Non-Invasive Diagnostic Imaging of Peripheral Arterial Disease

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Acknowledgements

Non-Invasive Diagnostic Imaging of
Peripheral Arterial Disease

Niet-Invasieve Beeldvormende Diagnostiek
voor Perifeer Arterieel Vaatlijden

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General Introduction
Chapter 1

Peripheral arterial disease (PAD) is an expression of atherosclerosis in the lower limb distal to the aortic bifurcation, which is a major problem in the population of 55 years and older (1). The first manifestation of symptomatic PAD is usually intermittent claudication. In a minority of patients, the disease progresses to critical limb ischemia, i.e. rest pain and tissue necrosis. The diagnosis of PAD is based on patient history, physical examination, and a decreased ankle-brachial pressure index.

Diagnostic imaging work-up is performed when PAD becomes lifestyle limiting and a revascularization procedure is considered. In patients with PAD the level, multiplicity, and severity of stenoses shows significant variation that ultimately impacts clinical decision-making (2, 3). Digital subtraction angiography (DSA) has traditionally been used for anatomic assessment of PAD. DSA provides a precise road map for planning treatment, but owing to its invasiveness, DSA is associated with a risk of morbidity and mortality (4). Therefore, non-invasive imaging tests including duplex ultrasound (DUS), multi-detector computed tomographic angiography (CTA), and contrast-enhanced magnetic resonance angiography (MRA) are increasingly used for the initial evaluation of patients with PAD.

DUS was introduced into clinical practise in the early eighties (5, 6). DUS provides both anatomical and functional information about the arterial system and has been shown to be a reliable modality with fairly good sensitivity and specificity (7, 8). DUS is, however, operator dependent (9) and does not provide a precise roadmap for planning treatment.

MRA became available for non-invasive imaging of the peripheral arteries in the early nineties (10-12). Subsequently, the introduction of contrast-enhanced MRA offered advantages in the terms of speed of acquisition, freedom of artifacts, and accuracy. Nowadays contrast-enhanced MRA has gained widespread use for imaging peripheral arterial disease (13-17). Disadvantages of MRA include the higher investment cost for equipment, the small number of cases in whom the image is uninterpretable due to artifacts, and also contraindications like having a pacemaker and being claustrofobic (18).

More recently, in the late nineties multi-detector row CT scanners have been introduced for the non-invasive diagnostic imaging work-up of PAD. The use of multi-detector row technology has resulted in shorter acquisition time, increased volume coverage, lower dose of contrast medium, and improved spatial resolution (19, 20). Results of several studies have shown that multi-detector row CTA is accurate for imaging peripheral arteries (21-28). The main disadvantages of CTA is the use of radiation (29), the use of potentially nephrotoxic iodinated contrast medium, the time-consuming 3D reconstruction techniques, and the difficulty in assessing arterial luminal stenosis in the presence of vessel wall calcifications (30-32).

The optimal non-invasive diagnostic imaging work-up for patients with PAD remains to be clarified. To determine which non-invasive test is preferred as initial imaging test in clinical practise we need to take into account not only the diagnostic accuracy of each test, but also the related effects of diagnostic imaging tests on treatment planning, functional improvement, quality of life, and costs.(33, 34)

Aim and outline of this thesis

The aim of this thesis was to determine the optimal non-invasive diagnostic imaging test for the initial evaluation of patients with PAD. In the evaluation of new diagnostic tests the study of its interobserver agreement plays an important role. Therefore, interobserver agreement of MRA and CTA was compared in chapter 2.

Quality of life is an important outcome measure in the evaluation of the effects of diagnostic imaging tests and subsequent treatment. Chapter 3 describes a comparison of generic and disease-specific questionnaires for the assessment of quality-of-life in patients with peripheral arterial disease.

The costs and effects of DUS, MRA, and CTA were evaluated using the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) multicenter randomized controlled trial (RCT), which assessed clinical utility, quality of life, functional patient outcomes, and actual diagnostic and therapeutic costs related to the initial imaging test during 6 months follow-up (chapter 4,5, and 6).

Another important point in assessing the optimal non-invasive imaging test for PAD is the difficulty in assessing arterial luminal stenosis in extensively calcified vessels on CTA. Chapter 7 evaluates the impact of vessel wall calcifications on the clinical utility of CTA and identifies clinical predictors of vessel wall calcifications to select patients for whom CTA is less clinically useful.

When implementing the optimal non-invasive diagnostic imaging test as found with the RCT, we may still make the wrong decision. Value of information analysis considers both the probability and the consequences of making the wrong decision based on the currently available evidence to estimate the expected benefit of a future study to decrease the remaining uncertainty (chapter 8).

Finally, chapter 9 summarizes the main findings of the preceding chapters and gives a general discussion on non-invasive imaging tests for PAD and the methodological issues involved.

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Interobserver Agreement for Interpretation of Contrast-Enhanced Three-Dimensional MR Angiography and Multi-Detector Row CT Angiography in Peripheral Arterial Disease

Chapter 2

Abstract

Purpose
To compare interobserver agreement for interpretation of contrast-enhanced three-dimensional magnetic resonance angiography (MRA) and multi-detector computed tomographic angiography (CTA) in patients with peripheral arterial disease.

Materials and Methods
Of 226 eligible patients, 69 were excluded. The remaining 157 consecutive patients were prospectively randomized to either MRA (n = 78) or CTA (n = 79). Two readers independently evaluated arterial stenosis/ occlusion on MRA (2157 segments) and CTA (2419 segments) by using a five-point ordinal scale. Vessel wall calcifications were noted. Interobserver agreement for each technique was evaluated with a weighted kappa (K_w) statistic.

Results
Although both were excellent, the interobserver agreement for MRA (K_w = 0.90; 95% CI: 0.89-0.92) was higher than that for CTA (K_w = 0.85; 95% CI: 0.83-0.86) for reporting the degree of arterial stenosis/ occlusion in all segments. For the different anatomic locations the interobserver agreement for MRA vs. CTA was: aortoiliac (K_w = 0.91 vs. K_w = 0.84), femoropopliteal (K_w = 0.91 vs. K_w = 0.87), and crural (K_w = 0.90 vs. K_w = 0.83). The interobserver agreement of CTA significantly decreased in the presence of calcifications but was still good for all anatomic locations. The lowest agreement was found for crural segments in the presence of calcifications (K_w = 0.67). With MRA there were 12-times more nondiagnostic segments than with CTA (81 vs. 7).

Conclusion
Interpretation of MRA and CTA for peripheral arterial disease has an excellent interobserver agreement, MRA has a higher interobserver agreement than CTA, and calcified segments on CTA significantly decrease the interobserver agreement.

Introduction

Peripheral arterial disease (PAD) is a local manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation, which is a major problem in the population of 55 years and older (1). In patients with PAD the level, multiplicity, and severity of stenoses shows significant variation that ultimately impacts clinical decision-making (2, 3). Digital subtraction angiography (DSA) has traditionally been used for anatomic assessment of PAD. DSA provides a precise road map for planning treatment, but owing to its invasiveness, DSA is associated with a risk of morbidity and mortality (4).

Both contrast-enhanced three-dimensional magnetic resonance angiography (MRA) and multi-detector computed tomographic angiography (CTA) are increasingly used for noninvasive vascular imaging. MRA has gained widespread use for imaging peripheral arterial disease (5-7). Disadvantages of MRA include difficulty in depicting small vessels because of the limited spatial resolution and a tendency to overestimate the degree of stenosis because of signal intensity loss in tightly stenotic lesions (8).

The recently introduced multi-detector row CT scanners have substantially improved CTA for peripheral arterial disease. The use of multi-detector row technology has resulted in shorter acquisition time, increased volume coverage, lower dose of contrast medium, and improved spatial resolution (9, 10). Results of several studies have shown that multi-detector row CTA is accurate for imaging peripheral arteries (11-16). The main disadvantages of CTA is the use of radiation, the use of potentially nephrotoxic iodinated contrast medium, the time-consuming 3D reconstruction techniques, and the difficulty in assessing arterial luminal stenosis in the presence of vessel wall calcifications (17-19). In the evaluation of new diagnostic tests the study of its interobserver agreement plays an important role (20). The accuracy of a test can never be perfect if assessment by different observers shows significant variation. Furthermore, it is likely that poor interobserver agreement can cause variation in clinical decision-making. Thus, apart from evaluating accuracy in comparison to a reference standard, it is important to evaluate the reproducibility, including interobserver agreement of a test.

The purpose of this study was to compare the interobserver agreement for the interpretation of contrast-enhanced 3D MR angiography and multi-detector row CT angiography in patients with peripheral arterial disease.

Materials and methods

Patients
The patient population recruited for this study are the patients of a randomized controlled trial concerning patient outcomes and costs of MRA compared to CTA as the initial imaging test in the diagnostic work-up of PAD.

Inclusion criteria for participation in the study were age older than 18 years, symptomatic PAD, an ankle-brachial index of less than 0.90 and referral for diagnostic

imaging work-up to evaluate the feasibility of a revascularisation procedure. Exclusion criteria included contraindications for MR angiography (eg, pacemaker or claustrophobia) or CT angiography (eg, severe renal insufficiency or adverse reactions to iodinated contrast agent), and the necessity of an acute intervention. The subjects were randomized across two diagnostic strategies consisting of MRA and CTA. The study was approved by the institutional review board, and informed consent for the study and all manuscripts deriving from the study was obtained from all patients.

MR Angiography

All examinations were performed with a 1.5-T imager (Signa; GE Medical Systems, Milwaukee, Wis), which was equipped with echospeed gradients (40 mT/m, 150 mT/m/msec). A dedicated peripheral vascular phased-array coil (USA Instruments, Inc, Aurora, Oh) was used for signal reception.

For bolus-chase MRA, commercially available software (SmartStep, GE Medical Systems) was used. The imaging protocol included the following imaging procedures. First localizer MR images were obtained with transverse time-of-flight (TOF) scout views of three locations: aortoiliac, femoropopliteal, and crural. Parameters for the TOF sequence were as follows: repetition time, 23 msec; echo time, 4.4 msec; flip angle, 70°; bandwidth, 15.63 kHz; slice thickness, 8.0 mm; matrix, 256x128. Acquisition times were between 1.31 min and 2.37 min.

On the basis of the localization study three MR angiographic volumes were prescribed that covered the abdominal and lower extremity vasculature. Then a contiguous three-dimensional MR angiographic mask image was acquired with integrated automated table movement. The imaging parameters for acquisition of the mask images were identical to those used for acquisition of the contrast-enhanced images. The following parameters were used: repetition time, 4.8/ 4.8/ 5.1 msec; echo time, 1.5/ 1.5/ 1.5 msec; flip angle, 30°/ 30°/ 30°; field of view, 400 x 280/ 400 x 320/ 400 x 360 mm; slice thickness, 2.6/ 2.0/ 2.0 mm; matrix, 384 x 192/ 384 x 192/ 512 x 512; phase encoding, centric/ centric/ elliptic centric for the aortoiliac, the femoropopliteal, and crural location, respectively. Zero interpolation was performed with adding of extra zeros to the k space in all three planes before Fourier transformation to improve image quality.

After the mask acquisitions, contrast-enhanced imaging was started at the aortoiliac location, which was automatically initialized after automated bolus detection (SmartPrep, GE Medical Systems). Subsequently, three-dimensional MR angiographic images of the femoropopliteal and crural location were acquired sequentially.

The contrast agent (gadopentetate dimeglumine (Magnevist); Schering, Berlin, Germany) was administered in the antecubital vein by using a 20 gauge intravenous catheter. Each patient received 45 ml of contrast agent (0.5 mmol/ ml) at a rate of 1.2 ml/sec for the first 10 ml, and 0.8 ml for the remaining 35 ml (total injection duration; 52 sec), followed by a saline flush of 15 ml, at 0.8 ml/sec. For this dual phase injection an automated injector (Spectris; Medrad, Indianola, Pa) was used to ensure precise contrast agent injections.

We used a subtraction technique before maximum intensity projections (MIP) reconstructions were performed. The mask images were subtracted from the contrast-enhanced images at each station. Twelve rotated volume MIP images ranging from -90° to +90° were reconstructed for each subtracted dataset. These volume MIP images were documented on film and sent together with the source data to a remote workstation (Advanced Windows 3.1, GE Medical Systems).

Multi-Detector Row CT Angiography

Multi-detector CTA was performed on a Sensation 16 scanner (Siemens Medical Systems, Forchheim, Germany). Patients were in the supine position on the CT table with their legs held together.

After obtaining an initial scout image (120 kV, 100 mAs), the scanning range was planned to encompass the entire vascular system from the diaphragm to the level of the ankles. For optimal intraluminal contrast enhancement, the delay time between start of contrast material administration and start of scanning was obtained for each patient individually by using a bolus-tracking technique (CARE-Bolus, Siemens). Subsequently, a nonionic contrast material (Visipaque 320 mgI/ ml, Amersham Health, Buckinghamshire, UK) was administered through a 20 gauge cannula that was placed into the patient's antecubital vein for a total volume of 120 ml.

The contrast material was administered with an automatic power injector (EnVision CT; Medrad, Indianola, Pa) at a flow rate of 3 ml/sec. Ten seconds after the start of contrast material administration, a series of dynamic low-dose monitoring scans (120 kV, 20 mAs, 0.5 second scanning time, 1.25-second interscan delay) were performed. After reaching the preset attenuation of +100 HU above baseline attenuation, the CT scan was automatically triggered. Data acquisition was performed craniocaudally with the following parameters: collimation 0.75 mm, number of detector rows 16, table feed 18 mm per rotation, gantry rotation period 0.5 sec, pitch 1.5, X-ray tube voltage setting 120 kV, current 140 mAs.

Transverse sections were reconstructed with a 2-mm slice thickness at an interval of 1 mm. Two orthogonal curved planar reformations were created along the longitudinal axis of the aorta through both common and external iliac arteries and the common femoral artery by using commercially available software on the CT console. All data were then transferred to a dedicated workstation (Easy Vision, Philips, Best, the Netherlands) that allowed postprocessing of the images.

The reconstructions were performed by one of two technologists experienced in 3D post-processing and segmentation techniques. Segmentation was performed of both bone structures and vessel wall calcifications resulting in images containing the contrast-enhanced vascular lumen without vessel wall calcifications and bones. Of these datasets rotating volume MIP images were generated by using the commercially available software installed on the workstation. This resulted in 12 angiogram-like images rotating over 180 degrees for aortoiliac, femoropopliteal, and crural arteries.

Image Analysis

All MR and CT angiograms were interpreted independently by two readers. Reader 1 is a vascular radiologist and reader 2 is a dedicated researcher with 2.5 years of general radiology training and one year experience in vascular radiology. Both readers have extensive experience in interpreting MRA and CTA.

The volume MIPs of both MRA and CTA and the curved planar reconstructions of CTA were printed. The reconstructed coronal MR and transverse CT images (source data), along with the standardized volume MIPs and curved planar reconstructions were available for both readers on dedicated workstations. For image interpretation, the readers used both the hard copies and the source data on the workstations. In almost all cases the readers used the source data. In a few cases, i.e. if the volumes MIPs provided a clear-cut map of all vessels the source data were not used.

For analysis purposes, the arterial vascular system was divided into 3 anatomic locations of in total 31 segments, namely the aortoiliac arteries consisting of the distal aorta, the paired common iliac arteries, and the external iliac arteries; the femoropopliteal arteries consisting of the paired common femoral arteries, the deep femoral arteries, the superficial femoral arteries (proximal and distal part), and the popliteal arteries (above and below the knee); the crural arteries consisting of the paired anterior tibial arteries (proximal and distal part), the tibial peroneal trunk, the posterior tibial arteries (proximal and distal part), and the peroneal arteries (proximal and distal part).

Segments not contained within the imaging volume or not interpretable because of venous enhancement or artifacts were considered nondiagnostic. All other segments were assessed for the presence of stenotic disease. The following five point ordinal scale was used to grade stenotic or occlusive disease: 0 for 0-19% stenosis, 1 for 20-49% stenosis, 2 for 50-74% stenosis, 3 for 75-99% stenosis, and 4 for occlusion. When two or more stenotic luminal lesions were detected in the same vessel segment, the most severe lesion was used for grading and analysis. The readers recorded the presence of vessel wall calcifications on CTA and recorded nondiagnostic segments on both MRA and CTA.

Statistical Analysis

Interobserver agreement was determined by calculating a weighted kappa (K_w) statistic, which takes the degree of disagreement into account and accounts for differences in the importance of disagreement. The K statistic indicates the agreement beyond chance. Strength of agreement can be interpreted as poor (K <0.20), fair (K =0.21 to 0.40), moderate (K =0.41 to 0.60), good (K =0.61 to 0.80), or excellent (K =0.81 to 1.0) (21). If a segment was classified as nondiagnostic by at least one of the observers the segment was omitted from the weighted -calculations for reporting the degree of arterial stenosis. In addition, the percent overall agreement including the nondiagnostic segments was calculated. We used an unweighted kappa statistic to calculate the interobserver agreement for classifying nondiagnostic versus diagnostic segments. The K-values can be expected to be higher if legs without symptoms are included in the analysis because it is likely that in nondiseased segments interobserver agreement is higher. Therefore, we performed a second analysis in which we included only the most symptomatic leg of each

patient. If symptoms were the same in both legs we randomly selected one leg. In each symptomatic leg one segment per anatomic location was randomly selected. Thus, in this secondary analysis the number of segments analyzed was reduced from 31 to 3 segments per patient (i.e. one aortoiliac, one femoropopliteal, and one crural segment).

Additional analyses were performed to examine the effect of vessel wall calcifications, the effect of disease severity (claudication vs. critical ischemia), and the effect of learning during the trial period (first half vs. second half). An unweighted kappa statistic was used to calculate the interobserver agreement for diagnosing hemodynamically insignificant (i.e. stenosis < 50%) versus significant (i.e. stenosis > 50%) arterial stenosis and for determination of non-occluded (i.e. stenosis < 99%) versus occluded arteries. Calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il) and SAS 8.2 for Windows (SAS Institute Inc., Cary, NC) statistical packages.

Results

From December 2001 to September 2003, we recruited consecutive patients who were referred from the Department of Vascular Surgery at our university hospital. A total of 262 patients were potentially eligible (*Figure 1*). Thirty-six patients did not fulfill all
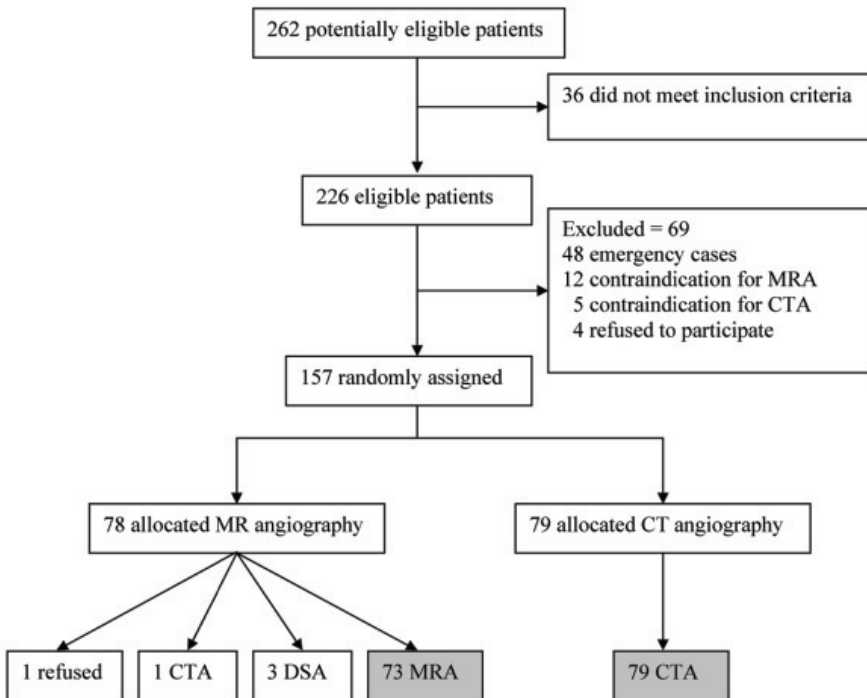
Figure 1. Flow diagram illustrates the reasons for exclusion, random assignment of patients to diagnostic test groups, and the diagnostic tests that the patients actually underwent.

inclusion criteria. Forty-eight patients were excluded because they needed an acute intervention, 12 patients because they had a contraindication for MRA, and 5 patients because they had a contraindication for CTA. Four patients refused to participate in the study. Seventy-eight patients were assigned to MRA and seventy-nine to CTA. Of the 78 patients assigned to MRA 73 actually underwent MRA. Three patients underwent digital subtraction angiography because of unknown claustrophobia (n = 2) and the necessity of acute intervention due to progressive disease (n = 1). One patient underwent CTA because of logistical problems. One patient refused MRA and underwent no other diagnostic test. Of the 79 patients allocated to CTA all underwent CTA. The baseline characteristics are described in *Table 1*.

Table1: Baseline Characteristics of Patients

Characteristic	MR angiography group (n = 78)	CT angiography group (n = 79)
Age (y)*	63 ± 11 (38-78)	64 ± 12 (20-93)
Male sex	52 (67)	50 (63)
Critical ischemia	19 (24)	14 (18)
Diabetes Mellitus	26 (33)	17 (22)
Arterial hypertension	39 (50)	40 (51)
Hyperlipidemia	41 (53)	41 (52)
Smoking	29 (37)	31 (39)
Cardiac disease	31 (40)	20 (25)
Cerebrovascular disease	14 (18)	14 (18)
Renal insuffiency[†]	4 (5)	1 (1)

Note. Data are numbers of patients and percentages in parentheses.
* Mean age ± SD, range in parentheses.
[†] Mild renal insuffiency or hemodialysis with permission of the nephrologist to undergo a CTA.

