seems reasonable that the same would apply for detecting failing bypass grafts. A MR angiography surveillance program would be cost-effective compared with a duplex US surveillance program if the MR angiography program will avoid more amputations and this will outweigh the higher costs of MR angiography compared with duplex US and the costs of more early repairs for detected failed grafts.

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NEDERLANDSE SAMENVATTING

Het onderwerp van dit proefschrift is de evaluatie van de beeldvormende diagnostiek voor patiënten met claudicatio intermittens. Patiënten met klachten van claudicatio intermittens krijgen kramp in hun benen bij inspanning wat wordt veroorzaakt door een vernauwing in de slagader van de benen. Na enkele minuten rust verdwijnt de kramp en kan de patiënt weer een stukje verder lopen. Claudicatio intermittens staat dan ook wel bekend als 'etalage-benen': de patiënt loopt een stukje, rust even uit voor een etalage en kan dan weer verder lopen naar de volgende etalage waar hij/zij weer moet stoppen vanwege de kramp in de benen. Wanneer de klachten zo erg zijn dat de patiënt geen voor hem/haar normale afstand meer kan afleggen, kan besloten worden om een dotterbehandeling of bypass operatie uit te voeren. Beeldvormend onderzoek wordt gedaan om te bepalen waar in de slagader in het been de vernauwing zit en welke behandeling de meest geschikte is. Er zijn op dit moment verschillende beeldvormende onderzoeken beschikbaar en elk ziekenhuis heeft zijn eigen strategie. Zo zijn er ziekenhuizen die duplex ultrageluid bij elke patiënt uitvoeren eventueel gevolgd door een röntgen-angiografie afhankelijk van de duplex uitslag maar er zijn ook ziekenhuizen die in plaats hiervan een magnetische resonantie angiografie (MRA) gebruiken. Elk van de onderzoeken heeft zijn eigen voor- en nadelen. Zo wordt de röntgen-angiografie beschouwd als de 'gouden standaard', maar deze heeft een klein risico op complicaties en brengt hoge kosten met zich mee omdat een ziekenhuisopname nodig is. De MRA heeft een goed diagnostisch onderscheidend vermogen maar er zijn ook contra-indicaties zoals bijvoorbeeld claustrofobie of het hebben van een pacemaker. Het duplex ultrageluid onderzoek heeft een redelijk diagnostisch onderscheidend vermogen maar de resultaten zijn afhankelijk van de laborant die het uitvoert en niet alle onderzoeken leveren interpreteerbare resultaten op.

In dit proefschrift worden de MRA, het duplex ultrageluid onderzoek en de röntgen-angiografie vergeleken voor de diagnostiek van patiënten met claudicatio intermittens. Hiertoe zijn uitgevoerd een systematisch literatuur-onderzoek, kosten-effectiviteits analyses en een studie waarin de voorkeuren van de patiënt werden bepaald.

In Hoofdstuk 2 is een systematisch literatuur-onderzoek uitgevoerd waarbij het diagnostisch onderscheidend vermogen van MRA en duplex ultrageluid zijn vergeleken met als referentie standaard de röntgen-angiografie. Het diagnostisch onderscheidend vermogen van MRA voor het vaststellen van een diameter reductie van meer dan 50% van de slagader is beter dan dat van duplex ultrageluid en MRA is bijna net zo accuraat als de röntgen-angiografie. Omdat in deze analyse is aangenomen dat de röntgen-angiografie de referentie standaard is, is ook aangenomen dat het diagnostisch onderscheidend vermogen van de röntgen-angiografie groter is dan dat van de MRA en het duplex ultrageluid onderzoek. Wat betreft het diagnostisch onderscheidend vermogen is de röntgen-angiografie dus het beste beeldvormende onderzoek maar hier wordt geen rekening gehouden met

het feit dat dit onderzoek een kans heeft op complicaties en hoge kosten met zich meebrengt. MRA en duplex ultrageluid mogen dan een iets minder diagnostisch onderscheidend vermogen hebben, er is in ieder geval geen risico op complicaties en de kosten zijn een stuk lager. In een besliskundig model kunnen alle relevante kosten en effecten van de drie beeldvormende onderzoeken worden beschouwd.