In the group of MRA 2238 segments were imaged. Twenty-five segments were not imaged because of lower leg amputation (n = 23) and congenital agenesis of the tibioperoneal trunk (n = 2). On MRA 81 segments were nondiagnostic, which were mainly crural segments and mainly due to venous enhancement. This leaves 2157 segments in the group of MRA on which the analyses for reporting the degree of arterial stenosis is based. In the group of CTA 2426 segments were imaged. Twenty-three segments were not imaged because of lower leg amputation (n = 17) and congenital agenesis of the tibioperoneal trunk (n = 6). On CTA only 7 segments were nondiagnostic, which were due to a total knee arthroplasty, leaving 2419 segments on wich the analyses for reporting the degree of arterial stenosis is based.

The interobserver agreement for reporting the degree of arterial stenosis/ occlusion in all segments was statistically significant lower for CTA (K_w = 0.85; 95%-CI, 0.83-0.86) than for MRA (K_w = 0.90; 95%-CI, 0.89-0.92, p<0.001). Nevertheless, there was excellent interobserver agreement of both MRA and CTA for reporting the degree of arterial stenosis/ occlusion in all segments (*Table 2*). The percent overall agreement was 89% (95%-CI, 88-90%) for MRA and 83% (95%-CI, 81-85%) for CTA (*Table 2*). The results of the primary and secondary analysis were similar within the different anatomic locations (*Table 3*).

Table 2A. Interobserver agreement of MR angiography for grading stenosis in all segments

	Reader 1						
Reader 2	0-19%	20-49%	50-74%	75-99%	Occlusion	Nondiagn	Total
0-19%	1393	39	8	3	3	2	1448
20-49%	59	92	19	0	2	0	172
50-74%	4	10	81	23	1	0	119
75-99%	4	1	16	82	7	0	110
Occlusion	5	1	3	11	290	2	312
Nondiagn	21	1	4	0	7	44	77
Total	1486	144	131	119	310	48	2238

Note. K_w = 0.90 (95%-CI, 0.89-0.92). Percent overall agreement is 89% (95%-CI, 88-90%). Data are the number of segments. Nondiagn = nondiagnostic.

Table 2B. Interobserver agreement of CT angiography for grading stenosis in all segments

	Reader 1						
Reader 2	0-19%	20-49%	50-74%	75-99%	Occlusion	Nondiagn	Total
0-19%	1225	88	18	3	6	0	1340
20-49%	102	223	23	8	5	0	361
50-74%	20	31	139	37	0	0	227
75-99%	4	6	16	121	14	0	161
Occlusion	12	1	3	12	302	0	330
Nondiagn	1	0	0	0	0	6	7
Total	1364	349	199	181	327	6	2426

Note. K_w = 0.85 (95%-CI, 0.83-0.86). Percent overall agreement is 83% (95%-CI, 81-85%). Data are the number of segments. Nondiagn = nondiagnostic.

Table 3 A. Interobserver agreement of the different anatomic stations including both legs (primary analysis)

Anatomic location	Interobserver agreement in MR angiography		Interobserver agreement in CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
Aortoiliac	353	0.91 (0.88-0.94)	395	0.84 (0.80-0.88)
Femoropopliteal	861	0.91 (0.89-0.93)	938	0.87 (0.85-0.89)
Crural	943	0.90 (0.88-0.92)	1086	0.83 (0.80-0.85)

Note. n = number of segments, K_w = weighted kappa, 95%-CI = 95% confidence interval.

Table 3B. Interobserver agreement of the different anatomic stations including only the symptomatic leg and only one segment per station (secondary analysis)

Anatomic location	Interobserver agreement in MR angiography		Interobserver agreement in CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
Aortoiliac	70	0.92 (0.86-0.98)	79	0.84 (0.76-0.92)
Femoropopliteal	72	0.88 (0.79-0.96)	78	0.84 (0.74-0.93)
Crural	71	0.88 (0.79-0.97)	78	0.82 (0.71-0.93)

Note. n = number of segments, K_w = weighted kappa, 95%-CI = 95% confidence interval.

Table 4. Interobserver agreement of CT angiography in segments with and without vessel wall calcifications

Anatomic location	Interobserver agreement in segments without vessel wall calcificationscalcifications		Interobserver agreement in segments with vessel wall	
	n	K_w (95%-CI)	n	K_w (95%-CI)
Aortoiliac	124	0.94 (0.90-0.98)	271	0.79 (0.73-0.84)
Femoropopliteal	549	0.91 (0.88-0.95)	389	0.79 (0.76-0.83)
Crural	841	0.84 (0.81-0.88)	245	0.67 (0.60-0.73)

Note. n = number of segments, K_w = weighted kappa, 95%-CI = 95% confidence interval.

Interobserver agreement for classifying nondiagnostic versus diagnostic segments was excellent for CTA (K= 0.92; 95% CI: 0.77-1.00) and was good for MRA (K = 0.70; 95% CI: 0.60-0.79). The interobserver agreement of CTA for reporting the degree of arterial stenosis/occlusion in all segments was statistically significant lower for arterial segments with vessel wall calcifications than for segments without vessel wall calcifications (*Table 4*).

In the presence of vessel wall calcifications there was still good interobserver agreement in all anatomic locations . The lowest agreement was found for crural segments in the presence of calcifications (K_w = 0.67: 95% CI: 0.60-0.73).

Subgroup analysis for disease severity (claudication vs. critical ischemia) showed no difference in interobserver agreement of MRA (K_w = 0.90; 95% CI: 0.88-0.92 vs. K_w = 0.92; 95% CI: 0.89-0.94) and CTA (K_w = 0.84; 95% CI: 0.82-0.86 vs. K_w = 0.86; 95% CI: 0.83-0.90) (*Table 5*). Subgroup analysis for trial period (first half vs. second half) showed no difference in interobserver agreement of MRA (K_w = 0.91; 95% CI: 0.90-0.93 vs. K_w =

Table 5: Interobserver agreement of MR angiography and CT angiography in different subgroups

Subgroup	Interobserver agreement in MR angiography		Interobserver agreement in CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
Claudication	1667	0.90 (0.88-0.92)	1997	0.84 (0.82-0.86)
Critical Ischemia	490	0.92 (0.89-0.94)	422	0.86 (0.83-0.90)
First half of trial period	1089	0.91 (0.90-0.93)	1235	0.88 (0.86-0.90)
Second half of trial period	1068	0.89 (0.87-0.91)	1184	0.81 (0.78-0.83)

Note. n = number of segments, K_w = weighted kappa, 95%-CI = 95% confidence interval.

0.89; 95% CI: 0.87-0.91). Interobserver agreement of CTA was lower for the second half of the trial period (K_w = 0.88; 95% CI: 0.86-0.90 vs. K_w = 0.81; 95% CI: 0.78-0.83) (*Table 5*). Interobserver agreement for diagnosing hemodynamically insignificant versus significant arterial stenosis was excellent for both MRA (K = 0.92; 95% CI: 0.91-0.94) and CTA (K = 0.86; 95% CI: 0.84-0.89). Interobserver agreement for determination of non-occluded versus occluded arteries was excellent for both MRA (K = 0.94; 95% CI: 0.92-0.96) and CTA (K = 0.91; 95% CI: 0.88-0.93).
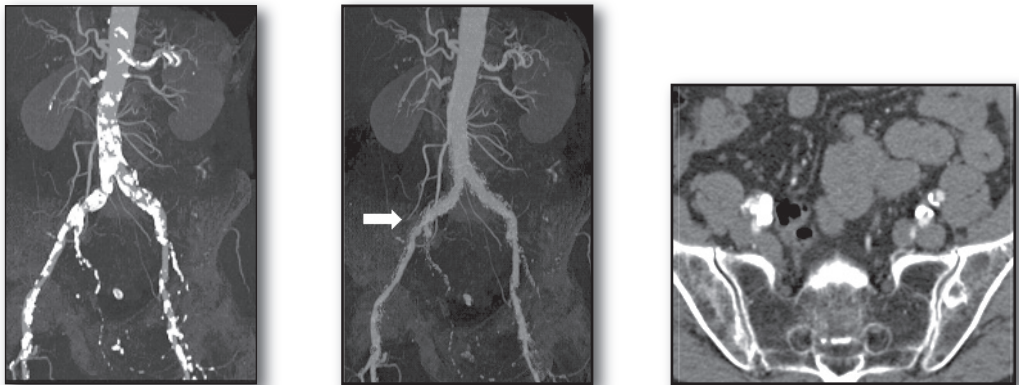
a.   b.   c.

Figure 2. Images in a 68-year-old man with right leg claudication and left leg critical ischemia. (a) A volume MIP image (anteroposterior view) of CTA with only bone segmentation. There are extensive vessel wall calcifications. (b) A volume MIP image (anteroposterior view) with segmentation of both bone and vessel wall calcifications. There seems to be an arterial stenosis just distal to the right iliac bifurcation (arrow). (c) Even on transverse source images it was difficult to assess the degree of stenosis due to vessel wall calcifications.

Discussion

Minimal invasive imaging techniques are increasingly used for clinical decision-making in patients with suspected arterial occlusive disease. Therefore, it is important that the image interpretation of these new techniques is reproducible. Our results demonstrate that interobserver agreement for interpretation of MRA and CTA for peripheral arterial disease is excellent in both, is significantly higher for MRA than for CTA, and significantly decreased for calcified segments on CTA.

Literature about interobserver agreement of MRA and CTA in patients with peripheral arterial disease is scarce. Most articles only describe agreement between two different techniques and if they report interobserver agreement it is difficult to compare with our results because they often use Cohen's kappa statistic instead of the weighted kappa statistic as we did. For MRA we only found one weighted K-value of 0.86 representing interobserver agreement in all segments (5). For CTA we did not find any weighted K-values in the literature. For DSA a weighted K-value of 0.87 has been reported (22), which is similar to our results for MRA and CTA.

Our expectation that K-values could have been overestimated by including nondiseased segments was not confirmed by the secondary analysis. In fact, including only the most symptomatic leg of each patient with only one segment per station yielded K-values very similar to the K-values of the primary analysis (*Table 3*). Furthermore, in both the primary and secondary analysis we found excellent interoberver agreement for both MRA and CTA in all locations.

Vessel wall calcifications on CT angiograms have been shown in several studies (19, 23, 24) to affect image interpretation. In our experience, extensive arterial wall calcifications of aortoiliac, femoropopliteal, and crural arteries are frequently seen in patients with peripheral arterial disease and interfere with image interpretation (*Figure 2*). The small vessel diameter combined with vessel wall calcifications may have contributed to the lowest agreement occurring in the crural arteries. It is important to note that the apparent obscuration of the arterial lumen by vessel wall calcifications strongly depends on the window settings. Therefore adjusting the window settings is a way to minimize "blooming" of calcium. Despite the impairment of vessel analysis in the presence of vessel wall calcifications, the possibility of localizing arterial wall calcifications that may have therapeutic relevance may be an advantage of multidetector CTA (25).

We expected that there might be a learning effect during the trial period, which would result in an increase of the interobserver agreement over time. To evaluate whether this effect was present we divided our data in two groups representing the first and second half of the trial period. Although this method does not reflect a true learning process on a case-by-case basis, it nevertheless is useful to document changes in data perception with increasing experience. For MRA interobserver agreement was similar for both the first and second half of the trial period. For CTA the interobserver agreement decreased during the trial period. A possible explanation for our findings may be that the observers became less meticulous in distinguishing between grade 0 (0-19% stenosis) and

1 (20-49% stenosis) or between grade 2 (50-74% stenosis) and 3 (75-99% stenosis) due to routine and the realisation that these distinctions are less important clinically. This was especially true for CTA because image interpretation is more time-consuming than for MRA due to the many source images and because image interpretation is hampered by vessel wall calcifications.

We acknowledge several limitations of our study. First, we did not study intra-observer agreement, although this information may have been interesting. However, since the interobserver agreement was excellent, it is likely that the intra-observer agreement is excellent too. A second possible limitation relates to the measurement of the severity of stenoses. The degree of stenoses was not measured with electronic or manual calipers, which as a consequence introduces a more subjective judgment. Quantitative computerized assessment of the degree of stenosis reduces interobserver variability (26). On the other hand, our scoring system, which was visual assessment, may well reflect daily clinical practice in our hospital and probably other hospitals in which computerized quantitative measurement will not yet be used on a routine basis.

An additional limitation is that we had a high number of nondiagnostic segments on MRA. Performing an initial high resolution MRA sequence of the tibial vessels may reduce the number of nondiagnostic segments. Furthermore, all nondiagnostic segments were omitted from the calculations of the weighted kappa values for reporting the degree of arterial stenosis. We omitted the nondiagnostic segments because there is no meaningful and logical position where the nondiagnostic category can be included in the categorical scale for grading arterial stenosis. Furthermore, our method of analysis is consistent with daily clinical practice where a nondiagnostic segment will be ignored or re-imaged before final treatment is planned. We acknowledge that it is important to have information about nondiagnostic segments and therefore we reported how many segments were nondiagnostic on MRA and CTA and calculated the percent overall agreement, which included the nondiagnostic segments. Furthermore, we calculated an unweighted kappa value for classifying segments as nondiagnostic versus diagnostic.

Finally, we did not include the dorsal pedal and the plantar arteries in the kappa calculations because the foot is not routinely examined with MRA and CTA in our hospital.

In conclusion, the results of our study demonstrated that interpretation of MRA and CTA for peripheral arterial disease has an excellent interobserver agreement, MRA has a higher interobserver agreement than CTA, and calcified segments on CTA significantly decrease the interobserver agreement. The results support the increasing use of both MRA and CTA in the diagnostic imaging work-up of patients with peripheral arterial disease.

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Comparison of generic and disease-specific questionnaires for the assessment of quality-of-life in patients with peripheral arterial disease

Chapter 3

Abstract

Purpose
The purpose of the present study was to compare the ability of generic and disease-specific questionnaires to assess quality of life (QoL) at baseline and to detect change in QoL after treatment in patients with peripheral arterial disease (PAD).

Materials and Methods
In the prospective multicenter trial, 514 patients with PAD who needed imaging workup and had an ankle brachial pressure index (ABPI) <0.90 were included. Patients with severe co-morbidity were excluded, leaving a study population of 450 patients. Patients completed two generic questionnaires (SF-36 and Euroqol-5D) and one disease-specific questionnaire (VascuQol) at baseline and after 6 months of follow-up. Rutherford classification, treadmill walking distance, were determined at baseline and after 6 months of follow-up and were considered indicators of disease severity. Each of the three questionnaires was evaluated for its ability to discriminate between severe and mild disease at baseline, and to discriminate between a large and small change in disease severity after follow-up, using receiver operating characteristic (ROC) curves and areas under the curves (AUCs). The underlying assumption was that disease severity is a major determinant of QoL. This implies that the validity of a QoL questionnaire is reflected by its ability to discriminate between mildly and severely diseased patients.

Results
At baseline 443 patients and after follow-up 386 patients completed questionnaires. At baseline no significant (P>.05) differences were observed between AUCs for the total scores of the three questionnaires, indicating that all three questionnaires assessed the disease severity equally well. After follow-up the AUCs for the VascuQol were significantly higher than the AUCs for the SF-36 and Euroqol-5D, with respect to detection of improvement in Rutherford classification (P<.05), indicating that change in disease severity after follow-up was best detected by the VascuQol.

Conclusion
The VascuQol is the preferred questionnaire as outcome measure for QoL in future trials and clinical follow-up of patients with PAD.

Introduction

Peripheral arterial disease (PAD) is a chronic condition with a high morbidity which is reflected in an impaired quality-of-life (QoL) (1-3). The major treatment goal for PAD is to improve functional status of the patient and to relieve disability. Treatment of PAD is usually evaluated in terms of clinical parameters such as Rutherford classification, ankle brachial pressure index (ABPI) and walking distance. A major drawback of these clinical parameters is that they poorly reflect the perspective of the patient after treatment (4-6). As a result several studies propose measurement of QoL as a primary endpoint in evaluating treatment effects (7-11). These studies have, however, used a wide variety of different questionnaires to evaluate QoL, because it is still unclear which questionnaire best serves this purpose.

One approach to measure QoL is the use of generic health questionnaires such as the Short Form 36 (SF-36) or the Euroqol-5D, which measure physical, social and emotional dimensions of health. The advantage of generic questionnaires is that they can be used for evaluating QoL for all kind of diseases, and for calculating utility values in cost-effectiveness analysis. However, these generic questionnaires are considered to be less sensitive to detect small but clinically important differences in treatment effects, because they do not focus on specific effects of disease (12).

Another approach for assessing QoL is the use of disease-specific questionnaires in patients with PAD, such as the VascuQol (9). The VascuQol measures more specific elements of peripheral arterial disease, and thus theoretically, is more responsive to measure more subtle effects after treatment (13).

To date, little is known about the comparative validity between generic and disease-specific questionnaires in patients with PAD. Comparative studies are needed to determine which questionnaire has the best ability to assess QoL at baseline and to capture change in QoL after treatment. A comparative study of Morgan et al. used the SF-36 mainly for validation of the VascuQol, instead of determining which questionnaire should be preferred in the assessment of QoL in patients with PAD (13).

The purpose of the present study was to compare the ability of generic with disease-specific questionnaires to assess QoL at baseline and to detect change in QoL after treatment in patients with PAD.
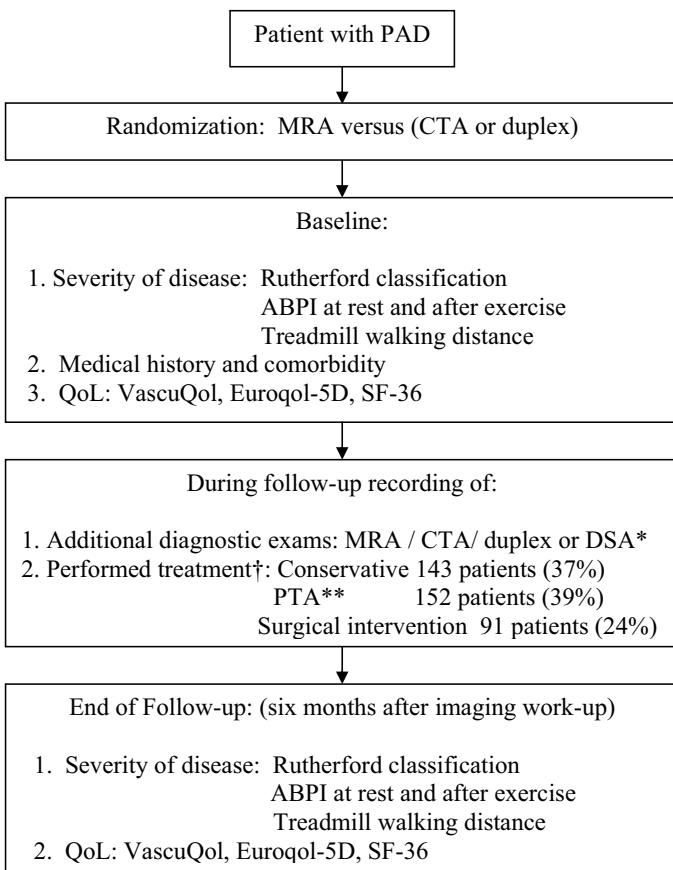
Materials and methods

Patients and Questionnaires
The present study was part of a large prospective Dutch multicenter study in which patients with PAD were randomized between MR angiography and the locally employed imaging protocol (duplex or CT angiography) to compare imaging work-up strategies. Four centres in the Netherlands participated in the study.

Between December 2001 and September 2003 all patients with PAD, who needed imaging workup to evaluate the feasibility and choice of revascularisation procedure, were included. The study population consisted of 514 patients with intermittent claudication or critical ischaemia and an ankle brachial pressure index (ABPI) < 0.90. Clinical utility, patient outcome, and costs between the different imaging work-up strategies were compared. For this purpose clinical parameters and QoL were collected at baseline and six months after imaging work-up (*Figure 1*).

Excluded were patients who needed an imaging workup within 3 days, patients with contraindications for MR angiography and CT angiography, and patients who already had had an imaging workup indicating that revascularisation was needed, because these patients could not participate in the randomized trial. In the present study, patients with severe co-morbidity were also excluded in order to avoid influence of co-morbidities affecting QoL on the comparison of disease-specific and generic questionnaires. Of the 514 patients who were included in the study, 64 patients with severe co-morbid diseases were excluded, leaving a study population of 450 patients without severe co-morbidity.

All patients signed written informed consent prior to the randomization. All patients completed two generic questionnaires (SF-36 and Euroqol-5D) and a disease-specific questionnaire (VascuQol). Patients returned their questionnaires by mail at baseline and six months after imaging work-up.

Figure 1. Flow diagram of the study and data collection.
* DSA, digital substraction angiography.
** PTA, percutaneous transluminal angioplasty.
† After follow-up, 386 patients returned their questionnaire. The percentages are calculated using these 386 patients.

Short Form 36 (SF-36)
The SF-36 is a well established generic questionnaire and has often been used for patients with various diseases (14). The SF-

36 comprises eight different health dimensions. In the present study we used four of these eight health dimensions: physical functioning (10 items), role physical functioning (4 items), bodily pain (2 items) and general health (5 items). We selected these four dimensions, because these have shown to be the most responsive for measuring changes in QoL after treatment of patients with PAD (8,13,15). Patients` responses were converted to a scale ranging from 0 (worst possible score) to 100 (best possible score).

Euroqol-5D
The other employed generic questionnaire was the Euroqol-5D. It contains five questions regarding mobility, self-care, usual activities, pain and anxiety / depression with each three levels of severity corresponding to "No problems (level 1) to some problems (level 2), and extreme problems" (level 3). The responses of the patients were converted to a scale ranging from −1 to +1 (16).

Vascular Quality of Life Questionnaire (VascuQol)
The VascuQol is developed as a disease-specific questionnaire for patients with PAD. It contains 25 items (questions) subdivided into five dimensions: pain, symptoms, activities, social and emotional. Each question has a seven point response option. Patients` responses were converted to a scale ranging from 1 (worst possible score) to 7 (best possible score) (13).

Data analysis
Data was analysed at the level of the symptomatic leg, defined as the leg in which treatment was performed. If the patient was treated on both legs or was treated conservatively, the symptomatic leg was defined as the leg with the most severe symptoms according to the patient at baseline. In case symptoms at baseline were comparable in both legs, we selected a leg with the lowest ABPI. When patients with critical ischemia could not complete a walking treadmill test due to severe pain complaints in their legs, the missing value for walking distance was imputed by the worst possible score. Missing items on returned questionnaires were imputed using the mean value of that variable. If questionnaires were not returned by patients, these patients were excluded from the respective analysis.

Because there is no gold standard for QoL, an important assumption underlying the analysis was that disease severity is a major determinant of QoL. This implies that the construct validity of a QoL questionnaire is reflected by its ability to discriminate between severely and less severely diseased patients. In order to make this assumption more plausible patients with severe co-morbidity (which is another important determinant of QoL) were excluded from analysis (17). Comorbidity was defined as a myocardial infarction within the previous 6 months, a cerebrovascular accident (CVA), or severe renal failure needing dialysis.

Moreover, the natural course of patients with critical ischemia is malignant due to high mortality in contrast to the often benign natural course for patients with claudication. As a result, the relevance of QoL measurements in patients with claudication and critical ischemia has different aspects. Therefore, the comparative validity of the questionnaires

was assessed separately for patients with claudication and for patients with critical ischemia.

The cross-sectional construct validity was assessed for all three questionnaires. It was assumed that the cross-sectional construct validity of a questionnaire is reflected by its ability to discriminate at baseline between patients with mild and severe disease by showing lower QoL scores in more severely diseased patients. Indicators for disease severity that were used were Rutherford classification, and treadmill walking distance. The median values of these indicators were used as cut-off points to classify patients into two groups of equal size with severe versus less severe disease. This approach was chosen, because it is statistically efficient.

Likewise, the longitudinal construct validity was assessed for all three questionnaires. It was assumed that the longitudinal construct validity of a questionnaire is reflected by its ability to capture change in QoL after treatment by showing larger changes in QoL scores in patients with larger changes in disease severity. Changes in indicators for disease severity (Rutherford classification, and treadmill walking distance) were calculated by subtracting the baseline score from the score measured at 6 months after the date of the diagnostic exam. Again, the median values of the changes in indicators of disease severity were used as cut-off point to classify patients into two groups of equal size with large improvement versus small or no improvement.

Both cross-sectional construct validity and longitudinal construct validity were compared between the three questionnaires. We present the mean QoL scores in the groups with severe versus less severe disease (cross-sectional construct validity) and the mean change in the groups with large improvement versus small or no improvement (longitudinal construct validity). The validity of the questionnaires was quantified by constructing receiver operating characteristic (ROC) curves and calculating areas under the curves (AUCs). The questionnaire with the highest AUC is superior in its ability to discriminate between severe and mild disease at baseline and to detect change during follow-up. The method of Hanley et al. was used to test statistical differences between the AUCs (P< .05) (18).

The primary analysis consisted of comparing AUCs based on total scores on each questionnaire. For calculating the total score on the SF-36 we used the algorithm of Brazier et al. (19,20). This algorithm uses 6 out of 8 dimensions and requires information on 11 of the original 36 items. In our study only 3 dimensions and 6 items were available. We selected four dimensions, because these have shown to be the most responsive for measuring changes in QoL after treatment of patients with PAD (8,13,15). Missing items in our study were set to zero in the algorithm of Brazier et al.

In additional analyses, we compared AUCs based on the score on dimensions measuring similar constructs such as physical functioning of the SF-36 and the dimension activities of the Vascuqol.

We also performed a subgroup analysis in patients with claudication without any co-morbid disease, excluding all patients with diabetes, CVA, myocardial infarction, angina pectoris, congestive heart failure, renal transplant, or severe renal failure needing dialysis (leaving 251 patients for analysis).

Results

At baseline, the VascuQol, SF-36, and Euroqol-5D were returned by 443 out of 450 patients. In 7 patients the questionnaires were not returned due to non-compliance (n= 4), comorbidity (n=1), or death (n= 2). After six months follow-up questionnaires were returned by 386 patients. In 64 patients no follow-up occurred because of non-compliance (n= 35), comorbidity (n=11), or death (n=18). All returned questionnaires had high completion rates. Completion rates for the individual dimensions varied from 98.7-99.5 % (Euroqol-5D) to 98.7-99.7 % (VascuQol) to 97.5- 99.5% (SF-36).

Table 1. Baseline characteristics of patients who returned questionnaires after follow-up

Characteristics of 386 patients	Claudication	Critical ischemia
Number of patients	348	38
Male / female	230 (66 %) / 118 (34 %)	24 (63 %) / 14 (37 %)
Age (mean,(SD))	64 (11)	65 (12)
Medical history		
Tobacco use (ever/ never)	325 (93 %) / 23 (7 %)	35 (92 %) / 3 (8 %)
Diabetes mellitus	62 (18 %)	20 (53 %)
Hypertension	162 (47 %)	21 (55 %)
Hyperlipidemia	174* (50 %)	16* (42 %)
Renal disease		
Mild renal insufficiency	13* (4 %)	3* (8 %)
Renal transplant	3 (1 %)	4 (11 %)
Cardiac disease		
Congestive heart failure	10 (3 %)	3 (8 %)
Myocardial infarction > 6 months ago	61 (18 %)	6 (16 %)
Angina pectoris	36 (10 %)	2 (5 %)
Transient ischemic attack (TIA)	20 (6 %)	3 (8 %)
Previous revascularisation	126 (36 %)	17 (45 %)
Rutherford classification		
None	2 (1 %)	
Mild claudication	38 (11 %)	
Moderate claudication	167 (48 %)	
Severe claudication	141 (41 %)	
Ischemic rest pain		17 (45 %)
Critical ischemia with minor ulcer		21 (55 %)
Critical ischemia major ulcer		0 (0 %)
Exercise data at baseline (mean (SD)) *		
ABPI at rest	0.62 (0.19)	0.52 (0.25)
ABPI after exercise	0.39 (0.23)	0.38 (0.33)
Walking distance (meter)	201 (93)	101 (110)

Note.   Data are in numbers of patients and percentages are in between parentheses.
     * For some patients information on these baseline characteristics was missing.
     The percentages refer to the number of patients for whom data was available.

Of the 386 patients who had returned their questionnaires after follow-up, 348 patients had intermittent claudication and 38 patients had critical ischemia. *Table 1* shows the baseline characteristics of these patients. *Figure 1* shows the number of patients who returned their questionnaires at follow-up and underwent conservative or interventional treatment. Of the 91 patients who underwent surgery, the time interval between date of surgery and returning their follow-up questionnaire was more than 2 months for 71 patients (78%).

Cross-sectional Construct validity

The construct validity was determined separately for patients with claudication and critical ischemia. *Table 2* presents the mean values of all questionnaires after classifying patients into two groups based on the respective indicators of disease severity at baseline. All questionnaires of patients with claudication and critical ischemia showed higher mean values of QoL in patients with less severe disease compared to patients with more severe disease irrespective of the indicators of disease severity (*Table 2*). Moreover, all QoL scores in critical ischemia patients were lower than the QoL scores in patients with claudication (*Table 2*). These results indicate that all three questionnaires meet the expectation that more severely diseased patients have lower scores on QoL.

Comparing AUCs based on total scores of all three questionnaires resulted in only minor differences between these AUCs. These differences were not statistically significant (all P>.05) (*Table 2*). Likewise, the ROC curve in *Figure 2* shows no differences between the AUCs after classifying claudication patients into two groups according to the Rutherford classification.
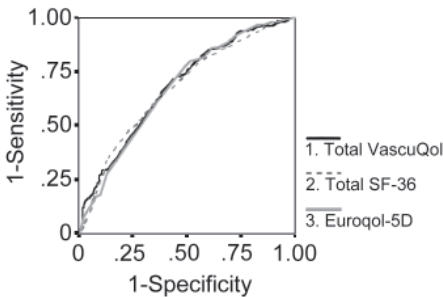
P 1-2 = .6 is the P-value comparing AUCs of the VascuQol with the SF-36.

P 1-3 = .8 is the P-value comparing AUCs of the VascuQol with the Euroqol-5D.

P 2-3 = .8 is the P-value comparing AUCs of the SF-36 with the Euroqol-5D

Figure 2. ROC Curve at baseline for patients with claudication.

Additional analyses comparing the dimensions Activity (Vascuqol) with Physical functioning (SF-36), the AUCs for the VascuQol showed minor differences between the AUCs for the SF-36. However, the AUC for discriminating between claudication patients with higher versus lower than median walking distance was significantly higher for the SF-36 (0.76) than for the VascuQol (0.68) (P < .002). The subgroup analysis for claudication patients without any co-morbid disease showed similar results.

Table 2. Cross-sectional construct validity.

	Walking distance			Rutherford classification			Walking distance			Rutherford classification		
	≤200 m*	>200m*	AUC	4 #	1-3 #	AUC	≤30m†	>30m†	AUC	= 6 ‡	= 5 ‡	AUC
VascuQol												
Activity	3.1	3.9	0.68	3.1	3.7	0.65	2.3	2.6	0.55	2.5	2.5	0.52
Symptoms	4.4	4.7	0.59	4.3	4.6	0.57	3.0	3.3	0.55	3.1	3.3	0.51
Pain	3.3	3.7	0.60	3.6	3.6	0.58	2.3	2.1	0.46	2.4	2.0	0.36
Social	3.8	4.7	0.67	3.8	4.5	0.60	2.7	3.1	0.57	2.9	3.0	0.48
Emotional	4.0	4.6	0.61	4.0	4.5	0.59	2.9	3.4	0.59	3.1	3.5	0.56
Total	3.7	4.2	0.65	3.6	4.1	0.62	2.9	2.9	0.57	2.8	2.8	0.52
SF-36												
Physical functioning	33	51	0.76[1]	34	46	0.66	28	31	0.54	27	31	0.56
Bodily pain	44	52	0.61	43	51	0.61	29	34	0.61	31	35	0.58
Role physical funct	27	51	0.66	28	45	0.60	21	16	0.46	20	17	0.46
General health	51	57	0.58	53	53	0.51	38	38	0.48	38	37	0.46
Total	51	51	0.78	53	53	0.64	38	38	0.57	38	37	0.59
Euroqol-5D	0.52	0.63	0.61	0.68	0.75	0.49	0.62	0.63	0.29	0.71	0.73	0.40

N= number of patients who returned their questionnaires at baseline.

* For patients with claudication, the median value (200 m) of walking distance was used as cut-off value to define patients with severe disease (≤ 200 m) and mild disease (>200 m).

\# The median value of Rutherford classification: 1-3 represents none to moderate claudication, 4 represents severe claudication.

†For patients with critical ischemia the median value of walking distance was 30 m.

‡ For patients with critical ischemia the median value of Rutherford classification was Rutherford category 6 (patients with critical ischemia with minor ulcer, i.e. the group with severe disease) and Rutherford category 5 (patients with ischemic rest pain, i.e. the group with "mild disease").

Role physical funct = Role physical functioning dimension of the SF-36

[1] AUC for the SF-36 based on score on the dimension physical activity is significantly higher than the AUC for the VascuQol based on score on the dimension activity ($P < .002$).

Table 3. Longitudinal construct validity after 6 months follow-up.

| Mean change (Δ) in QoL | PATIENTS WITH CLAUDICATION N = 348 | | | | | | PATIENTS WITH CRITICAL ISCHEMIA N=38 | | | | | |
| | Δ Walking distance* | | | ΔRutherford classification | | | Δ Walking distance* | | | ΔRutherford classification | | |
	≤7m*	>7m*	AUC	≤0	≥1 #	AUC	≤3m*	>3m*	AUC	≤3	≥4 ‡	AUC
VascuQol												
Δ Activity	0.9	1.4	0.58	0.1	1.8	0.82 [3]	0.7	1.6	0.72	0.4	1.4	0.74
Δ Symptoms	0.6	1.0	0.59	0.1	1.2	0.75	1.4	2.2	0.67	0.8	2.0	0.78
Δ Pain	0.9	1.4	0.58	0.3	1.8	0.80	1.4	2.7	0.76	0.7	2.2	0.83
Δ Social	0.6	1.0	0.59	0.0	1.3	0.72	0.9	1.3	0.62	0.5	1.5	0.72
Δ Emotional	0.6	1.1	0.60	0.0	1.4	0.79	0.4	1.4	0.76	0.2	1.1	0.74
Δ Total	0.8	1.2	0.60	0.1	1.5	0.82 [1,2]	0.9	1.8	0.76	0.5	1.6	0.81 [2]
SF-36												
Δ Physical functioning	11	18	0.57	1	22	0.77	2	11	0.66	-4	12	0.68
Δ Bodily pain	8	14	0.57	-1	19	0.73	18	27	0.52	2	27	0.77
Δ Role phys functioning	13	17	0.55	2	21	0.63	0	23	0.69	2	18	0.58
Δ General health	-1	0	0.51	-3	1	0.56	-3	4	0.69	-6	3	0.69
Δ Total	0.01	0.02	0.53	0.00	0.03	0.67	0.01	0.05	0.60	0.02	0.04	0.63
Δ Euroqol-5D	0.06	0.11	0.55	-0.02	0.13	0.68	0.11	0.37	0.74	0.18	0.21	0.51

N = number of patients who returned their questionnaires after 6 months follow-up.

* The median value 7 and 3m of the change in walking distance was used as cut-off value to define patients with little or no improvement (<7 and 3m) and large improvement (>7 and 3m) for patients with claudication and critical ischemia, respectively. The change in walking distance for the group with large improvement seems small, due to the low median values. However, for the group with large improvement the mean change in walking distance was 87 and 142 meter for patients with claudication and critical ischemia, respectively

Patient group with an upward shift by one of more (≥ 1) clinical categories of the Rutherford classification.

‡ Patient group with an upward shift by four of more (≥ 4) clinical categories of the Rutherford classification

1 AUC for the VascuQol based on change in total score is significantly higher than the AUC for the SF-36 based on change in total score (P< .05).

2 AUC for the VascuQol based on change in total score is significantly higher than the AUC based on change in score on the Euroqol-5D (P <.05).

3 AUC for the VascuQol based on change in score on dimension activity is significantly higher than the AUC for the SF-36 based on change in score on the dimension physical activity (P <.05).

Longitudinal construct validity

After separating patients with claudication from critical ischemia patients, *Table 3* shows the mean values of change in QoL for patients with large improvement versus patients with small or no improvement at 6 months after imaging workup. All three questionnaires had higher mean values for change in QoL in patients with larger improvement compared to patients with small to no improvement. This trend was observed irrespective of which indicator of disease severity is considered.

To determine which questionnaire detected the largest change after follow-up, ROC curves and AUCs were calculated based on change in the total scores (*Table 3 and Figure 3*). AUCs for the Vascuqol were higher than the AUCs for the SF-36, which was significant for discriminating between claudication patients with more and less than median change in Rutherford classification (AUCs 0.82 versus 0.67, P < .001) (*Table 3*). The group of critical ischemia patients was too small to demonstrate statistical differences. The AUCs for the VascuQol were also higher than the AUCs for the Euroqol-5D. Significant differences in AUCs were found for discriminating between more and less than median change in Rutherford classification for both patients with claudication (0.82 versus 0.68) and patients with critical ischemia (0.81 versus 0.63) (P< .003). This is also expressed in *Figure 3*, which shows a higher ROC curve for the VascuQol compared to ROC curves for the SF-36 and Euroqol-5D, after classifying claudication patients based on changes in Rutherford classification.

In additional analyses, comparing the dimensions Activity (Vascuqol) with Physical functioning (SF-36), the AUCs for the VascuQol were higher compared to the AUCs for the SF-36 (*Table 3*). The AUC for the Vascuqol (0.82) for discriminating between claudication patients with more and less than median change in Rutherford classification was significantly higher than the AUC for the SF-36 (0.67) (P= .002). The subgroup analysis for claudication patients without any co-morbid disease showed similar results.
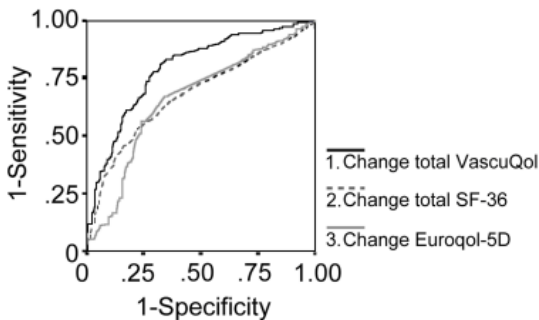
P 1-2 < .001 is the P-value comparing the AUCs of the VascuQol with the SF-36.
P 1-3 < .001 is the P-value comparing the AUCs of the VascuQol with the Euroqol-5D.
P 2-3 = .7   is the P-value comparing the AUCs of the SF-36 with the Euroqol-5D

Figure 3. ROC curve after follow-up for patients with claudication.

Discussion

The present study shows that the generic and the disease-specific questionnaires performed equally well in discriminating severe from mild disease at baseline in both patients with claudication and critical ischemia (*Table 2*). However, the disease-specific questionnaire (VascuQol) was better in discriminating a large versus a small change in disease severity after follow-up than the generic questionnaires (SF-36 and the Euroqol-5D) (*Table 3*) for both patients with claudication and critical ischemia. These results suggest that the VascuQol is a better questionnaire than the SF-36 or Euroqol-5D to detect change in QoL in patients with PAD.

Our findings are consistent with other studies, which showed that the disease severity of PAD at baseline and change in disease severity are reflected by QoL scores as measured by VascuQol, SF- 36 and Euroqol-5D (4,13,21,22). However, the unique feature of our study is the statistically grounded comparison of a disease-specific questionnaire with generic questionnaires, with respect to their ability to assess QoL at baseline and to capture change in QoL during follow-up.

A frequently applied method for comparing questionnaires is to calculate correlation coefficients (4,13,21,22). However, we opted for calculating areas under the ROC curves, because this provides a method to quantify the differences between the questionnaires with respect to cross-sectional and longitudinal construct validity, and these differences can easily be tested.

The reason for the overall limited use of disease-specific questionnaires, might be that these questionnaires are relatively new and have undergone a limited validation process (12). One recommended disease-specific questionnaire, the CLAU-S, has often been used in trials using specific medication, but it measures only QoL in patients with intermittent claudication (23-25). We preferred to use the VascuQol, because both patients with intermittent claudication and patients with critical ischaemia were included in our study.

A major problem in comparing the validity of QoL questionnaires is that there is no golden standard. The approach in this study is driven by the assumption that disease severity is a major determinant of quality of life. However, it might be argued that "objective " disease severity is not always directly related to loss of quality of life, and that other parameters like the patients' expectations of life and co-morbidity are also major determinants of QoL. To avoid confounding by co-morbidity we restricted the study population to patients without severe co-morbidity. We think, that the assumption, that in such a population differences in disease severity are reflected by differences in QoL, is valid.

A limitation of this present study was that not all dimensions of the SF-36 questionnaire were used. Selection of dimensions may have induced loss of information and, consequently a sub-optimal calculation of a total score on the SF-36. Our reason for selecting specific dimensions was that the length of the SF-36 has been shown to be unfavorable for full completion of all questions by the patient (26). In our opinion, full completion of a selected number of dimensions was more important than poor

completion of all dimensions in the SF-36 questionnaire. Indeed, the completion rate of the four dimensions of SF-36 was substantially higher (range, 98-99%) than reported in previous studies which used all dimensions SF-36 (70-91 %) (26,27). We used the dimensions physical functioning, role physical functioning, bodily pain and general health because these items have proved to be the most responsive in detecting changes after follow-up in patients with PAD (8,13,15). The dimensions and items that were excluded, have previously been shown to change little during follow-up of patients with PAD (8,13,15). Based on the results of these studies, we assumed that the excluded items would remain constant in our population and may not affect the change in the total score of the SF-36 (8,13,15).

Another limitation of our study was the substantial proportion of patients with missing data after follow-up, because 64 patients had not returned their questionnaire. It is not to be expected that the missing data influenced the outcome of the comparison between the questionnaires.

Moreover, the questionnaires were returned for practical reasons by mail, instead of administration of the SF-36 by a third party. However, we had high completion rates of the returned questionnaires, indicating that patients had no difficulties for completing questionnaires.

Furthermore, it must be noted that the results of this study pertain only to a subgroup of patients with PAD, namely patients who needed imaging work-up to determine treatment policy. From a clinical viewpoint, the question which type of questionnaire has the best ability to detect changes in QoL after treatment, is most relevant for this subgroup. The results of this study, however, may not be generalized to patients with uncomplicated claudication who do not need an image work-up.

Calculation of the total score of the SF-36 has been criticized in the literature because it has not been thoroughly validated in patients, although some studies showed that the total score of the SF-36 is a valid measure (28-30). Comparison of total scores of different questionnaires might be more valid to determine which questionnaire is preferred instead of comparing several not always corresponding health dimensions. Although our calculation of the total score of the SF-36 was difficult because not all items were included in our study, the AUCs based on the total score of the SF-36 were similar to the AUCs based on the scores in the four individual dimensions of the SF-36 (*Tables 2 and 3*). Furthermore, to verify our results of comparing AUCs based on total scores of all questionnaires, we compared in additional analyses the AUCs based on the score of the most responsive dimension of the SF-36 ("physical activity") with the corresponding dimension of the VascuQol ("activities"). These additional analyses showed similar results as the comparison of AUCs based on total scores (*Tables 2 and 3*).