In dit proefschrift zijn drie kosten-effectiviteits analyses voor patiënten met claudicatio intermittens beschreven: de kosten-effectiviteit van invasieve behandelingen versus looptraining, de kosten-effectiviteit van beeldvormende diagnostiek voor de Verenigde Staten en voor de Nederlandse situatie. In de eerste analyse werden invasieve behandelingsstrategieën met dotteren en bypass operaties vergeleken met looptraining. Voor het evalueren van de diagnostiek is het belangrijk de kosten en effecten van de behandeling te weten en de uitgevoerde analyse in Hoofdstuk 3 voorzag in deze resultaten. In een besliskundig model werden alle relevante kosten en effecten beschouwd van behandeling en nabehandeling. De resultaten lieten zien dat behandeling van patiënten met dottertechnieken kosten-effectief is en behandeling met bypass operatie effectiever is dan een dotterbehandeling maar zeer hoge kosten met zich meebrengt.

In de tweede kosten-effectiviteits analyse werden de verschillende beeldvormende diagnostische onderzoeken vergeleken (Hoofdstuk 4). Hierbij werden twee behandelingsscenario's onderscheiden: een scenario waarin dotterbehandeling beschikbaar was voor patiënten die een geschikte lesie hadden en de overige patiënten werd een looptraining aangeboden. In het tweede scenario werd een bypass operatie uitgevoerd bij patiënten die geen geschikte lesie voor een dotterbehandeling hadden. Dit werd gedaan om dat er geen overeenstemming bestaat over of het gebruik van bypass operatie voor patiënten met claudicatio intermittens gerechtvaardigd is. Daarnaast is het ook mogelijk dat de resultaten van de kosten-effectiviteit van beeldvormdende onderzoeken afhangen van de behandeling die beschouwd wordt. Wanneer de behandeling werd beperkt tot dotteren dan waren de verschillen tussen MRA, duplex ultrageluid en röntgen-angiografie minimaal. Als ook bypass operatie werd toegestaan voor klachten van claudicatie dan waren de verschillen iets groter maar nog steeds klein: het uitvoeren van de röntgen-angiografie had de hoogste kwaliteits-gecorrigeerde levensverwachting tot gevolg met de laagste kosten. De resultaten impliceren dat MRA en duplex ultrageluid de röntgen-angiografie kunnen vervangen indien de behandeling wordt beperkt tot dotteren. Hiermee kan een kleine daling in de kosten worden bereikt zonder dat dit een belangrijk verlies in effectiviteit tot gevolg heeft. Wanneer zowel dotteren en bypass operatie als behandelmogelijkheden worden beschouwd dan is de beste strategie om met een MRA of duplex ultrageluid onderzoek te beginnen en een röntgen-angiografie uit te voeren wanneer een bypass operatie wordt overwogen op basis van een niet-invasieve test. De combinatie van niet-invasieve onderzoeken gevolgd door een röntgen-angiografie in een deel van de patiënten levert dezelfde resultaten op als in

alle patiënten een röntgen-angiografie uitvoeren.

In de derde kosten-effectiviteits analyse werden ook MRA, het duplex ultrageluid onderzoek en de röntgen-angiografie vergeleken maar dan voor de Nederlandse situatie (Hoofdstuk 5). De absolute kosten-effectiviteits ratio's tussen Nederland en de Verenigde Staten waren verschillend maar de practische implicaties voor de beeldvormende diagnostiek en behandeling zijn gelijk. Achteraf bezien is dit resultaat niet verrassend, maar vooraf viel niet te voorspellen hoe de kosten-effectiviteits ratio zou veranderen wanneer de kosten voor de Nederlandse situatie zouden worden beschouwd. Over het algemeen zijn de kosten in de Nederlandse gezondheidszorg lager dan in de Verenigde Staten en wanneer bijvoorbeeld alle kosten in Nederland de helft zouden zijn van de kosten in de Verenigde Staten dan zou de kosten-effectiviteits ratio voor Nederland makkelijk te berekenen zijn. Echter, de verhouding tussen de Nederlandse en Amerikaanse kosten was niet dezelfde voor alle medische handelingen en daardoor was de incrementele ratio voor de Nederlandse situatie niet direct voorspelbaar. Hierbij is dan wel aangenomen dat de effectiviteit van de behandelingen in Nederland gelijk is aan de effectiviteit van de behandelingen in de Verenigde Staten.