Practical application

The treatment of patients with PAD is, or should be, predominantly aimed at improving QoL(7-11). QoL is important to evaluate different treatment strategies and their cost-effectiveness. Therefore, assessment of QoL could be a stronger basis for evaluating effects of treatment than the traditional clinical outcomes such as ABPI and walking distance. As was demonstrated in other studies changes in ABPI correlate poorly with changes in QoL scores (5,13,15). This finding indicates that a frequently used "hard" measure of outcome does not always reflect the patient's perceived QoL.

Currently, most patients with claudication are treated conservatively, and only those patients who have severe symptoms according to the opinion of the surgeon are considered for interventional treatment. Hicken et al. showed that surgeons misjudged their patients' QoL in everyday clinical practice (2). Consequently, the surgeons might assign interventional treatment to the wrong patients. Standardised assessments of QoL by means of questionnaires can help surgeons decide which patients are eligible for interventional treatment. Based on the assumption that disease severity is an important determinant of quality of life, the results of our study favor the use of the VascuQol due to its the superior construct validity compared to the SF-36 and Euroqol-5D for assessing changes in QoL in patients with PAD.

Conclusion

All three questionnaires VascuQol, SF-36 and Euroqol-5D performed equally well in assessing QoL at baseline in patients with PAD. The disease-specific VascuQol is superior to the generic questionnaires SF–36 and Euroqol-5D with respect to the detection of changes in QoL after follow-up. The VascuQol is the preferred questionnaire as outcome measure for QoL in future trials and clinical follow-up of patients with PAD.

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Contrast-Enhanced Three-Dimensional MR Angiography versus Multi-Detector Row CT Angiography in Patients with Peripheral Arterial Disease: a Randomized Controlled Trial

Chapter 4

Abstract

Purpose
To prospectively evaluate the clinical utility, patient outcomes, and costs of contrast-enhanced magnetic resonance angiography (MRA) compared to multi-detector computed tomographic angiography (CTA) as the initial imaging test in the diagnostic workup of patients with peripheral arterial disease.

Materials and Methods
The study was approved by the hospital institutional review board, and informed consent was obtained from all patients. Patients referred for diagnostic imaging work-up to evaluate the feasibility of a revascularisation procedure were randomly assigned to either MRA or CTA. Clinical utility was assessed with therapeutic confidence (0-10) in the initial imaging test and the need for additional imaging. Patient outcomes included ankle-brachial index, maximum walking distance, change in clinical status, and health-related quality of life. The actual diagnostic and therapeutic costs were calculated from the hospital perspective. We assessed the significance of differences between group means with unpaired t tests and calculated 95% confidence intervals (CI).

Results
One hundred and fifty-seven consecutive patients with peripheral arterial disease were prospectively randomized to either MRA (n = 78; mean age, 63 years; 66% men) or CTA (n = 79; mean age, 64 years; 63% men). For 1 of 78 patients in the MRA group we had no data available. The mean confidence for MRA (7.7) was slightly lower than for CTA (8.0, p=0.8). During 6 months follow-up, 13 patients in the MRA group compared to 10 patients in the CTA group underwent additional vascular imaging (p=0.5). Although not statistically significant, there was a consistent trend of less improvement in the MRA group across all patient outcomes. The average cost for diagnostic imaging was 359 euros ($438) (95%CI 209 to 511 ($255 to 623), p<0.0001) higher in the MRA group compared to the CTA group. The therapeutic costs were higher in the MRA group, but this was not statistically significant.

Conclusion
The results suggest that CTA has some advantages over MRA in the initial evaluation of peripheral arterial disease.

Introduction

Peripheral arterial disease (PAD) refers to the manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation, which is a major problem in the population of 55 years and older (1). The first manifestation of PAD is usually intermittent claudication. In a minority of patients, the disease progresses to critical limb ischemia, i.e. rest pain and tissue necrosis. If PAD is suspected on the basis of patient history and physical examination, ankle-brachial indices are generally measured to document the severity of the disease.

Diagnostic imaging is performed when PAD becomes lifestyle limiting and a revascularization procedure is considered. Decision-making prior to surgery or percutaneous intervention depends on accurate characterization of the level, multiplicity, and severity of stenoses (2,3). Both magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) are increasingly used for noninvasive vascular imaging. Both techniques provide a precise road map for planning treatment. Disadvantages of MRA include the higher investment cost for equipment, the small number of cases in whom the image is uninterpretable due to artifacts, and the fact that some patients are claustrofobic or have a contraindication for MR scanning. The main disadvantages of CTA are the use of radiation, the use of potentially nephrotoxic iodinated contrast media, vessel wall calcifications that hamper image interpretation, and the time-consuming 3D reconstruction techniques.

Both MRA and CTA have been shown to be sensitive and specific techniques for the evaluation of peripheral arteries (4-11). However, the clinical utility, patient outcomes, and the associated costs have not yet been evaluated, and therefore the decision whether MRA or CTA should be used in the diagnostic work-up of PAD remains to be clarified (12,13).

Thus, the purpose of this study was to prospectively compare outcomes following contrast-enhanced MRA and multi-detector CTA as the initial imaging test in the diagnostic work-up of patients with peripheral arterial disease. The primary outcome evaluated was total diagnostic costs. Secondary outcomes evaluated were clinical utility, patient outcomes, and therapeutic and follow-up costs.

Materials and methods

Patients
Inclusion criteria for participation in this randomized controlled trial comparing MRA and CTA were age older than 18 years, symptomatic atherosclerotic PAD, an ankle-brachial index of less than 0.90, and referral for diagnostic imaging work-up to evaluate the feasibility of a revascularisation procedure. Exclusion criteria included contraindications for MRA (eg, pacemaker or claustrophobia) or CTA (eg, severe renal insufficiency or adverse reactions to iodinated contrast agent), and the necessity of an acute intervention, which was defined as an intervention necessary within 5 days.

We recruited consecutive patients who were referred from the Department of Vascular Surgery at our tertiary care university hospital. The study was approved by the hospital institutional review board, and informed consent was obtained from all patients. The study was performed following Good Clinical Practice guidelines (14). Data are analysed and reported in accordance with the CONSORT guidelines (15).

Study Design
We used an empirically based and pragmatic trial design. That is, the trial evaluated two diagnostic strategies, either of which could become routine clinical practise. For our hospital CTA is current practise and MRA is considered the new imaging test.

The patients were randomly assigned to undergo either MRA or CTA as the initial imaging test. Randomization was performed centrally and took place through the Trial Coordinating Center by telephone. A computer generated list for the strategy assignment was used. Block randomization was used with a block size of 8 to obtain equal numbers in both strategies. Eligible patients were enrolled by one of several researchers who were all unaware of the randomization sequence. Following randomization, patients and clinicians were not blinded for the imaging strategy because this would have been highly impractical and inconsistent with our pragmatic study design.

Imaging Techniques and Evaluation
MRA was performed on a 1.5-T imager (Signa; GE Medical Systems, Milwaukee, Wis). A dedicated peripheral vascular phased-array coil (USA Instruments, Inc, Aurora, Oh) was used for signal reception.

We used bolus-chase MRA with commercially available software (SmartStep, GE Medical Systems). The following parameters were used for the aortoiliac, femoropopliteal, and crural regions, respectively: repetition time, 4.8/ 4.8/ 5.1 msec; echo time, 1.5/ 1.5/ 1.5 msec; flip angle, 30°/ 30°/ 30°; field of view, 400 x 280/ 400 x 320/ 400 x 360 mm; slice thickness, 2.6/ 2.0/ 2.0 mm; matrix, 384 x 192/ 384 x 192/ 512 x 512; phase encoding, centric/ centric/ elliptic centric; acquisition time, 15/ 18/ 73 sec. Zero interpolation was performed to improve image quality. Each patient received 45 ml of contrast agent (gadopentetate dimeglumine (Magnevist) 0.5 mmol/ ml; Schering, Berlin, Germany) at a rate of 1.2 ml/sec for the first 10 ml, and 0.8 ml for the remaining 35 ml (total injection duration; 52 sec), followed by a saline flush of 15 ml, at 0.8 ml/sec.

CTA was performed on a Sensation 16 scanner (Siemens Medical Systems, Forchheim, Germany). After obtaining an initial scout image (120 kV, 100 mAs), the scanning range was planned to encompass the entire vascular system from the diaphragm to the level of the ankles. Data acquisition was performed craniocaudally with the following parameters: collimation 0.75 mm, number of detector rows 16, table feed 18 mm per rotation, gantry rotation period 0.5 sec, pitch 1.5, X-ray tube voltage setting 120 kV, current 140 mAs. Each patient received 120 ml of contrast agent (Visipaque 320 mgI/ ml; Amersham Health, Buckinghamshire, UK) at a flow rate of 3 ml/sec.

Postprocessing of both MRA and CTA resulted in 12 angiogram-like images rotating over 180 degrees for aortoiliac, femoropopliteal, and crural arteries. Two readers with extensive experience in interpreting MRA and CTA, a vascular radiologist (MGMH) with 13 years of post-residency experience and a dedicated researcher (RO) with 2,5 years of general radiology training and one year of experience in vascular radiology, evaluated all images for arterial stenosis or other pathology. The following five point ordinal scale was used to grade stenotic or occlusive disease: 0 for 0-19% stenosis, 1 for 20-49% stenosis, 2 for 50-74% stenosis, 3 for 75-99% stenosis, and 4 for occlusion. When two or more stenotic luminal lesions were detected in the same vessel segment, the most severe lesion was used for grading. We performed visual assessment of the degree of stenosis. The images were first evaluated independently and subsequently all by a consensus reading. These consensus readings were used for the data analysis. All images were evaluated without knowledge of further workup.

Measurement of Clinical Utility

We assessed the therapeutic confidence of vascular radiologists and surgeons during the weekly vascular conference where therapeutic decisions were made by consensus. In addition to patient history and physical examination, the findings of the initial imaging test were discussed and each clinician was asked to rate his/her individual confidence in making a well-founded therapeutic choice on a ten-point rating scale. Three radiologists (including PMTP and MGMH) and four vascular surgeons (including MRHMS), who were aware of the study design completed the confidence forms during the vascular conferences.

Furthermore, we measured the recommendations for additional imaging (duplex ultrasound, digital subtraction angiography, MRA, or CTA) during the vascular conference. Any additional vascular imaging test performed within 60 days after the initial test was noted.

Measurement of Patient Outcomes

Health related quality of life was assessed using a self-administrated questionnaire sent to all patients at the time of randomization and 2 weeks, 3 months, and 6 months after the initial imaging test. The questionnaires contained the EuroQol-5D (EQ-5D), the Rating Scale (RS), the generic Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), and the disease specific VascuQol.

The EQ-5D covers five different health dimensions including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, which give a total of 243 different health states. Using a published population-based utility function, a single index score was calculated for each patient (16). A value of 0 equals death and a value of 1 equals maximum health.

The RS is a valuative instrument and consists of one question in which the patient was asked to rate his or her current state of health on a scale from 0 to 100, where 0 represents death and 100 perfect health (17).

The SF-36 is a multi-item scale and covers eight different health dimensions (18). Based on a previous study, we determined that physical functioning, role functioning limitations due to physical problems, bodily pain, and general health were the relevant dimensions to describe the health status of PAD (19). Each dimension is valued on a 100-point scale, in which 0 means death and 100 indicates maximum health.

The VascuQol is a disease specific descriptive quality of life instrument especially for patients with peripheral arterial disease and contains five domains (activity, symptom, pain, emotion, and social functioning) (20). These 5 domains give a total score, which is valued on a 7-point scale, in which 1 means poor quality of life and 7 indicates maximum health.

For each patient we compared the scores of the different quality of life measures at 2 weeks, 3 months, and 6 months follow-up with the baseline score of that particular measure, which resulted in a mean improvement for each quality of life measure. We used standard rules for item recoding, treatment of missing items, and scoring (16-18,20). If a questionnaire was not returned because the patient had died, we gave the value zero to the EQ-5D, RS, and SF-36 scores. The score of the VascuQol was set as missing because this is a disease specific questionnaire, which does not cover the health status of death.

The brachial, dorsal pedal, and posterior tibial arterial systolic pressure were assessed by a blood pressure cuff and continuous-wave Doppler ultrasound, both before starting and immediately after completion of the treadmill test, to determine resting and postexercise ankle-brachial indices (ABI). The measurements were performed by two vascular technologists who each had more than 5 years of experience at the time. To calculate the ABI the highest ankle pressure was divided by the highest brachial pressure. A treadmill test, based on a standard protocol (4.0 km/h; at 0%), was performed to assess the maximum walking distance (MWD). The patients walked until they had to stop due to leg pain or they reached the time limit of 5 minutes. Both ABI and MWD were measured at baseline and after 6 months follow-up.

Furthermore, we assessed the change in clinical status during 6 months follow-up. For this purpose we used the criteria for reporting significant change in clinical status according to Rutherford (21). These criteria are a combination of standard clinical categories with objective ankle-brachial indices.

Improvement in ABI and change in clinical status during the trial period was assessed for the treated leg only. If both legs or neither leg were treated, we selected the leg with the most severe symptoms at baseline. In case a patient had the same symptoms of both legs at baseline, we selected a leg at random.

If a patient was treated with an amputation, the ABI and MWD were scored as zero. Patients that did not undergo a treadmill test because they had died were excluded from this analysis.

Measurement of Costs

For the cost analysis, we collected information concerning all relevant items of medical care (i.e. diagnostic and therapeutic) used by each patient during the entire trial to calculate the mean cost per imaging strategy per patient. The cost of diagnostic imaging included the initial imaging test, all additional vascular imaging, and the associated hospital admissions during 6 months follow-up. If the initial imaging test was technically inadequate, either a new MRA or CTA was performed or an additional imaging test was performed. This would result in a more expensive initial test or in higher costs for additional imaging. The therapeutic cost included costs for percutaneous vascular interventions (i.e. percutaneous angioplasty, stent placement, and thrombolysis), vascular surgery (i.e. aortic bifurcation reconstruction, bypass surgery, endarterectomy, and amputation), and associated hospital admissions during 6 months follow-up. In addition, the number and kind of percutaneous vascular interventions and vascular surgery were compared between the groups. Futhermore, we assessed the costs for outpatient visits during 6 months follow-up. All costs were computed from the hospital perspective according to the Dutch guidelines for cost calculations in health care (22).

Diagnostic costs can be divided in directly and non-directly assignable costs. Directly assignable costs include personnel costs, material costs such as film, and equipment costs such as investment, servicing, and construction costs. Personnel costs were computed using the measured time spent on a diagnostic imaging test for each involved personnel-category and the mean wage rates from our hospital. Social security of 37% of the wage was added in accordance with national guidelines. Costs of supplies used in diagnostic procedures were based on cost prices and summed. The annuitized costs (23) of the radiological equipment and the annual equipment servicing costs were summed and divided by the proportion of the total available room time (80% of a 40 hour work-week) (22,23). Costs were discounted at a rate of 3% per annum (24). Non-directly assignable costs include costs of supporting departments, housing costs, and overhead costs. Information on costs of supporting departments was obtained from records of our Financial and Economics Department. The costs for housing were computed for the involved radiological rooms by multiplying the surface space with the housing costs of 204 euros per m2 per year. The overhead costs for MRA and CTA were estimated to be 15% of directly assignable costs (22).

The costs of percutaneous vascular interventions were measured and calculated in a similar fashion. We obtained unit costs of surgery from another study with a comparable study domain and setting to calculate an overall cost per patient per surgical procedure (25). Of some surgical procedures performed in our study, the unit costs were not available from this article and we had to estimate these costs (personal communication MRHMS). The number of days of hospital admission and the number of outpatient visits were collected, and the associated costs were calculated using national estimates of hospital admission, intensive care unit admission, and outpatient visits (22). All costs were reported in euros and dollars for the year 2002 (the exchange rate was 0.82 euro per US dollar, Sep, 2004).

Statistical Analysis

For each moment in time we calculated the response-rate of the quality of life questionnaires. Furthermore, for 20% of both the quality of life data and the data of the case record form double entry was performed to calculate the entry error. The required sample size was estimated based on the primary outcome, which was the mean estimated strategy costs (i.e. total diagnostic costs) per patient. Estimates for the total diagnostic costs were obtained from a previously performed cost analysis in our hospital. To demonstrate a significant difference between the strategy costs of MRA (estimated to be 550 euros with a standard deviation (SD) of 400 euros) and the strategy costs of CTA (estimated to be 350 euros with a SD of 300 euros), a power of 0.90, and an alpha level of 0.05 would require at least 66 patients per strategy. To allow for some redundancy we included at least 12 extra patients per strategy.

The results were analyzed according to the intention-to-diagnose-and-treat principle. This implies that once a patient has been randomly assigned, he or she will remain in the assigned group for the analysis irrespective of whether crossover occurred to the other strategy and of whether follow-up was complete or not. We calculated the means (SDs) of the therapeutic confidence scores of the initial imaging test, the number of additional imaging tests performed, the quality of life scores at follow-up, the ABI, the MWD, the change in clinical status, the diagnostic costs, the therapeutic costs, the costs of outpatient visits, and the total costs for both groups. When data were normally distributed we assessed the significance of differences between group means with unpaired t tests and calculated 95% CIs. We used the chi-squared test for dichotomous outcomes and the Mann-Whitney test for ordinal outcomes. In addition, we analyzed the differences adjusted for predictive baseline characteristics with multivariable linear and logistic regression. Based on previous studies (26) and on clinical experience we assumed that severity of disease (critical ischemia vs claudication), renal disease (i.e. renal insufficiency and renal transplantation), cerebrovascular disease, cardiac disease, and diabetes mellitus at baseline were potentially predictive for the outcomes. To adjust for the learning curve of the physicians and analyze trends in the outcome measures we included the rank order of the initial imaging tests in the regression analysis. We expressed the rank order by ranking the dates when the initial imaging tests were performed. To analyze the improvement in quality of life, ABI, and maximal walking distance during follow-up we also adjusted for the baseline scores of these outcome measures. To adjust for variability of interpretation we normalized confidence scores from each physician (27). To analyze the trend of increasing experience over time for the confidence we plotted the confidence scores as function of chronological ranking of the dates when the initial imaging tests were performed and fitted a regression line. A one-way sensitivity analysis was performed for the diagnostic costs by exploring a range of 50% to 200% of the investment costs of radiology equipment. Another sensitivity analysis was done for the costs of surgical procedures excluding the outliers. Outliers were defined as a cost more than the mean surgical costs plus 3 SDs.

For all outcome measures we used mean imputation for missing values. A p-value of 0.01 was considered statistically significant for the quality of life outcomes and the costs because of multiple testing. For other tests a significance level of 0.05 was used. Calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il).

Results

Patient Enrolment

From December 2001 to September 2003, a total of 264 patients were assessed for eligibility (*Figure 1*). One hundred and seven patients were excluded because they did not fulfill all inclusion criteria (n=38), they refused to participate (n=4), they needed an acute intervention (n=48), they had a contraindication for MRA (n=12), or they had a contraindication for CTA (n=5). The 38 patients who did not fulfill all inclusion criteria had already undergone diagnostic imaging in another hospital and were referred to our hospital for a therapeutic intervention. Seventy-eight patients were assigned to MRA
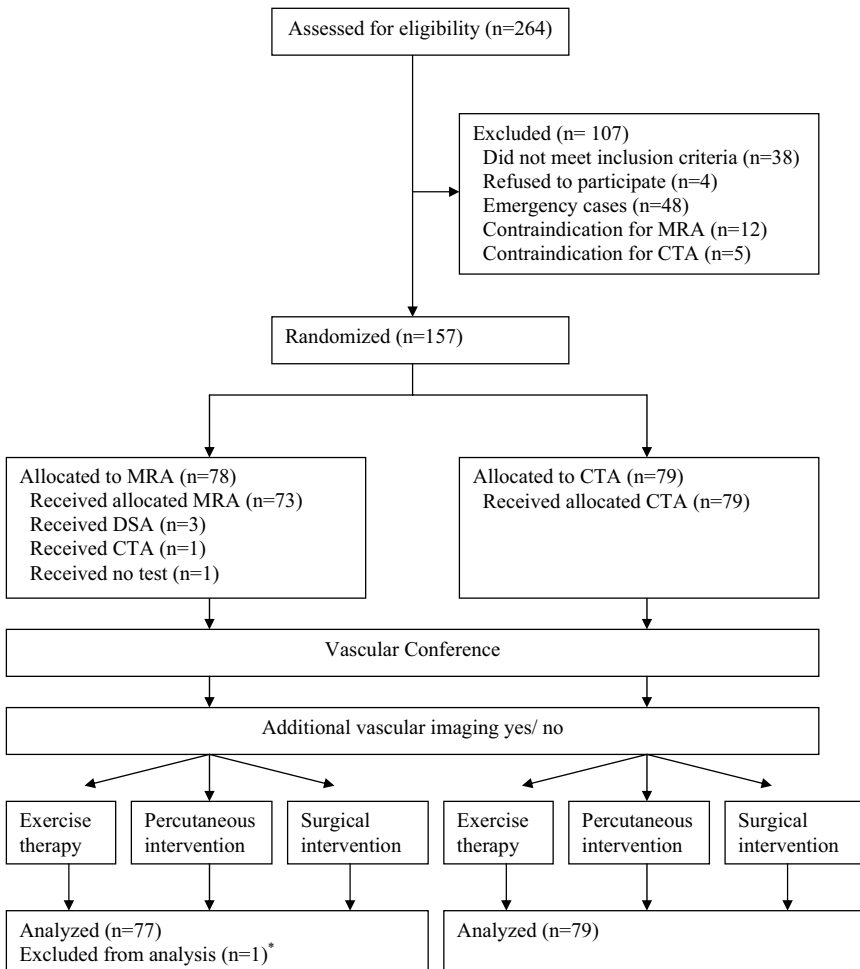
Figure 1. Flow diagram illustrates the reasons for exclusion, random assignment of patients to diagnostic test groups, the diagnostic tests that the patients actually underwent, schematic representation of follow-up, and actual number of patients included in the analysis.
* One patient did not undergo any diagnostic or therapeutic intervention and did not have data of any kind available.

and seventy-nine to CTA. Of the 78 patients assigned to MRA 73 actually underwent MRA. Three patients underwent digital subtraction angiography because of unexpected claustrophobia when they were confronted with the MR scanner (n = 2) and the necessity of acute intervention due to progressive disease (n = 1). One patient underwent CTA because of logistical problems. One patient changed his mind after randomization and refused MRA and underwent no other diagnostic or interventional procedure. This patient decided to delay the diagnostic workup for at least another year and therefore we had no data

Table 1. Baseline Characteristics of Patients.

Characteristics	MRA[‡] (n=77)	CTA (n=79)
Age, y*	63 (11)	64 (12)
Male sex	51 (66)	50 (63)
Diabetes mellitus	26 (34)	17 (22)
Hyperlipidemia	40 (52)	41 (52)
Smoking	29 (38)	31 (39)
Arterial hypertension	39 (51)	40 (51)
Cardiac disease	30 (39)	20 (25)
Cerebrovascular disease	14 (18)	14 (18)
Renal Disease		
Renal insufficiency[†]	4 (5)	1 (1)
Renal transplantation	5 (7)	1 (1)
Previous revascularization	25 (33)	30 (38)
Amputation	5 (7)	5 (6)
Critical Ischemia	19 (25)	14 (18)
Ankle/brachial index, treated limb*		
At rest	0.63 (0.20)	0.62 (0.17)
After exercise	0.40 (0.21)	0.40 (0.26)
Quality of life*		
EQ-5D	0.44 (0.33)	0.58 (0.24)
Rating scale	53 (23)	59 (21)
SF-36		
Physical functioning	35 (22)	38 (18)
Role physical	35 (40)	34 (40)
Bodily pain	43 (25)	45 (21)
General health	44 (22)	52 (21)
VascuQol	3.5 (1.3)	3.8 (1.2)

Note. - Data are numbers of patients and percentages in parentheses.
    * Data are mean scores, SD in parentheses.
    † Mild renal insuffiency or hemodialysis with permission of the nephrologist to undergo a CTA.
    ‡ One patient of the 78 assigned to MRA withdrew from the study prior to undergoing imaging. No data were available for this patient

available for this patient. Of the 79 patients allocated to CTA all underwent CTA. The baseline characteristics are described in *Table 1*. We found an error percentage of 0.9% for double entry of the quality of life data and an error percentage of 0.7% for double entry of the case record form data.

Clinical Utility

The mean therapeutic confidence for MRA (7.7) was slightly lower than that for CTA (8.0, p=0.8). For CTA the confidence remained constant with increasing experience over time (rank order), but for MRA a trend towards increased confidence with increasing experience was observed, which finally resulted in equal confidence for MRA and CTA (*Figure 2*). However, the trend for MRA towards increased confidence with increasing experience was not statistically significant.

Within 60 days after the initial test, 8 patients in the MRA group compared to 7 patients in the CTA group received additional vascular imaging (p=0.7). With adjustment for predictive variables at baseline and rank order, a similar result was found. During the total follow-up of 6 months, 13 patients in the MRA group compared to 10 patients in the CTA group underwent additional vascular imaging (p=0.5). Twelve patients in the MRA group and 8 patients in the CTA group underwent 1 additional test and one patient in the MRA group and two patients in the CTA group underwent two tests (p=0.5). On average more additional imaging tests per patient were performed in the MRA group than in the CTA group (0.18 vs. 0.15, difference 3% (95% CI −9% to 15%, p=0.6). For both MRA and CTA we observed a significant trend of decreased additional vascular imaging tests during the trial period (p=0.03).

Patient Outcomes

The response rate of the quality of life questionnaires was 99% at baseline, 93% at 2 weeks, 89% at 3 months, and 89% at 6 months follow-up.

The improvement in the EQ-5D index from baseline to 2 weeks, 3 months, and 6 months of follow-up was not statistically significant for both the MRA and CTA group (*Table 2*). The improvement was slightly smaller in the CTA group than in the MRA group. With
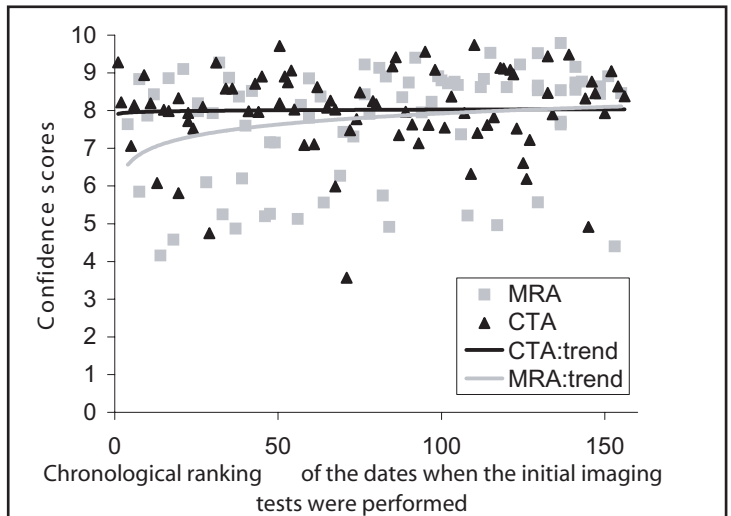
Figure 2. Therapeutic confidence in MRA and CTA with increasing experience expressed as chronological ranking of the vascular conferences. Individual symbols indicate the mean confidence score of all physicians for a single patient. The lines represent the linear regression.

Table 2. Mean improvement in different measures of quality of life during follow-up compared to baseline and differences between the groups (MRA compared to CTA†).

Measure of Quality of Life	Mean Score Improvement (95% CI)*		Unadjusted Mean Difference (95% CI)†	Adjusted Mean Difference (95% CI)†‡
	MRA (n=77)	CTA (n=79)		
EQ-5D 2 weeks§	-0.01 (-0.08 to 0.05)	-0.04 (-0.10 to 0.01)	0.03 (-0.05 to 0.11)	-0.02 (-0.10 to 0.06)
EQ-5D 3 months	0.05 (-0.03 to 0.13)	0.04 (-0.03 to 0.10)	0.01 (-0.09 to 0.11)	-0.06 (-0.15 to 0.04)
EQ-5D 6 months	0.08 (0.00 to 0.16)	0.05 (-0.02 to 0.12)	0.03 (-0.07 to 0.14)	-0.02 (-0.12 to 0.07)
SF36-Physical function 2 weeks‖	-2 (-6 to 2)	1 (-2 to 5)	-3 (-8 to 2)	-5 (-10 to 0)
SF36-Physical function 3 months	5 (-1 to 10)	14 (9 to 19)	-9 (-17 to -2)	-10 (-17 to -2)
SF36-Physical function 6 months	10 (4 to 16)	15 (9 to 21)	-5 (-13 to 3)	-4 (-12 to 4)
SF36-Role physical 2 weeks‖	-6 (-14 to 2)	-1 (-8 to 6)	-5 (-15 to 6)	-3 (-13 to 7)
SF36-Role physical 3 months	2 (-7 to 11)	11 (1 to 20)	-9 (-22 to 5)	-7 (-19 to 5)
SF36-Role physical 6 months	5 (-5 to 14)	19 (9 to 29)	-14 (-28 to 0)	-11 (-23 to 1)
SF36-Bodily pain 2 weeks‖	0 (-5 to 5)	5 (0 to 9)	-5 (-11 to 2)	-4 (-10 to 2)
SF36-Bodily pain 3 months	8 (2 to 14)	14 (7 to 21)	-6 (-15 to 3)	-6 (-14 to 3)
SF36-Bodily pain 6 months	11 (4 to 18)	14 (7 to 21)	-3 (-12 to 7)	-2 (-11 to 7)
SF36-General health 2 weeks‖	1 (-3 to 5)	-3 (-6 to 0)	4 (-1 to 9)	3 (-1 to 8)
SF36-General health 3 months	-2 (-7 to 3)	0 (-4 to 4)	-2 (-8 to 4)	-3 (-9 to 2)
SF36-General health 6 months	-1 (-7 to 4)	-2 (-6 to 2)	1 (-6 to 7)	0 (-6 to 6)
Vascuqol 2 weeks¶	0.1 (-0.1 to 0.2)	0.2 (0 to 0.3)	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)
Vascuqol 3 months	0.7 (0.5 to 1.0)	0.9 (0.6 to 1.2)	-0.2 (-0.5 to 0.3)	-0.2 (-0.6 to 0.2)
Vascuqol 6 months	1.1 (0.9 to 1.4)	1.2 (0.9 to 1.5)	-0.1 (-0.5 to 0.3)	-0.1 (-0.5 to 0.2)
Rating scale 2 weeks#	-1 (-5 to 3)	0 (-4 to 3)	-1 (-6 to 5)	-1 (-6 to 4)
Rating scale 3 months	-2 (-7 to 3)	0 (-5 to 5)	-2 (-9 to 5)	-3 (-10 to 3)
Rating scale 6 months	2 (-4 to 8)	2 (-4 to 8)	0 (-8 to 8)	-1 (-9 to 6)

* Positive number indicates improvement and negative number indicates deterioration during follow-up compared to baseline.
† Negative difference indicates that the MRA group has a smaller improvement in quality of life than the CTA group and vice versa.
‡ Adjusted for baseline quality of life score, severity of disease, diabetes mellitus, renal disease, cerebrovascular disease, cardiac disease at baseline, and rank order.
§ Index scores=0-1 (worst-best) scale.
‖ Dimension scores=0-100 (worst-best) scale.
¶ Minimum number of paired observations in MRA group was 70 and in CTA group 74. Index scores=1-7 (worst-best) scale.
# Scores=0-100 (worst-best) scale.

adjustment for baseline scores, potentially predictive variables, and rank order the improvement was slightly smaller in the MRA group than in the CTA group, but there was no statistically significant difference between the groups (*Table 2*).

The improvement in RS from baseline to follow-up was slightly smaller in the MRA group than in the CTA group, but there was no statistically significant difference between the groups with and without adjustment for baseline scores, potentially predictive variables, and rank order (*Table 2*).

 The improvement in all dimensions of SF-36 was slightly smaller in the MRA group than in the CTA group (*Table 2*). With adjustment for baseline scores, predictive variables, and rank order, we found a statistically significant difference in favor of CTA for the dimension physical functioning (-10, 95%CI −17 to −2, p=0.01) at 3 months follow-up (*Table 2*).

The improvement in the VascuQol was statistically significant for both the MRA and CTA group at 3 and 6 months follow-up (*Table 2*). Also for the VascuQol the improvement from baseline to follow-up was slightly smaller in the MRA group than in the CTA group, but there was no statistically significant difference between the groups with and without adjustment for baseline scores, predictive variables, and rank order (*Table 2*). For both the MRA and CTA group no significant trend with increasing experience could be demonstrated for improvement in all measures of quality of life.

Both the MRA and CTA group showed a significant improvement in resting ABI, post-exercise ABI, and MWD during follow-up (*Table 3*). However, the improvement was slightly smaller in the MRA group than in the CTA group. This difference in improvement was not statistically significant between the groups with and without adjustment for baseline scores, potentially predictive variables, and rank order. For both the MRA and CTA group no significant trend with increasing experience could be demonstrated for improvement in ABI and MWD. The significant change in clinical status was slightly higher in the MRA group than in the CTA group (*Table 3*).

Costs

The mean unit cost of the individual imaging tests was 514 euros ($627) for all MRAs (range 331 to 1098 ($404 to 1340)), and 163 euros ($199) for all CTAs (range 118 to 238 ($144 to 290)). For the additional imaging tests, the mean unit cost for all diagnostic DSAs was 1223 euros ($1492) (range 688 to 2474 ($839 to 3018)) and 43 euros ($52) for all duplex ultrasound tests (range 40 to 49 ($49 to 60)).

The total diagnostic costs per patient were significantly higher in the MRA group compared to the CTA group (difference=359 euros ($438), 95%CI 209 to 511 ($255 to 623), p<0.0001; *Table 4*). This increase in diagnostic costs was not caused by more additional imaging, but was caused by the higher unit costs of the initial imaging test in the MRA group (*Table 4*). With adjustment for potentially predictive variables and rank order, the increase in diagnostic costs remained significant (326 euros ($398), 95%CI 174 to 478 ($212 to 583), p<0.0001).

Table 3. Mean improvement in different measures of clinical outcome during 6 months of follow-up compared to baseline and differences between the groups (MRA compared to CTA‡).

Measure of Clinical Outcome*	Mean Score Improvement		Unadjusted Mean Difference‡	Adjusted Mean Difference‡§
	MRA (n=77)	CTA (n=79)		
ABI rest	0.10 (0.03to 0.17)	0.17 (0.11 to 0.23)	-0.07 (-0.16 to 0.02)	-0.05 (-0.13 to 0.03)
ABI exercise	0.19 (0.12 to 0.27)	0.22 (0.14 to 0.30)	-0.03 (-0.13 to 0.09)	-0.01 (-0.10 to 0.09)
Maximum Walking Distance	42 (21 to 62)	51 (27 to 74)	-9 (-40 to 22)	-14 (-41 to 14)
Change in Clinical Status†	37 (53)	36 (49)	4 (-12 to 20)	N/a

Note.- Paired observations in MRA group were 70 and in CTA group 74. In MRA group 37% completed the maximum walking time of 5 minutes (mean 313 meter) and in CTA group 53% (p=0.06). Data are means and 95% confidence interval in parentheses.

* Only measured for the treated leg.

† Data are numbers of patients and percentages in parentheses.

‡ Negative difference indicates that the MRA group has a smaller improvement in clinical outcome than the CTA group and vice versa.

§ Adjusted for baseline scores of ABI or maximum walking distance, severity of disease (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, and rank order.

With one-way sensitivity analysis we reduced the investment costs of MR equipment with 50%, which still resulted in a significant difference in diagnostic costs of 274 euros ($334) (95%CI 125 to 423 ($153 to 516), p<0.0001). A 200% increase of investment costs of CT equipment demonstrated a similar result (difference = 343 euros ($418), 95%CI 192 to 494 ($234 to 603), p<0.0001). Even the combination of a 50% reduction of the investment costs of MR equipment and a 200% increase of the investment costs of CT equipment resulted in a significant difference in favor of CTA of 258 euros ($315) (95%CI 108 to 407 ($132 to 497), p=0.001). One-third of thepatients in each group received a percutaneous intervention, one-third a surgical intervention, and one-third conservative treatment.

Table 4 A. Mean costs (in euros) during 6 months of follow-up and differences between the groups (MRA compared to CTA†).

Cost component	Mean Cost (SD)*		Unadjusted Mean Difference (95% CI)[†]	Adjusted Mean Difference (95% CI)[†‡]
	MRA (n=77)	CTA (n=79)		
Additional Imaging within 60 days (cost initial test not included)[§]	85 (303)	121 (437)	-35 (-155 to 84)	-28 (-151 to 95)
Additional Imaging within 60 days (cost initial test included)	605 (358)	284 (440)	321 (194 to 448)	306 (178 to 435)
Additional Imaging during follow-up[‖]	72 (312)	33 (201)	39 (-44 to 121)	19 (-66 to 105)
Total Diagnostic costs	676 (477)	317 (477)	359 (209 to 511)	326 (174 to 478)
Percutaneous interventions[¶]	1379 (1834)	1078 (1636)	301 (-249 to 850)	361 (-201 to 923)
Surgical procedures[#]	4594 (8987)	2476 (4694)	2118 (-142 to 4378)	1802 (-410 to 4013)
Outpatient visits	198 (57)	192 (57)	6 (-12 to 24)	3 (-15 to 21)
Total costs	6848 (8957)	4064 (4521)	2784 (549 to 5020)	2491 (293 to 4690)

Table 4 B. Mean costs (in dollars) during 6 months of follow-up and differences between the groups (MRA compared to CTA†).

Cost component	Mean Cost (SD)*		Unadjusted Mean Difference (95% CI)[†]	Adjusted Mean Difference (95% CI)[†‡]
	MRA (n=77)	CTA (n=79)		
Additional Imaging within 60 days (cost initial test not included)[§]	104 (370)	148 (533)	-43 (-189 to 103)	-34 (-184 to 116)
Additional Imaging within 60 days (cost initial test included)	738 (437)	347 (537)	392 (237 to 547)	373 (217 to 531)
Additional Imaging during follow-up[‖]	89 (381)	40 (245)	48 (-54 to 148)	23 (-81 to 128)
Total Diagnostic costs	825 (582)	387 (582)	438 (255 to 623)	398 (212 to 583)
Percutaneous interventions[¶]	1682 (2238)	1315 (1996)	367 (-304 to 1037)	440 (-245 to 1126)
Surgical procedures[#]	5605 (10964)	3021 (5727)	2584 (-173 to 5341)	2198 (-500 to 4896)
Outpatient visits	242 (70)	234 (70)	7 (-15 to 29)	4 (-18 to26)
Total costs	8355 (10928)	4958 (5516)	3397 (670 to 6124)	3039 (357 to 5722)

Note.- Only diagnostic and therapeutic costs of PAD were included.
[*] Purchasing power in euros and dollars for the year 2002.
[†] Positive cost difference indicates that MRA is more costly than CTA.
[‡] Adjusted for severity of disease (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, and rank order.
[§] In MRA group 8 patients received additional imaging within 60 days after the initial test and in the CTA group 7 patients.
[‖] In MRA group 5 patients received additional imaging during follow-up and in the CTA group 4 patients.
[¶] In MRA group 35 patients underwent percutaneous intervention and in the CTA group 29 patients.
[#] In MRA group 30 patients underwent a surgical procedure and in the CTA group 26 patients.

Table 5. Number of percutaneous interventions and surgical procedures in both groups during 6 months follow-up.

Procedures	MRA (n=77)	CTA (n=79)	p-value
Percutaneous interventions	47 (61)	38 (48)	0.1
Iliac PTA	17 (22)	12 (15)	0.3
Femoropoliteal PTA	11 (14)	2 (3)	0.008
Crural PTA	1 (1)	1 (1)	1.0
Aorta PTA+stent	0 (0)	1 (1)	0.3
Iliac PTA+stent	13 (17)	22 (28)	0.1
Femoropopliteal PTA+stent	3 (4)	0 (0)	0.08
Crural PTA+stent	2 (3)	0 (0)	0.1
Surgical procedures	53 (69)	31 (39)	<0.0001
Aortic bifurcation prosthesis	9 (12)	5 (6)	0.2
Femoropopliteal bypass	9 (12)	11 (14)	0.7
Femorocrural bypass	9 (12)	4 (5)	0.1
Endarteriectomy	6 (8)	5 (6)	0.7
Above-knee amputation	0 (0)	2 (3)	0.2
Below-knee amputation	5 (7)	0 (0)	0.02
Toe amputation/ debridement	15 (20)	4 (5)	0.006

Note. - Data are numbers of procedures and percentages in parentheses. Both legs treated counted as 2 procedures.

On average more percutaneous interventions and surgical procedures per patient were performed in the MRA group than in the CTA group. For the surgical procedures this difference was statistically significant (*Table 5*). The total costs of percutaneous interventions averaged 1379 euros ($1682) (SD 1834 ($2238)) per patient in the MRA group and 1078 ($1315) (SD 1636 ($1996)) in the CTA group, which was not a statistically significant difference (301 euros ($367), 95%CI −249 to 850 (-$304 to 1037), p=0.3; *Table 4*). The mean cost for surgical procedures was 2118 euros ($2584) (95%CI −142 to 4378 (-$173 to 5341), p=0.07) higher in the MRA group. With one-way sensitivity analysis for the surgical costs two outliers in the MRA group were excluded, which also resulted in higher costs in the MRA group compared to the CTA group (difference=1100 ($1342), 95%CI −697 to 2920 (-$850 to 3562), p=0.2). With adjustment for predictive variables and rank order, similar results were demonstrated for the costs of percutaneous and surgical interventions.

With and without adjustment for potentially predictive variables and rank order, the average cost for outpatient visits for PAD was similar for both groups. The total costs were 2784 euros ($3397) (95%CI 549 to 5020 ($670 to 6124)) higher in the MRA group, which was not a statistically significant difference when considering the multiple comparisons that we performed (p=0.02). Also with adjustment this difference was not statistically significant (p=0.03) (*Table 4*).

Both MRA and CTA showed a significant trend of decreased diagnostic costs with increasing experience and a trend of increased costs of percutaneous interventions. The costs for surgical procedures, outpatient visits, and total costs showed no significant trend with increasing experience.

Discussion

We performed a randomized controlled trial to evaluate the clinical utility, patient outcomes, and costs of two diagnostic strategies. There was no statistically significant difference in clinical utility and patient outcomes between MRA and CTA, but CTA provided a statistically significant reduction of the total diagnostic costs compared to MRA. The results suggest that CTA has some advantages over MRA in the initial imaging evaluation of patients with peripheral arterial disease. A decision which test should be implemented in routine clinical practise also depends on local expertise, availability of equipment, and considerations concerning ionizing radiation and renal insufficiency.