Bij de uitgevoerde kosten-effectiviteits analyses werd niet gekeken naar de voorkeur van de patiënten. Het is mogelijk dat patiënten het ene onderzoek duidelijk prefereren boven het andere onderzoek en deze voorkeur hangt met name af van de mate van ongemak die patiënten ervaren bij het ondergaan van een onderzoek. In Hoofdstuk 7 is een studie uitgevoerd waarbij patiënten die ervaring hebben met de onderzoeken gevraagd werd naar hun voorkeuren. Voorkeuren werden gemeten met drie verschillende maten: een score van 0 (helemaal niet vervelend) tot 10 (heel erg vervelend), een techniek waarbij bepaald werd hoeveel de patiënt bereid is te betalen om het onderzoek te laten vervangen door een ander onderzoek en een techniek waarbij bepaald werd hoeveel vrije tijd de patiënt bereid is op te geven om het onderzoek te laten vervangen door een ander onderzoek. De resultaten lieten zien dat patiënten een voorkeur hadden voor MRA en duplex boven de röntgen-angiografie en er geen duidelijk verschil in voorkeur was tussen de MRA en duplex ultrageluid. Wanneer deze bevindingen worden meegenomen in de evaluatie van de beeldvormende diagnostiek dan versterkt dit de conclusie dat de MRA en het duplex ultrageluid onderzoek de röntgen-angiografie kunnen vervangen als initieel beeldvormend onderzoek.

Als de resultaten van de vorige paragrafen kort worden samengevat dan blijkt dat het systematisch literatuur-onderzoek verschillen aantoonde tussen de drie beeldvormende onderzoeken: MRA heeft een beter diagnostisch onderscheidend vermogen dan duplex ultrageluid en is bijna net zo accuraat als de röntgen-angiografie. De kosten-effectiviteits analyse, waarin alle relevante kosten en effecten van de drie beeldvormende onderzoeken werden beschouwd, toonde aan dat er geen belangrijke verschillen tussen de drie onderzoeken zijn. In deze analyse werd niet gekeken naar de voorkeuren van de patiënten. Deze waren echter

wel verschillend: patiënten gaven de voorkeur aan niet-invasieve onderzoeken boven de röntgen-angiografie. Als zowel naar de resultaten van de kosten-effectiviteits analyse als naar de resultaten van de studie met de patiënten-voorkeuren werd gekeken dan is de conclusie dat de MRA en het duplex ultrageluid onderzoek de röntgen-angiografie in vele gevallen zou kunnen vervangen bij patiënten met klachten van claudicatie en alleen selectief gebruik van de röntgen-angiografie nodig kan zijn als een bypass operatie wordt overwogen op basis van een MRA of duplex ultrageluid onderzoek.

In de Hoofdstukken 2 tot en met 5 en Hoofdstuk 7 werd steeds een vergelijking gemaakt tussen MRA, duplex ultrageluid en röntgen-angiografie, waarbij werd aangenomen dat deze onderzoeken op dit moment gebruikt worden in de klinische praktijk. De ontwikkeling van nieuwe beeldvormende onderzoeken voor de diagnostiek van perifeer arterieel vaatlijden staat niet stil. Vroeg in de ontwikkeling van nieuwe onderzoeken zijn parameters zoals diagnostisch onderscheidend vermogen en de kosten van het onderzoek vaak nog onzeker en hierdoor is het niet mogelijk om te bepalen of een nieuw onderzoek kosten-effectief zou zijn vergeleken met de onderzoeken die nu worden gebruikt in de kliniek. Echter, deze parameters zijn wel bekend van de onderzoeken die nu worden gebruikt en op basis hiervan kan geschat worden aan welke eisen een nieuw onderzoek zou moeten voldoen om kosten-effectief te kunnen zijn. In Hoofdstuk 6 zijn waarden voor onder andere diagnostisch onderscheidend vermogen en de kosten van het onderzoek geschat waarmee een nieuw beeldvormend onderzoek kosten-effectief zou kunnen zijn in vergelijking met de onderzoeken die nu worden gebruikt. De eisen die aan het nieuwe beeldvormende onderzoek worden gesteld lijken redelijk en zijn waarschijnlijk haalbaar voor beeldvormende onderzoeken in ontwikkeling.