We found that the therapeutic confidence for CTA was slightly higher than for MRA, but both were comparable to the mean therapeutic confidence of 8.2 for DSA, which was observed in a previous study (27). For CTA the confidence remained constant with increasing experience but for MRA we found a trend of increased confidence with increasing experience. This is exactly what we expected beforehand because CTA is current practise and MRA is the new test in our hospital. Probably due to the lower confidence in MRA, the physicians requested additional imaging tests more frequently in the MRA group than in the CTA group. Because this learning curve could have an effect on the outcomes we adjusted for this learning curve in the regression analysis.

Although not statistically significant we observed a consistent trend of more improvement in the CTA group compared to the MRA group in all patient outcomes. This occurred despite the fact that the MRA group had lower quality of life scores at baseline and therefore had more to gain with treatment. As expected, with adjustment for baseline scores, potentially predictive variables, and rank order, the difference in improvement in quality of life was even larger in favor of the CTA group. This could indicate that CTA more accurately identifies the extent and localization of disease, which results in better treatment and better patient outcomes. On the other hand, the larger number of interventions performed in the MRA group could have had a negative influence on the patient short-term outcomes. Furthermore, the different measures of quality of life are correlated and this consistent trend could simply be a chance finding.

The mean diagnostic cost was significantly higher in the MRA group than in the CTA group and is explained by higher costs of the initial imaging test. MRA is more expensive than CTA due to higher investment costs, construction costs, costs for the contrast agent, and personnel costs.

Although not statistically significant, both the cost for percutaneous interventions and surgical procedures were higher for the MRA group compared to the CTA group.

One third of the patients in each group received a percutaneous intervention and one third a surgical intervention, but on average more percutaneous interventions and surgical procedures per patient were performed in the MRA group than in the CTA group. For the surgical procedures this difference was statistically significant. Also here one can reason that better identification of extent and localization of disease led to less therapeutic interventions in the CTA group, but this too could be a chance finding.

A cohort study has traditionally been used for the evaluation of new diagnostic imaging tests by performing both the new test and the reference test in all patients to determine the sensitivity and specificity. For both MRA and CTA a sensitivity between 91-98% and a specificity between 92-99% have been reported (4-11). These results are, however difficult to translate into a meaningful clinical decision with respect to whether the new diagnostic strategy should actually be implemented. A decision about the usefulness of a new diagnostic strategy requires either a decision analysis or a randomized controlled trial (12). Although randomized controlled trials are not frequently used to evaluate diagnostic tests, we found our pragmatic randomized trial to be both feasible and inexpensive (13,28-31).

We acknowledge several limitations of our study. A limitation of the study was that although patients were randomized, there were differences between the groups at baseline in diabetes mellitus, cardiac disease, renal disease, and critical ischemia. These baseline differences were not statistically significant, but we felt it would be prudent to adjust for predictive baseline variables that may lead to differences in outcomes (32,33). Therefore, adjustment for potentially predictive variables in a multivariable or logistic regression was used to correct the estimates of the outcomes for any imbalance that by chance may have occurred between the randomized groups.

A possible limitation was that patients and physicians were not blinded for group allocation. At the same time, the goal of our study was to evaluate the outcomes of the diagnostic tests as they are used in routine clinical practice. Patients could not be blinded and blinding of the treating physicians by for example, transferring the diagnostic information to a schematic drawing would have introduced an artificial step that could have hampered diagnostic interpretation and therapeutic planning. Furthermore, although schematic drawings are used in routine clinical practice as adjunct, they are not used solely when the imaging test provides a good roadmap. Finally, we chose not to blind physicians for clinical findings because this would have hampered therapeutic planning and would have been inconsistent with our goal of comparing the tests as they are used in clinical practise.

Another possible limitation is related to the generalizability of the results. In our study population 79% of the patients had intermittent claudication and only 21% had critical ischemia. One could argue that this study population is very healthy and that we used an aggressive treatment strategy for this group, which raises the question of generalizability. However, the PAD population in several other articles about the accuracy of MRA or CTA also consisted of 20-23% patients with critical ischemia (5,7,34,35). All these patients were referred for DSA to plan treatment. Furthermore, the management algorithm

for intermittent claudication in the TASC document recommends invasive therapy if a patient has severe disabling claudication and walking exercise is not successful. In addition, a review of the literature about above-knee femoropopliteal bypass described a PAD population of 39-45% patients with intermittent claudication (36), which is consistent with the percentage of patients in our study who underwent surgery for intermittent claudication. Thus, our study population is comparable to study populations in other institutions supporting generalizability of our results.

Another limitation is that the reported costs may be unique to our institution and thus not generalizable to other hospitals. Therefore, we compared our cost estimates with two other national university hospitals and one national private hospital. We found our costs to be within the range of costs in other settings. Furthermore, we performed a one-way sensitivity analysis to analyze the effect of uncertainty in the diagnostic cost estimates. Varying the investment costs of equipment did not affect our conclusions.

Finally, the costs were calculated from a hospital perspective instead of a societal perspective. There is international consensus that an economic evaluation should be performed from the societal perspective. A societal perspective implies that not only the costs within the healthcare sector, but also the direct (i.e. patient costs) and indirect costs (i.e. costs of production losses) outside the healthcare sector have to be included in the cost analysis (24). In our study we chose for the hospital perspective because other studies which assessed the costs related to the management of PAD showed that patient costs were low in both the Dutch and US settings (37,38). Furthermore, in the setting of PAD the costs of production losses are negligible since most patients are retired (39).

In conclusion, the results suggest that CTA has some advantages over MRA in the initial imaging evaluation of patients with peripheral arterial disease. There were no statistically significant differences in outcomes between the groups, except for the total diagnostic costs, which were statistically significantly lower in the CTA group compared to the MRA group.

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Cost-effectiveness of Duplex Ultrasound compared to Contrast-Enhanced Magnetic Resonance Angiography in Patients with Peripheral Arterial Disease: a Randomized Controlled Trial

Chapter 5

Abstract

Purpose
To determine clinical and economic consequences of replacing duplex ultrasound (DUS) by contrast-enhanced MR angiography (CE-MRA) for the initial imaging workup of patients with peripheral arterial disease (PAD).

Materials and methods
In a randomized multicenter trial, 357 patients with PAD (mean age, 65 years), who needed imaging workup and had an ankle brachial pressure index (ABPI) <0.90, were recruited by vascular surgeons between January 2002 and September 2003. The study was approved by the institutional review board, and all patients signed written informed consent. Patients were randomly assigned to CE-MRA or DUS, the new versus the current imaging workup. Primary outcome measure were costs. Secondary outcomes included therapeutic confidence, change in disease severity and change in quality of life (QoL) assessed during 6 months follow-up. Indicators for disease severity were Rutherford classification, treadmill walking distance, ABPI at rest, and ABPI after exercise. QoL was assessed by Short-Form 36, EuroQol-5D, and VascuQol. All costs of (additional) imaging, therapeutic interventions and outpatient visits were calculated from a hospital perspective. Data were evaluated with Student ttest, and multivariable linear regression analysis.

Results
At 6 months, 352 patients were analyzed. Use of CE-MRA reduced the number of additional vascular imaging procedures by 42% compared to DUS, and CEMRA was associated with a higher therapeutic confidence. Total diagnostic costs of CEMRA were 167 higher than the costs of DUS. This difference was statistically significant (P<.001). No statistically significant differences were found for the total costs, change in disease severity, and change in QOL between DUS and CE-MRA (all P>.05).

Conclusion
The choice between DUS and CE-MRA for the initial imaging workup for patients with PAD depends on local expertise with these techniques and cost considerations relevant to the local setting.

Introduction

A challenge in the imaging workup for patients with peripheral arterial disease (PAD) is choosing the best imaging workup which provides all information and is cost-effective. Peripheral arterial disease (PAD) of the lower legs is a common and disabling disease (1,2). Revascularisation strategies for patients with PAD require assessment by means of imaging workup. If revascularisation is being considered, most centres in the Netherlands use duplex ultrasound (DUS) as the initial imaging modality, sometimes followed by digital subtraction angiography (DSA) (3,4). Only a few centres use contrast-enhanced MR angiography (CE-MRA) as the initial imaging modality for detecting stenoses in patients with PAD.

DUS is a well-established non-invasive modality with good sensitivity and specificity (5), and its performance can be further improved by the addition of functional (colour flow) imaging (6). However, DUS is operator-dependent, and does not provide an easy-to-interpret image ("roadmap") of the vascular system which is useful for treatment planning. Finally, it is often difficult to depict the infra-popliteal vessels.

Some studies (7,8) have preferred CE-MRA to DUS, for several reasons. An often mentioned argument is that CE-MRA does produce a "roadmap" of the arteries, making CE-MRA a more effective tool for treatment planning compared to DUS. Moreover, some studies showed that CE-MRA is a more effective tool for treatment planning compared to DUS and even to DSA (8-11). In addition, a meta-analysis by Visser et al. showed that CE-MRA has better discriminatory power than DUS (7). On the other hand, CE-MRA has the disadvantage that it requires a contrast agent, and some patients have contraindications to undergo MR imaging.

Despite favorable reports on CE-MRA, many centres use this technique only as an additional exam instead of an initial imaging exam. It is currently unknown whether CE-MRA or DUS is most cost-effective as initial imaging test in everyday clinical practice. Therefore, the purpose of the present study was to determine the clinical and economic consequences of replacing DUS by CE-MRA for the initial imaging workup of patients with PAD.

Materials and methods

Setting, Patients and Randomization

The present study was a prospective multicenter study in which 357 patients with PAD were randomized between CE-MRA and DUS to compare imaging workup strategies (the new versus the current imaging workup, respectively). Two university hospitals and one general hospital in the Netherlands participated in the study. Between January 2002 and September 2003 all patients with PAD, who were referred by the vascular surgeons for imaging workup to evaluate the feasibility and choice of revascularisation procedure, were eligible for enrolment (*Figure 1*). The study population consisted of patients with intermittent claudication or critical ischaemia and an ankle brachial pressure index

(ABPI) <0.90. Patients were excluded if they needed imaging workup within 3 days, had contraindications for MR angiography, and already had had a previous imaging workup indicating that revascularisation was needed.

The study was approved by each hospital institutional review board, and all patients signed written informed consent prior to randomization. Randomization was performed centrally and took place through the Trial Coordinating Center by telephone. The random allocation scheme used a computer-generated block design with a block size of 8. Patients, the referring vascular surgeons and research assistants were all unaware of the

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                    ┌──────────────────────────────┐
                    │ 720  Assessed for eligibility │
                    └──────────────────────────────┘
                                  │
                                  │      ┌─────────────────────────────────────────────┐
                                  │      │ 363  Excluded                               │
                                  ├──────┤   172  Did not meet inclusion criteria       │
                                  │      │    14  Patient refused to participate        │
                                  │      │    93  Emergency cases                       │
                                  │      │    19  Contraindication for MRA              │
                                  │      │    65  Other reasons (Not referred to        │
                                  │      │  study, research coordinator unavailable)    │
                                  │      └─────────────────────────────────────────────┘
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357 Randomized

180 Allocated to MRA
  176   Received allocated MRA
    2   Received DUS : 1 claustrophobic
                    1 obese
    2   Received no test:1 died
                   1 withdrew

177 Allocated to DUS
  173   Received allocated DUS
    1   Received MRA: logistical problems
    3   Received no test : 2 died
                     1 withdrew

Vascular Conference

Additional vascular imaging yes/ no

| 72 Exercise therapy | 96* Percutaneous intervention | 39* Surgical intervention | 64 Exercise therapy | 93* Percutaneous intervention | 39* Surgical intervention |

2   Lost to follow-up #

3   Lost to follow-up #

178 Included in primary analysis

174 Included in primary analysis

*   Number of interventional procedures, (some patients underwent several interventional procedures).

\#   Lost to follow-up were patients that received no imaging test.

Figure 1. Study Flow Chart.

randomization sequence. Given the nature of the procedure, patients and physicians were not blinded to the assigned imaging workup.

Imaging and Evaluation
Each participating hospital was equipped with state-of the art MR-scanners (1.5 Tesla), and DUS equipment. Due to variety of the manufacturers and models of imaging equipment each hospital was allowed to use the imaging protocols, which it considered to be optimal. *Table 1* presents the information about manufacturers, imaging protocols and equipment of the DUS and CE-MRA. Radiologists interpreted images as part of their normal workflow.

In all three hospitals, DUS was performed by experienced ultrasonographers. The referring vascular surgeon determined the extent of the DUS examination (aortoiliac and / or femoropopliteal arteries only, or the need for imaging of the crural ateries), based on the history and findings on physical examination of the patient.

Outcome Measures
The outcome measures were therapeutic confidence, change in disease severity, change in quality of life (QoL), and costs, during 6 months follow-up. Primary outcome measures were costs, provided that improvement in QoL was equal for the CE-MRA and DUS group.

Therapeutic confidence was assessed by the radiologists' and vascular surgeons' confidence with respect to their ability to make a therapeutic decision based on the performed imaging modality and was rated on a scale of 0-10 (0= no confidence, 10= extremely confident to take a treatment decision). Furthermore, it was recorded whether additional vascular imaging was necessary and performed, and which treatment policy was recommended.

Indicators for disease severity were Rutherford classification, treadmill walking distance, ABPI at rest, and ABPI after exercise, which were determined at baseline and 6 months after imaging workup.

Change in QoL was assessed by the rating scale (RS) (12), two generic questionnaires (Short Form 36 (SF-36) (13,14) and Euroqol-5D (15)) and a disease-specific questionnaire (VascuQol (16)), which were completed at baseline, 2 weeks, 3 months and 6 months after imaging workup. Patients returned their questionnaires by mail. We selected the following four most responsive health dimensions of the SF-36 for patients with PAD: physical functioning, role physical functioning, bodily pain and general health (14,16,17).

Costs
Costs calculations were performed from a hospital perspective and according to the Dutch guidelines for cost calculations in health care (18). To calculate the mean cost per imaging strategy per patient, we collected all diagnostic costs, outpatient visits costs and therapeutic costs. Costs were collected at each hospital during 6 months after the date of the initial imaging workup. All costs were reported in euros for the year 2002 (the exchange rate was 0.90 euro per US dollar, Jan, 2002).

Table 1. Protocols for DUS and CE-MRA

	Hospital 1	Hospital 2	Hospital 3
DUS imaging			
Manufacturer DUS ¶	Siemens	Aloka	Philips
Aortoiliac transducer	4 and 5 MHz	3.5 and 5 MHz	2-4 MHz
Upper and lower legs transducer	5 and 7.5 MHz	7.5 MHz	4-7 MHz
Stenose Severity: ‡			
1= 0-19 %	PSV = 50-130 cm/sec	PSVR< 1.5	PSV 45-150 cm/s
2= 20-49 %	PSV ↑ of 30%	1.5> PSVR < 2.5	1.5> PSVR < 2.5
3= 50-75 %	PSV ↑ of 50%+ spectral broadening↑	PSVR ≥2.5 and EDV < 60 cm/sec	PSVR ≥2.5* and EDV < 60 cm/sec
4= 75-99 %	PSV ↑ of 50% and EDV > 20 cm/sec	PSVR ≥2.5 and EDV > 60 cm/sec	PSVR ≥2.5 and EDV> 60 cm/sec
5= Occlusion	no signal	no signal	no signal
MR imaging			
Manufacturer MR scanner and field strength ¶	Philips 1.5 T (release 8.1.3)	Philips 1.5 T (release 8.2)	Siemens 1.5 T (release VB 33G)
Coil †	Quadrature body coil	Peripheral vascular coil	Body phased array coil
Name contrast agent	gadoteridol	gadolinium DTPA	gadolinium DTPA
Manner of contrast injection #	1 injection of 40 ml	1 injection of 35 ml	3 separate injections of 15 ml each
Bolus arrival ††	BolusTrak	BolusTrak	Test bolus with 1 ml contrast agent
Injection rate (ml/sec) phase	First 20 ml at 0.6 ml/sec and the last 20 ml at 0.3 ml/sec	First 20 ml at 0.6 ml/sec and the last 20 ml at 0.3 ml/sec	2.5 ml/sec
Name of MR protocol ‡‡	MobiTrak or flexible parameters	Flexible parameters	Three separate injections

Siemens, Siemens Medical Systems, Erlangen, Germany. Aloka, Aloka Co, Tokyo, Japan/ Aloka GmbH, Meerbusch, Germany. Philips, Philips Medical Systems, Best, The Netherlands.

‡ PSVR = peak systolic velocity ratio, EDV = end diastolic velocity * A stenose was > 50 % when the PSV> 2.0 for patients with a bypass in the upper legs.

† The peripheral vascular coil is a dedicated, 129 cm long, 12-element phased array coil (Philips Medical Systems, Best, The Netherlands) that was used for all three stations. # All injections were done with a remote controlled MR compatible injection system (Medrad Specris, Indianola, PA, USA). †† Appropriate start of CE-MRA acquisition was determined using real time bolus monitoring software ((BolusTrak, Philips Medical Systems, Best, The Netherlands), or with (Test Bolus, Siemens, Siemens Medical Systems, Erlangen, Germany)). ‡ ‡ To obtain MR arteriograms of the entire peripheral arterial tree, Hospital 1 uses a commercially available software package (MobiTrak, Philips Medical Systems, Best, The Netherlands). MobiTrak uses for all three stations the same fixed imaging parameters.

To improve spatial and temporal resolution, Hospital 2 and 3 used different imaging parameters for the aortoiliac station , upper leg and lower leg station.

Diagnostic costs consisted of the costs of initial and additional vascular imaging, and were computed by adding the directly and non-directly assignable costs. Directly assignable costs contained equipment costs (such as investment), dedicated MR coils, maintenance, room construction costs, personnel costs, and material costs. The equipment costs were computed by adding the annualized costs of radiological equipment and the annual equipment maintenance costs, both with an annual 3% discount rate (18-20). Personnel costs were based on multiplying the mean wages (including the social security of 37%) with the measured time spent on an imaging test for each personnel-category. Material costs were computed by adding cost prices of the materials used during imaging such as contrast agent, syringes and/or interventional catheters.

Non-directly assignable costs comprised housing costs, costs of supporting departments, and overhead costs. The housing costs for the radiological rooms were based on the housing costs per m2 per year multiplied with the room surface. Costs of supporting departments was based on the records of Financial and Economics Department of each hospital. The overhead costs were estimated to be 15% of directly assignable costs (18).

Therapeutic costs included costs for percutaneous vascular interventions (i.e. percutaneous angioplasty, stent placement, and thrombolysis), vascular surgery (i.e. bypass surgery, endarteriectomy, and amputation), and costs associated hospital admissions or due to complications. Costs of vascular surgery were measured and calculated in a similar fashion as the diagnostic costs using the data of another comparable study (21). The costs of the number of outpatient visits, days of hospital and / or intensive care admissions were based on the national estimates (18).

Statistical Analysis
The results were analyzed according to the intention-to-(diagnose)-and-treat principle and the CONSORT guidelines (22,23). As a result, patients who died during follow-up were not excluded from cost analysis and the worst possible scores were used to represent QoL at 6 months follow-up. For all other patients, data that was missing due to questionnaires that were not returned had to be excluded from the analysis of change in QoL. Missing items on returned questionnaires were imputed using the mean value of that variable.

The sample size calculation was based on improvement in QoL. It was expected that after treatment 40-50% of the patients had a considerable improvement of their symptoms as detected by the dimensions pain and physical functioning of the SF-36 (14). In order to detect a clinically important difference of 15% with 80% power, and a 2-tailed level of .05, we calculated a final target sample of 340 patients. Anticipating a 5% drop out rate our recruitment goal was 357 patients.

Differences in costs between DUS and CE-MRA were adjusted for slight imbalances in baseline characteristics using a multivariable linear regression analysis. According to the Trans Atlantic Inter-Society Consensus (TASC) (24), the following determinants at baseline were assumed to potentially influence the outcomes: the presence of renal diseases (i.e. renal transplantation and renal insufficiency), cardiac diseases, cerebrovascular diseases, or diabetes mellitus, disease severity (critical ischemia vs. claudication), and hospital setting.

The Student t-test was used to test differences between the other outcome measures of both imaging workup strategies. Since multiple statistical tests were performed a P-value L .01 was considered to be statistically significant. All analyses were performed using SPSS version 11.0 (SPSS, Inc., Chicago, II).

Results

A total of 720 patients were evaluated for trial eligibility, of whom 363 patients were excluded for different reasons. *Figure 1* shows more details on the flow of patients through the trial. After randomization, 180 patients were allocated to CE-MRA and 177

Table 2. Baseline Characteristics

	CE-MRA	DUS
Number of patients (N)	178	174
Male / female	117 (66%) / 61 (34 %)	122 (70%) / 52 (30%)
Age years (mean, (SD))	65 (11)	65 (11)
Medical history		
Tobacco use (ever/ never)	167 (94 %) / 11 (6%)	160 (92%) / 14 (8 %)
Diabetes mellitus	41 (23 %)	30 (17 %)
Hypertension	88 (49 %)	79 (45 %)
Hyperlipidemia	83* (51 %)	77* (49 %)
Renal failure	16* (9 %)	10* (6 %)
Cardiac disease	72 (40%)	63* (36 %)
Cerebrovascular disease	27 (15 %)	27 (16 %)
Previous revascularisation	67 (38 %)	60 (35 %)
Rutherford classification		
Mild- severe (Rutherford 1-4)	159 (89 %)	154 (89 %)
Ischemia-ulcers (Rutherford 5-7)	19 (11 %)	20 (11 %)
Exercise data at baseline (mean (SD))		
ABPI at rest	0.60 (0.20)	0.60 (0.20)
ABPI after exercise	0.40 (0.23)	0.37 (0.25)
Walking distance (meter)	178 (100)	189 (100)
Quality-of-life (mean)		
Rating Scale (RS)	56	60
SF-36 physical functioning	38	40
SF-36 role physical	34	35
SF-36 pain	44	45
SF-36 general health	49	52
Euroqol-5D	0.52	0.55
VascuQol total	3.7	3.7

Data are numbers of patients and percentages in parentheses. * For some patients data on baseline characteristics were not available. The percentages are calculated based on the number of patients for whom data was available.

patients were allocated to DUS. Two patients in the CE-MRA group and three patients in the DUS group either died or withdrew from the study prior to undergoing imaging, and were therefore excluded from analysis. Consequently, the cost analysis was performed on 178 patients in the CE-MRA group and 174 patients in the DUS group. During follow-up 4 other patients died in the CE-MRA and 5 patients died in the DUS group.

The distribution of baseline characteristics was similar in the CE-MRA and DUS group (*Table 2*), except for co-morbidity that occurred slightly more often in the CEMRA group. The distribution of the severity of PAD expressed as Rutherford classification was equal for both groups. The CE-MRA group included 19 patients (11%) and DUS group included 20 patients (11%) with critical ischemia.

Outcome Measures

Both CE-MRA and DUS were associated with high therapeutic confidence scores for making a treatment decision after the imaging workup. The mean therapeutic confidence score was 8.2 for the CE-MRA group and 7.5 for the DUS group, which was significantly higher for the CE-MRA group (P < .001).

With respect to changes in Rutherford classification, maximum treadmill walking distance, ABPI at rest and ABPI after exercise, there was no statistically significant difference between both groups with respect to improvement of disease severity (*Table 3*).

Table 3. Change in Outcome Measurements after Follow-up

(Δ) Mean change	2 Weeks			3 Months			6 Months		
	CE-MRA	DUS	P-value*	CE-MRA	DUS	P-value*	CE-MRA	DUS	P-value*
Δ Disease severity									
Δ Rutherford classification (category)							+1	+1	.16
Δ Walking distance (meters)							25	23	.86
Δ ABPI at rest							0.15	0.14	.67
Δ ABPI after exercise							0.22	0.25	.59
Δ Quality-of-life									
Δ Rating Scale	2	-2	.03	3	1	.47	3	1	.41
Δ SF-36 physical functioning	-2	2	.03	9	8	.78	10	10	.99
Δ SF-36 role physical functioning	0	1	.72	7	8	.76	6	13	.15
Δ SF-36 bodily pain	-1	1	.21	9	9	.98	8	9	.85
Δ SF-36 general health	-1	-1	.83	-1	-2	.84	-3	-2	.67
Δ Euroqol-5D	-0.04	-0.01	.28	0.04	0.03	.83	0.05	0.03	.53
Δ VascuQol total	0.0	0.1	.16	0.7	0.7	.99	0.8	0.9	.59

Δ = Changes in indicators for disease severity and QoL were calculated by subtracting the baseline score from the score measured at 6 months after the date of the diagnostic exam. Change in disease severity was only determined after 6 months.
*Considering multiple statistical tests, a P value of ≤ .01 was considered to be statistically significant.

Table 4. Number of imaging Exams and Interventions and Distribution of Costs

Costs (in euros per patient)	Frequency		Costs mean (5 and 95% percentile)				Adjusted difference* (95% CI)		
	CE-MRA	DUS	CE-MRA (N=178)		DUS (N=174)		CE-MRA versus DUS †		P-value
Initial test	180 ‡	174	473	(305-599)	105	(40-168)	349	(334 to 364)	<.001
Additional imaging before therapy #	19	47	46	(0-105)	207	(0-1121)	-167	(-246 to –89)	<.001
Additional imaging after therapy #	21	22	28	(0-96)	46	(0-125)	-15	(-54 to 24)	.45
Total additional imaging #	40	69	118	(0-728)	323	(0-1766)	-202	(-314 to –91)	<.001
Total diagnostic costs (including initial test)			532	(308-960)	356	(57-1434)	167	(79 to 255)	<.001
Outpatient visits	516	527	182	(80-280)	189	(80-350)	-8	(-23 to 7)	.30
Percutaneous interventions	96	93	1193	(0-3541)	1131	(0-3252)	91	(-214 to 407)	.54
Surgical procedures	39	39	1105	(0-6808)	1037	(0-5207)	16	(-540 to 572)	.95
Total costs			3012	(499-10474)	2713	(180-7769)	272	(-377 to 921)	.41

N = Number of patients
‡ Two extra CE-MRA exams were necessary (in1 patient due to reconstruction failure of the CE-MRA dataset and in 1 patient the aorta was not depicted).
# The costs of the initial test are not included.
* Adjusted for small imbalances in disease severity (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, and for hospital.
† Positive cost difference indicates that MRA is more expensive than DUS and negative cost difference indicates that DUS is more expensive than CE-MRA.
The costs are calculated in euros for the year 2002 (the exchange rate was 0.90 euro per US dollar, Jan 2002).

The response rates for the QoL questionnaires were 98% at baseline, 95% at 2 weeks, 91% at 3 months, and 88% after 6 months follow-up. Moreover, all returned questionnaires had high completion rates for the individual dimensions (completion rates varied from 97.2% to 99.7%). *Table 3* shows no statistically significant differences in improvement of QoL after 2 weeks, 3 and 6 months between CE-MRA and DUS.

Table 4 shows that before therapy, 19 additional vascular imaging exams were performed in the CE MRA group, whereas in the DUS group 47 additional vascular imaging exams were performed. During 6 months follow-up, in total 40 additional vascular imaging exams were performed in the CE-MRA group compared to 69 additional vascular imaging exams in the DUS group. Thus, the total number of additional vascular imaging exams was reduced by 42% in the CE-MRA group (P< .001). For the DUS group, these additional exams consisted mainly of DSA and CEMRA exams. The total number of additional diagnostic DSA exams was reduced by 63% in the CE-MRA compared to the DUS group (11 versus 30 DSA exams, P = .001). In the DUS group 20 additional CE-MRA exams were performed compared to 1 additional CEMRA exam in the CE-MRA group.

Costs
Overall, the mean total costs per patient, consisting of all diagnostic, therapeutic and outpatient visits costs, were   272 higher in the CE-MRA group than in the DUS group (*Table 4*). This difference was not significant (95%CI, –   377 to   921; P = .41).

The mean unit cost for the initial test per patient was 105 for a DUS exam and 473 for a CE-MRA exam. The mean costs for total additional imaging per patient during 6 months follow-up was 118 in the CE-MRA group compared to 323 in the DUS group (*Table 4*). The total additional imaging costs were significantly lower in the CEMRA group compared to the DUS group (mean difference was 202 per patient, P < .001). Although, the CE-MRA was associated with lower total additional imaging costs, the total diagnostic costs of the CE-MRA were 167 higher compared to DUS (P < .001). One-way sensitivity analysis showed that the higher total diagnostic costs for the CE-MRA were explained by the higher costs of the initial imaging test in the CE-MRA group, due to the high investment costs of the MR scanner. In the one-way sensitivity analysis, the investment costs of the MR scanner were reduced by 50%, which resulted in a non-statistically significant difference of total diagnostic costs between the CE-MRA and DUS (adjusted difference 52; 95%CI – 33 to 138; P = .23).

Furthermore, *Table 4* shows that the costs for outpatient visits were not significantly different between the CE-MRA and DUS groups (P = .30). The number and costs for revascularisation through percutaneous transluminal angioplasty (PTA) and surgical procedures were not significantly different between both groups (P > .05). A subgroup analysis showed no statistically significant differences in total additional imaging costs, total diagnostic costs and total costs between DUS and CEMRA between the three hospitals.

Discussion

CE-MRA and DUS performed equally well in the initial imaging workup for patients with PAD, albeit that the two imaging modalities had different qualities that counted in their favor. CE-MRA reduced the number of additional vascular imaging tests and improved the therapeutic confidence score. On the other hand DUS was associated with significantly lower total diagnostic costs compared to CE-MRA due to the high investment costs of the MR scanner. The total costs (i.e. all diagnostic, therapeutic and outpatients visits costs as well as improvement in QoL and disease severity after 6 months) were comparable for the CE-MRA and the DUS group.

Ultimately the choice between DUS and CE-MRA for the initial imaging workup for patients with PAD will depend on local expertise with these techniques and cost considerations relevant to the particular setting. DUS has very good results in terms of sensitivity and specificity even regarding depiction of the lower legs, provided that the ultrasonographers performing the exam are highly experienced (25-27). Similarly, the image quality of MRA depends on the quality of the equipment and experience of the MR technologists. For example, high spatial resolution is a prerequisite for optimal depiction of the vascular tree, and high temporal resolution is important to avoid projection of disturbing veins over the arteries. As a result, dedicated MR receiver coils, up-to-date imaging protocols and the use of contrast agents are necessary to obtain optimal image quality. Studies have shown that MRA without the use of contrast agents (e.g. using time of flight sequences) reduced diagnostic accuracy compared to MRA using contrast agents (28,29).

A major advantage of DUS is that the total diagnostic costs are lower compared to CE-MRA. The higher total diagnostic costs of CE-MRA are explained by the higher costs of the initial CE-MRA exam, particularly due to high investment costs of the MR scanner. It should be noted, however, that MRA is a relatively new imaging technique, which may in part explain the high investment costs of the MR scanner. One may expect that in the future these costs decrease as MR scanners become more widely available. As was shown in this study, with a 50% reduction in the investment costs of the MR scanner, the total diagnostic costs were almost equal for CE-MRA and DUS. Furthermore, although the difference in diagnostic costs was statistically significant, the magnitude of the difference was not that large and a department may consider the additional expense justified.

Using CE-MRA resulted in a lower need for additional vascular imaging, particularly diagnostic DSA exams than for DUS. This finding was in accordance with the findings of Leiner et al. who showed that surgeons who had to define treatment plans were less likely to order diagnostic DSA after CE-MRA than after DUS (8). In our study the reduction in additional vascular imaging exams is consistent with the significantly higher therapeutic confidence score after CE-MRA than after DUS. The higher therapeutic confidence of the surgeons after CE-MRA indicates that treatment planning was more efficient after CE-MRA than after DUS. An explanation is that CE-MRA presents the arteries as a roadmap, which allows better visualization of the location, severity and extent of the stenosis and quality of the outflow arteries.

Although treatment planning was more efficient after CE-MRA, neither CE-MRA nor DUS seemed to influence the therapeutic decision, as is suggested by the fact that the number and nature of interventional procedures as well as therapeutic costs were similar for both groups. The foremost contributors of the total costs were the costs of therapy and possible complications after therapy (30). Our study also showed that despite the higher total diagnostic costs in the CE-MRA group, similar therapeutic costs resulted in similar total costs for both DUS and CE-MRA groups.

Our study had several limitations. It is expected that the CE-MRA strategy might be more cost-effective in patients with critical ischemia. These patients often undergo distal bypass surgery and require more adequate depiction of the lower leg arteries, which may be better obtained by CE-MRA. However in our study, only 39 (11 %) of all 352 patients had critical ischemia, and consequently this group was too small to allow a separate subgroup analysis.

Another study limitation was that the computation of costs was performed using a hospital perspective, instead of using a societal perspective as frequently recommended. (22,23). Calculating costs according to the societal perspective requires adding all costs inside and outside the healthcare sector, such as direct costs (patient costs) and indirect costs (costs due to production losses). We chose for a hospital perspective, because previous cost analyses concerning the management of patients with PAD showed that patient costs were relatively low in both Dutch and United States settings (31,32). Furthermore, the majority of the patients with PAD were retired from the workforce, therefore the costs due to production losses will be negligible (33).

Several small imbalances in the distribution of baseline characteristics between the CE-MRA and the DUS group were observed in spite of randomization. For example, comorbidity occurred somewhat more frequently in the CE-MRA group than in the DUS group. Although the differences were small, we adjusted for relevant baseline characteristics in a multivariable linear regression analysis. In addition, we adjusted for hospital setting.

In conclusion, the choice between DUS and CE-MRA for the initial imaging workup for patients with PAD depends on the local expertise with these techniques and cost considerations relevant to the local setting. Centers that seek to improve their imaging workup might opt to expand their expertise in CE-MRA (rather than DUS), as the diagnostic value of CE-MRA outweighs DUS, and work towards a decrease in the cost of CE-MRA by improving the efficient use of the MR equipment.

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Multicenter Randomized Controlled Trial of the Costs and Effects of Non-Invasive Diagnostic Imaging in Patients with Peripheral Arterial Disease: The DIPAD Trial

Chapter 6

Abstract

Purpose

To compare the costs and effects of three non-invasive imaging tests as the initial imaging test in the diagnostic workup of patients with peripheral arterial disease.

Materials and Methods

Of 984 patients assessed for eligibility, 514 patients with peripheral arterial disease were randomized to magnetic resonance angiography (MRA) or duplex ultrasound (DUS) in three hospitals and to MRA or computed tomographic angiography (CTA) in one hospital. The outcome measures included the clinical utility, functional patient outcomes, quality of life, and actual diagnostic and therapeutic costs related to the initial imaging test during 6 months follow-up. Clinical utility was assessed with therapeutic confidence (0-10) in the initial imaging test and the number of additional vascular imaging tests performed. Patient outcomes included change in ankle-brachial index, maximum walking distance, and clinical status.

Results

With adjustment for potentially predictive baseline variables, the learning curve, and hospital setting, a significant higher confidence and less additional imaging were found for MRA and CTA compared to DUS. There were no statistically significant differences in improvement in functional patient outcomes and quality of life between the groups. The total costs were significantly higher for MRA and DUS compared to CTA.

Conclusion

The results suggest that both CTA and MRA are clinically more useful than DUS and that CTA leads to cost-savings compared to both MRA and DUS in the initial imaging evaluation of peripheral arterial disease.

Introduction

Peripheral arterial disease (PAD) is the expression of atherosclerosis in the lower limb distal to the aortic bifurcation, which is a major problem in the population of 55 years and older (1). The first manifestation of symptomatic PAD is usually intermittent claudication. In a minority of patients, the disease progresses to critical limb ischemia, i.e. rest pain and tissue necrosis. If PAD is suspected on the basis of patient history and physical examination, ankle-brachial indices (ABI) are generally measured to document the severity of the disease.

Diagnostic imaging is performed when PAD becomes lifestyle limiting and a revascularization procedure is considered. Non-invasive imaging tests including duplex ultrasound (DUS), computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) are increasingly used for the initial evaluation of patients with PAD. DUS provides both anatomical and functional information about the arterial system and has been shown to be a reliable modality with fairly good sensitivity and specificity (2,3). DUS is, however, operator dependent and does not provide a precise roadmap for planning treatment. Both MRA and CTA are relatively new non-invasive vascular imaging tests used in the diagnostic workup of peripheral arterial disease. Both modalities provide three-dimensional images of the arterial system with high sensitivity and specificity (4-11). Disadvantages of MRA include the higher investment cost for equipment, the small number of cases in whom the image is uninterpretable due to artifacts, and the fact that some patients are claustrofobic or have a contraindication for MR scanning. The main disadvantages of CTA are the use of radiation, the use of potentially nephrotoxic iodinated contrast media, vessel wall calcifications that affect image interpretation, and the time-consuming 3D reconstruction techniques. The question arises which imaging test is preferred in the diagnostic work-up of PAD.

To determine which non-invasive test is preferred as initial imaging test in clinical practise we need to take into account not only the diagnostic accuracy of each test, but also the related effects of diagnostic imaging tests on treatment planning, functional improvement, quality of life, and costs (12,13). For this purpose we designed the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) randomized trial to compare outcomes following DUS, MRA, and CTA as the initial imaging test in the diagnostic workup of patients with peripheral arterial disease. Primary outcomes evaluated were quality of life and costs. Secondary outcomes evaluated were clinical utility and functional patient outcomes.

Materials and methods

Study Patients
Between December 2001 and September 2003, the DIPAD trial consecutively enrolled 514 patients at 4 Dutch hospitals. Men and women at least 18 years old with symptomatic PAD who were referred from the Department of Vascular Surgery for diagnostic imaging

workup to evaluate the feasibility of a revascularization procedure were eligible for enrollment. PAD was defined as symptoms of intermittent claudication and/ or critical ischemia with an ABI < 0.90 (14,15).

Patients were excluded if they had contraindications for MRA (eg, pacemaker, cerebral vessel clipping, or claustrophobia) or CTA (eg, severe renal insuffiency or adverse reactions to iodinated contrast agent), or if they needed an acute intervention at the time of randomization.

Study Design
This was an empirically based and pragmatic multicenter randomized controlled trial evaluating the costs and effects of non-invasive diagnostic imaging in patients with PAD. That is, we designed the trial to reflect clinical practise as it can be implemented rather than creating a strictly controlled, but probably unrealistic, experimental setting (13). The study protocol was approved by the hospital institutional review board for all participating centers, and informed consent was obtained from all patients. The study was performed following Good Clinical Practice guidelines (16). Data were analyzed and reported in accordance with the CONSORT guidelines (17). Patients meeting all eligibility criteria were randomly assigned to undergo MRA or the currently employed test, which was DUS in three hospitals and CTA in one hospital as the initial imaging test. Randomization was performed centrally and took place through the Trial Coordinating Center by telephone. A computer generated list for the strategy assignment was used. Eligible patients were enrolled by one of several researchers who were all unaware of the randomization sequence. Following randomization, patients and clinicians were not blinded for the imaging strategy because this would have been highly impractical and inconsistent with our pragmatic study design.

Imaging Techniques and Evaluation
DUS was performed by qualified, experienced vascular technologists with 5 and 7.5 MHz transducers. On the basis of patient history and findings at physical examination, the referring vascular surgeons determined the extent of the DUS examination (aortoiliac, femoropopliteal, crural). The hemodynamic significance of lesions was graded by peak systolic velocity (PSV) ratios, calculated as the PSV in the stenosis divided by the PSV in the prestenotic or poststenotic region. The technologists graded stenosis on a five-point ordinal scale and recorded the findings on a standardized reporting sheet.

All MR examinations were performed on a 1.5-T imager. A body coil or a dedicated peripheral vascular phased-array coil was used for signal reception. In 3 hospitals the protocol included a bolus-chase MRA with single biphasic contrast material injection, automated table movement, and real time bolus monitoring. In one hospital a multi-injection protocol was used. In all hospitals a subtraction technique was used before maximum intensity projections (MIP) were generated.

CTA was performed on a 16-slice multi-detector scanner. A bolus-tracking technique was used with automated table movement and automated bolus detection. Before generating MIPs, a segmentation technique was used to remove bony structures and vessel wall calcifications.

Radiologists with extensive experience in interpreting MRA and CTA evaluated all MR and CT images for arterial stenosis or other pathology. All images were evaluated without knowledge of further workup.

Measurement of Quality of life
Health related quality of life was assessed using a self-administrated questionnaire sent to all patients at the time of randomization and 2 weeks, 3 months, and 6 months after the initial imaging test. The questionnaires contained the EuroQol-5D (EQ-5D), the Rating Scale (RS), the generic Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), and the disease specific VascuQol.

The EQ-5D covers five different health dimensions including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, which give a total of 243 different health states. Using a published population-based utility function, a single index score was calculated for each patient (18). A value of 0 equals death and a value of 1 equals maximum health.

The RS is a valuative instrument and consists of one question in which the patient was asked to rate his or her current state of health on a scale from 0 to 100, where 0 represents death and 100 perfect health (19).

The SF-36 is a multi-item scale and covers eight different health dimensions (20). Based on a previous study, we determined that physical functioning, role functioning limitations due to physical problems, bodily pain, and general health were the relevant dimensions to describe the health status of PAD (21). Each dimension is valued on a 100-point scale, in which 0 means death and 100 indicates maximum health.

The VascuQol is a disease specific descriptive quality of life instrument especially for patients with peripheral arterial disease and contains five domains (activity, symptom, pain, emotion, and social functioning) (22). These 5 domains give a total score, which is valued on a 7-point scale, in which 1 means poor quality of life and 7 indicates maximum health.

For each patient we compared the scores of the different quality of life measures at 2 weeks, 3 months, and 6 months follow-up with the baseline score of that particular measure, which resulted in a mean improvement for each quality of life measure. We used standard rules for item recoding, treatment of missing items, and scoring (18-20,22).

Measurement of Costs
For the cost analysis, we collected information concerning all relevant items of medical care (i.e. diagnostic and therapeutic) used by each patient during the entire trial. The cost of diagnostic imaging included the initial imaging test, all additional vascular imaging, and the associated hospital admissions. The therapeutic cost included costs for percutaneous vascular interventions (i.e. percutaneous angioplasty, stent placement, and thrombolysis), vascular surgery (i.e. aortic bifurcation reconstruction, bypass surgery, endarterectomy, and amputation), and associated hospital admissions. Futhermore,

we assessed the costs for outpatient visits during 6 months follow-up. All costs were computed from the hospital perspective according to the Dutch guidelines for cost calculations in health care (23).

Diagnostic costs can be divided in directly and non-directly assignable costs. Directly assignable costs include personnel costs, material costs such as film, and equipment costs. Personnel costs were computed using the measured time spent on a diagnostic imaging test for each involved personnel-category and the mean wage rates from our hospital. Social security of 37% of the wage was added in accordance with national guidelines. Costs of materials used in diagnostic procedures were based on cost prices and summed. The annuitized costs (24) of the radiological equipment and the annual equipment servicing costs were summed and divided by the proportion of the total available room time (80% of a 40 hour work-week) (23,24). Costs were discounted at a rate of 3% per annum (25). Non-directly assignable costs include costs of supporting departments, housing costs, and overhead costs. Information on costs of supporting departments was obtained from records of our Financial and Economics Department. The costs for housing were computed for the involved radiological rooms by multiplying the surface space with the housing costs of 204 euros per m2 per year. The overhead costs for MRA, DUS, and CTA were estimated to be 15% of directly assignable costs (23).