Beeldvormend onderzoek voor perifeer arterieel vaatlijden wordt niet alleen gebruikt om vast te stellen welke behandeling het meest geschikt is voor de patiënt maar wordt ook gebruikt om regelmatig te controleren of de aangelegde bypass graft nog doorgankelijk is, zogenaamde surveillance. Surveillance van bypass grafts heeft als doel om vroegtijdig grafts op te sporen die dreigen te vernauwen of verstoppen. Er kan dan een hersteloperatie worden uitgevoerd om een eventuele amputatie van het been te voorkomen. Een amputatie van het been heeft een grote invloed op de kwaliteit van leven van de patiënt en brengt daarnaast hoge kosten met zich mee. In Hoofdstuk 8 werd gevonden dat de kosten van een surveillance programma met duplex ultrageluid gerechtvaardigd zijn ten opzichte van het aantal voorkomen amputaties wanneer werd vergeleken met het niet uitvoeren van een surveillance. Deze studie werd uitgevoerd in de periode van 1993 tot en met 1996 toen de MRA nog niet standaard overal beschikbaar was. Waarschijnlijk zal een surveillance programma met MRA de voorkeur hebben boven een surveillance programma met duplex ultrageluid. Surveillance met röntgen-angiografie is geen geschikte keuze omdat een patiënt zonder klachten dan wordt blootgesteld aan de

kleine maar toch bestaande risico's van het onderzoek.

Het laatste Hoofdstuk (9) begint met de Engelse samenvatting van dit proefschrift. Vervolgens worden de voor- en nadelen van besliskundige modellen en klinische studies op een rijtje gezet waarbij werd geconcludeerd dat de twee studie types elkaar aanvullen in plaats van uitsluiten. In kosten-effectiviteits analyses worden vaak incrementele kosten-effectiviteits ratio's gebruikt als uitkomstmaat met als nadeel dat kleine verschillen tussen alternatieven niet gezien worden. Het gebruik van zogenaamde 'net health benefits', een maat waarin de kosten en effecten worden gecombineerd in een getal, zou hier een oplossing voor kunnen zijn. Daarnaast wordt in Hoofstuk 9 ook uitgebreid besproken hoe patiënten-voorkeuren meegenomen zouden kunnen worden in kosten-effectiviteits analyses. Tot slot worden de nieuwe ontwikkelingen op het gebied van de beeldvormende diagnostiek voor perifeer arterieel vaatlijden besproken.

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Karen Visser was born on April 27th, 1974 in Apeldoorn, the Netherlands, where she graduated in 1992 at the "Katholiek Veluws College". In 1997 she obtained her degree in Biomedical Health Sciences study at the University of Nijmegen. During her study she performed a research project at the Julius Centre for Patient Oriented Research, Utrecht Medical Centre and the St. Antonius Hospital Nieuwegein. In August 1997 she started as a PhD-student on the research project as described in this thesis at the University of Groningen under the supervision of Prof.Dr. MGM Hunink. In May 1998 she continued her research project at the Assessment of Radiological Technology (ART) group at the Erasmus University Medical Centre Rotterdam (under supervision of Prof. Dr. MGM Hunink), which is a collaboration between the department of Epidemiology & Biostatistics (chairman Prof. Dr. AB Hofman) and the department of Radiology (chairman Prof. Dr. GP Krestin). One year later she received her Master of Science in Clinical Epidemiology at the Netherlands Institute of Health Sciences (NIHES). Part of the research described in this thesis was done at the Harvard School of Public Health and Decision Analysis and Technology Assessment group, department of Radiology, Massachusetts General Hospital, Harvard Medical School in Boston (under supervision of KM Kuntz, ScD and GS Gazelle, MD, PhD). Since August 2001 she works as a post-doc at the ART-group where she continues her research on diagnostic imaging tests, especially in the field of peripheral arterial disease.