The costs of percutaneous vascular interventions were measured and calculated in a similar fashion. We obtained unit costs of surgery from another study with a comparable study domain and setting to calculate an overall cost per patient per surgical procedure (26). For a limited number of surgical procedures performed in our study, the unit costs were not available from this article and we had to estimate these costs using the published values as starting point (personal communication van Sambeek, MD, PhD, 2002). The number of days of hospital admission and the number of outpatient visits were collected, and the associated costs were calculated using national estimates of hospital admission, intensive care unit admission, and outpatient visits (23). All costs were reported in euros for the year 2002 (the exchange rate was 0.75 euro per US dollar, Dec, 2004).

Measurement of Clinical Utility

We assessed the therapeutic confidence of vascular radiologists and surgeons during the weekly vascular conference where the findings of the initial imaging test were discussed and each clinician was asked to rate his/her individual confidence in making a well-founded therapeutic choice on a ten-point rating scale. To adjust for variability in using the rating scale we normalized scores from each physician (27).

Furthermore, we measured the recommendations for additional imaging (DUS, digital subtraction angiography (DSA), MRA, or CTA) during the vascular conference. Any additional vascular imaging test performed within 60 days after the initial test was noted. In addition, all additional vascular imaging tests performed during 6 months follow-up were collected.

Measurement of Functional Patient Outcomes

The brachial, dorsal pedal, and posterior tibial arterial systolic pressure were assessed by a blood pressure cuff and continuous-wave Doppler ultrasound, both before starting and immediately after completion of the treadmill test, to determine resting and postexercise ankle-brachial indices (ABI). To calculate the ABI the highest ankle pressure was divided by the highest brachial pressure. A treadmill test, based on a standard constant-load protocol, was performed to assess the maximum walking distance (MWD). The patients walked until they had to stop due to leg pain or they reached the time limit. Both ABI and MWD were measured at baseline and after 6 months follow-up.

Furthermore, we assessed the change in clinical status during 6 months follow-up. For this purpose we used the criteria for reporting significant change in clinical status according to Rutherford (28). These criteria are a combination of standard clinical categories with objective ankle-brachial indices.

Improvement in ABI and change in clinical status during the trial period was assessed for the treated leg only. If both legs or neither leg were treated, we selected the leg with the most severe symptoms at baseline. In case a patient had the same symptoms of both legs at baseline, we selected a leg at random.

Statistical Analyses

For each moment in time we calculated the response-rate of the quality of life questionnaires. Furthermore, we entered 20% of both the quality of life data and the data of the case record form twice in the database to calculate the entry error.

The intention of the study was to demonstrate cost-savings for the diagnostic work-up while quality of life and other patient outcomes are not detrimental affected. The sample size calculation was based on quality of life outcomes because we felt it would be essential not to miss a clinically relevant difference in this outcome. With adequate treatment approximately 40-50% of patients could be expected to have a substantial improvement of their symptoms after 6 months as measured by the physical functioning and pain attributes on the SF-36 (21). A percentage difference of 10%-15% would be considered clinically relevant. A sample size of 500 would be adequate to avoid missing a percentage difference of at least 12.5% if 45% of patients improve.

The results were analyzed according to the intention-to (-diagnose-and)-treat principle. For continuous variables, statistical significance of differences between the 3 groups was evaluated using ANOVA. The statistical significance of differences in dichotomous variables between the 3 groups was assessed using the chi-squared test. We determined the statistical significance of differences in improvement in primary and secondary outcomes between the 3 groups with multivariable and logistic regression. Differences in improvement between the 3 groups are presented with adjustment for predictive baseline characteristics, learning curve of physicians, and hospital setting. Based on previous studies (29) and on clinical experience we assumed that severity of disease (critical ischemia vs claudication), renal disease (i.e. renal insufficiency and renal transplantation), cerebrovascular disease, cardiac disease, and diabetes mellitus at baseline were potentially predictive for the outcomes. To adjust for the learning curve

of the physicians we included the rank order of the initial imaging tests in the regression analysis. We expressed the rank order by ranking the dates when the initial imaging tests were performed. To analyze the improvement in quality of life, ABI, and maximum walking distance during follow-up we also adjusted for the baseline scores of these outcome measures. A one-way sensitivity analysis was performed for the diagnostic costs by exploring a range of 50% to 200% of the investment costs of radiology equipment.

For all outcome measures we used mean imputation for missing values. A p-value of 0.01 was considered statistically significant for the quality of life outcomes and the costs because multiple measures were tested within these groups of outcomes. For other tests a significance level of 0.05 was used. Calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il).

Results

Patients

Of 984 patients assessed for eligibility, 514 patients were enrolled, and 470 were excluded because they did not fulfill all inclusion criteria (n=210), were not asked to participate (n=70), refused to participate (n=18), needed an acute intervention (n=141), or had contraindications for MRA or CTA (n=31) (*Figure 1*). Of the 258 patients assigned to MRA 249 actually underwent MRA. Digital subtraction angiography was performed in two patients because of unexpected claustrophobia when they were confronted with the MR scanner and in one patient because an acute intervention was necessary due to progressive disease. One patient underwent CTA because of logistical problems. DUS was performed in one patient because this patient did not fit in the MR scanner and one patient because of claustrophobia. Three patients did not undergo MRA or any other diagnostic or interventional procedure. One patient died prior to the imaging test and two patients decided to delay the diagnostic workup for at least another year and therefore we had no data available for these patients. Of the 177 patients assigned to DUS 173 actually underwent DUS. One patient received MRA due to logistical problems. Three patients did not undergo DUS or any other diagnostic or interventional procedure because two patients died prior to the imaging test and one patient was diagnosed with a lethal disease and withdrew from the study. Of the 79 patients allocated to CTA all underwent CTA.

Table 1 shows baseline characteristics of participants according to imaging strategy. The EQ-5D and the domain general health of the SF-36 showed significantly lower values in the MRA group compared to the other 2 groups. The other baseline characteristics were comparable among the 3 groups. We found an error percentage of 0.9% for double entry of the quality of life data and an error percentage of 0.7% for double entry of the case record form data.
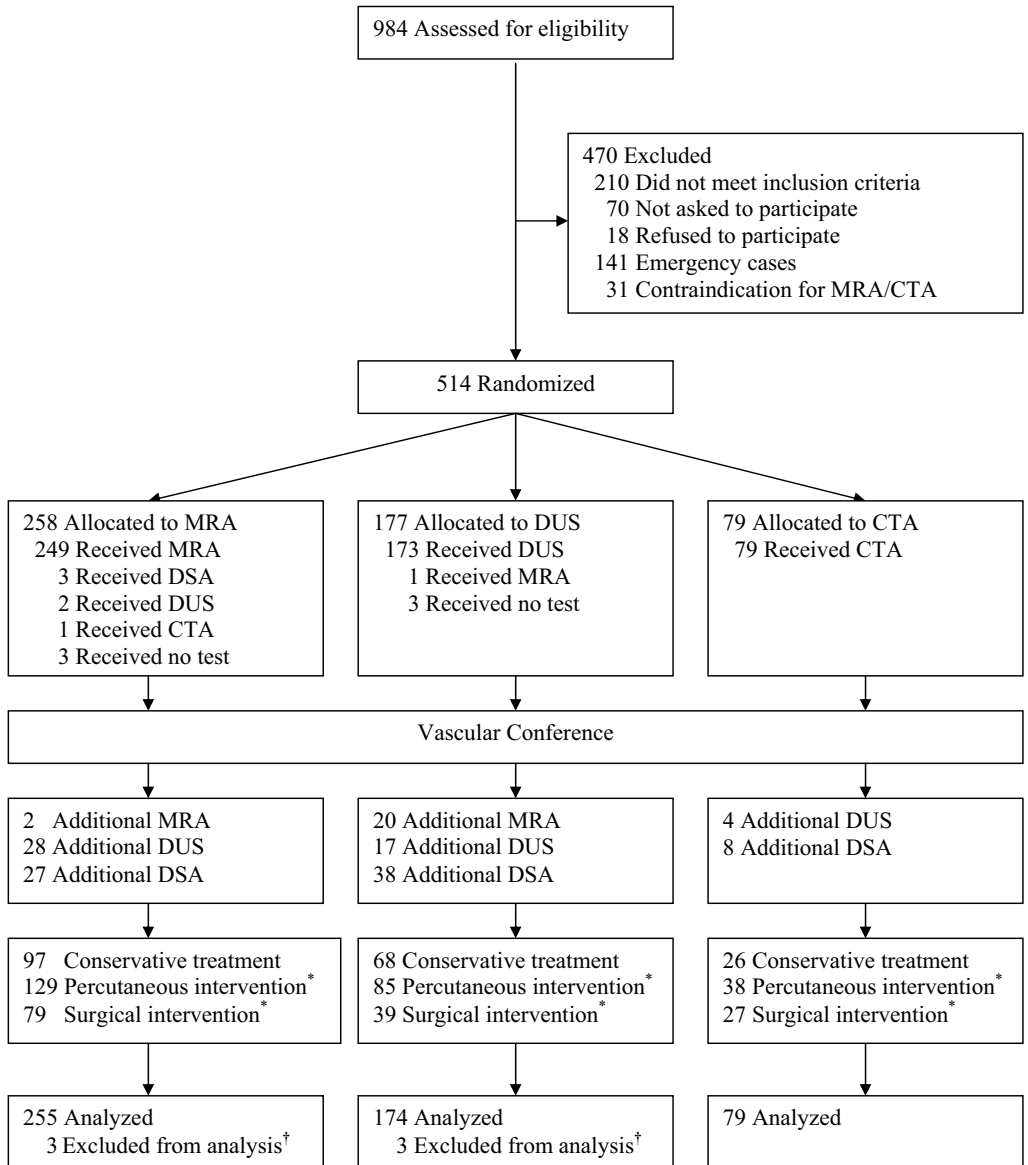
Figure 1. Flow diagram illustrates the reasons for exclusion, random assignment of patients to diagnostic test groups, the diagnostic tests that the patients actually underwent, schematic representation of follow-up, and actual number of patients included in the analysis.

* Some patients underwent several interventional procedures.

† These patients did not undergo any diagnostic or therapeutic intervention and did not have any data available.

Table 1. Baseline Characteristics of Patients.

Characteristics	MRA (n=255)	DUS (n=174)	CTA (n=79)	p-value
Age, y*	64 (11)	64 (11)	64 (12)	1.0
Male sex	168 (66)	122 (70)	50 (63)	0.5
Diabetes mellitus	67 (26)	30 (17)	17 (22)	0.09
Hyperlipidemia	123 (51)	77 (49)	41 (52)	0.9
Smoking	114 (45)	74 (43)	31 (39)	0.7
Arterial hypertension	127 (50)	79 (45)	40 (51)	0.6
Cardiac disease	102 (40)	63 (36)	20 (25)	0.06
Cerebrovascular disease	41 (16)	27 (16)	14 (18)	0.9
Renal Disease				0.09
Renal insufficiency†	16 (7)	9 (5)	1 (1)	
Renal transplantation	9 (4)	1 (1)	1 (1)	
Previous revascularization	92 (36)	60 (35)	30 (38)	0.9
Amputation	10 (4)	4 (2)	5 (6)	0.3
Critical Ischemia	38 (15)	20 (12)	14 (18)	0.4
Ankle/brachial index, treated limb*				
At rest	0.61 (0.20)	0.60 (0.20)	0.62 (0.17)	0.9
After exercise	0.43 (0.21)	0.41 (0.23)	0.40 (0.26)	0.6
Quality of life*				
EQ-5D	0.49 (0.30)	0.55 (0.26)	0.58 (0.24)	0.03
Rating scale	55 (21)	60 (20)	59 (21)	0.06
SF-36				
Physical functioning	37 (22)	40 (20)	38 (18)	0.4
Role physical	34 (40)	35 (40)	34 (40)	1.0
Bodily pain	44 (22)	45 (21)	45 (21)	0.8
General health	48 (21)	53 (21)	52 (21)	0.02
VascuQol	3.7 (1.2)	3.7 (1.1)	3.8 (1.2)	0.4

Data are numbers of patients and percentages in parentheses.
* Data are mean scores, SD in parentheses.
† Mild renal insuffiency or hemodialysis with permission of the nephrologist to undergo a CTA.

Quality of Life

The response rate of the quality of life questionnaires was 99% at baseline, 93% at 2 weeks, 89% at 3 months, and 89% at 6 months follow-up. The improvement in all quality of life measures from baseline to 2 weeks, 3 months and 6 months follow-up was not statistically significant between the groups (*Table 2*). However, there was a consistent difference in one direction among all (except one) quality of life measures of slightly more improvement in the CTA group compared to the MRA group.

Costs

The mean unit cost of the individual imaging tests was 104 euros (SD 38) for all DUS tests, 472 euros (SD 133) for all MRAs, and 163 euros (SD 18) for all CTAs performed during

the trial. For the additional vascular imaging tests, the mean unit cost for all diagnostic DSAs (including hospital stay) was 1207 euros (SD 542). The total diagnostic costs per patient were 206 euros higher in the DUS group compared to the CTA group, which was not a statistically significant difference when considering the multiple comparisons that we performed (p=0.04). However, the total diagnostic costs per patient were significantly higher in the MRA group compared to the DUS group (difference 138; 95% CI 31 to 245; p=0.01) and CTA group (difference 344; 95% CI 182 to 506; p<0.001; *Table 3*).

Table 2. Differences in improvement of quality of life between the groups.

Measure of Quality of Life	Adjusted Mean Difference (95% CI)*		
	MRA vs. DUS[†]	MRA vs. CTA[†]	DUS vs. CTA[‡]
EuroQol-5D			
2 weeks	-0.04 (-0.10 to 0.01)	-0.02 (-0.10 to 0.06)	0.02 (-0.07 to 0.12)
3 months	0 (-0.05 to 0.06)	-0.05 (-0.13 to 0.04)	-0.05 (-0.15 to 0.05)
6 months	0 (-0.06 to 0.05)	-0.02 (-0.11 to 0.06)	-0.02 (-0.12 to 0.08)
SF36-Physical functioning			
2 weeks	-4 (-6 to 5)	-4 (-8 to 1)	1 (-5 to 6)
3 months	0 (-5 to 5)	-9 (-16 to -2)	-9 (-17 to 0)
6 months	-1 (-6 to 4)	-4 (-11 to 4)	-3 (-11 to 6)
SF36-Role physical			
2 weeks	-3 (-10 to 3)	-3 (-13 to 6)	0 (-12 to 12)
3 months	-1 (-9 to 6)	-7 (-18 to 5)	-5 (-19 to 8)
6 months	-6 (-13 to 2)	-11 (-23 to 0)	-5 (-19 to 8)
SF36-Bodily pain			
2 weeks	-3 (-6 to 1)	-5 (-10 to 1)	-2 (-8 to 4)
3 months	0 (-5 to 5)	-6 (-13 to 1)	-6 (-15 to 3)
6 months	-1 (-6 to 4)	-3 (-11 to 5)	-2 (-11 to 8)
SF36-General health			
2 weeks	-1 (-4 to 2)	2 (-3 to 7)	4 (-2 to 9)
3 months	0 (-4 to 3)	-4 (-9 to 1)	-3 (-10 to 3)
6 months	-2 (-6 to 2)	-1 (-6 to 5)	1 (-5 to 8)
Vascuqol			
2 weeks	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)	0 (-0.3 to 0.2)
3 months	0 (-0.2 to 0.3)	-0.2 (-0.6 to 0.2)	-0.2 (-0.7 to 0.2)
6 months	-0.1 (-0.3 to 0.2)	-0.2 (-0.6 to 0.2)	-0.1 (-0.5 to 0.4)
Rating Scale[§]			
2 weeks	2 (-1 to 5)	-2 (-7 to 3)	-4 (-10 to 2)
3 months	0 (-4 to 4)	-4 (-10 to 2)	-4 (-11 to 3)
6 months	0 (-4 to 5)	-2 (-8 to 5)	-2 (-10 to 6)

For each quality of life measure, the baseline score was subtracted from the score at follow-up to yield the improvement scores. The improvement scores were compared across the groups.

*   Adjusted for baseline quality of life score, severity of disease, diabetes mellitus, renal disease, cerebrovascular disease, cardiac disease at baseline, hospital, and rank order.
†   Negative difference indicates that the MRA group has a smaller improvement of quality of life than the DUS or CTA group and vice versa.
‡   Negative difference indicates that the DUS group has a smaller improvement of quality of life than the CTA group and vice versa.
§   Minimum number of paired observations in MRA group was 244, in DUS group 170, and in CTA group 74

This increase in diagnostic costs was not caused by more costs for additional imaging, but was caused by the higher unit costs of the initial imaging test in the MRA group (*Table 3*). With one-way sensitivity analysis only the difference in total diagnostic costs between the MRA and DUS group was sensitive to variation of the investment costs of radiological equipment with a range of 50% to 200% (*Table 4*). If the investment costs of MR equipment were 50% than the baseline estimate, the difference in total diagnostic costs between the MRA and DUS group was not statistically significant anymore, but the difference between the MRA and CTA group was still significant. Note that the difference in diagnostic costs between the CTA and DUS group also changed with varying the investment costs of MR equipment. This is explained by the additional MRA exams in the DUS group. The costs for percutaneous interventions and surgical procedures were not statistically significant between the groups when considering the multiple comparisons that we performed (*Table 3*). The costs for outpatient visits were comparable between the groups (*Table 3*). The total costs including diagnostic, therapeutic, and outpatient visit costs were significantly lower in the CTA group compared to the MRA group (p=0.001) and compared to the DUS group (p=0.01). The total costs were comparable between the MRA and DUS group (p=0.6; *Table 3*).

Table 3. Differences in Costs Between the Groups.

Cost component	Adjusted Mean Difference (95% CI)[*]		
	MRA vs. DUS[†]	MRA vs. CTA[†]	DUS vs. CTA[‡]
Additional Imaging within 60 days (cost initial test not included)	-158 (-241 to -75)	-39 (-164 to 86)	119 (-31 to 269)
Additional Imaging within 60 days (cost initial test included)	188 (103 to 273)	308 (180 to 437)	120 (-34 to 273)
Additional Imaging during follow-up	-50 (-111 to 10)	36 (-56 to 127)	86 (-23 to 196)
Total Diagnostic costs[§]	138 (31 to 245)	344 (182 to 506)	206 (13 to 399)
Percutaneous interventions[||]	120 (-209 to 450)	337 (-160 to 835)	217 (-377 to 811)
Surgical procedures[||]	18 (-909 to 945)	1853 (453 to 3252)	1834 (162 to 3506)
Outpatient visits	-9 (-24 to 5)	1 (-20 to 23)	11 (-15 to 36)
Total costs	267 (-693 to 1228)	2535 (1085 to 3985)	2268 (535 to 4000)

Only diagnostic and therapeutic costs of PAD during 6 months follow-up were included.
Purchasing power in euros for the year 2002. Exchange rate was 0.90 euro per US dollar, Jan, 2002
[*] Adjusted for severity of disease (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, hospital, and rank order.
[†] Positive cost difference indicates that MRA is more costly than DUS or CTA and vice versa.
[‡] Positive cost difference indicates that DUS is more costly than CTA and vice versa.
[§] Diagnostic cost include hospital stay, if necessary, for pre-procedural work-up and post-procedural observation.
[||] Including hospital stay.

Table 4. One-way Sensitivity Analysis of the Difference in Total Diagnostic Costs Between the Groups.

Total Diagnostic costs	Adjusted Mean Difference (95% CI)[*]		
	MRA vs. DUS[†]	MRA vs. CTA[†]	DUS vs. CTA[‡]
Baseline	138 (31 to 245)	344 (182 to 506)	206 (13 to 399)
Investment cost MRA 50%	69 (-37 to 175)	259 (99 to 419)	190 (1 to 381)
Investment cost MRA 200%	279 (169 to 390)	516 (349 to 683)	237 (37 to 436)
Investment cost DUS 50%	152 (45 to 259)	344 (182 to 506)	192 (1 to 386)
Investment cost DUS 200%	111 (4 to 218)	344 (182 to 506)	233 (40 to 426)
Investment cost CTA 50%	138 (31 to 245)	353 (191 to 515)	214 (20 to 407)
Investment cost CTA 200%	138 (31 to 245)	328 (166 to 490)	189 (5 to 382)

Exploring a range of 50% to 200% of the investment costs of radiological equipment.
Baseline is all investment costs of radiological equipment fixed at 100%.
Purchasing power in euros for the year 2002.
[*] Adjusted for severity of disease (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, hospital, and rank order.
[†] Positive cost difference indicates that MRA is more costly than DUS or CTA and vice versa.
[‡] Positive cost difference indicates that DUS is more costly than CTA and vice versa.

Therapeutic Confidence and Additional Imaging

The mean therapeutic confidence was 8.1 (SD 1.4) for MRA, 8.0 (SD 1.1) for CTA, and 7.5 (SD 1.7) for DUS. The therapeutic confidence was significantly higher for MRA compared to DUS (difference 0.8; 95% CI 0.5 to 1.1; p<0.001) and for CTA compared to DUS (difference 1.0; 95% CI 0.4 to 1.5; p<0.001). Within 60 days after the initial imaging test on average more additional vascular imaging tests per patient were performed in the DUS group compared to the MRA group (23% versus 8%; p<0.001) and compared to the CTA group (23% versus 6%; p=0.01). During the total follow-up of 6 months this difference was 19% more imaging tests per patient for DUS compared to MRA (p=0.001) and 22% for DUS compared to CTA (p=0.03). There were no significant differences in the confidence or the number of additional vascular imaging tests between the MRA group and the CTA group.

Ankle-Brachial Index, Maximum Walking Distance, and Clinical Status

The difference in improvement in ABI, MWD, and clinical status from baseline to 6 months follow-up was not statistically significant between the groups (*Table 5*). For ABI, MWD, and clinical status there was a consistent difference in one direction of slightly more improvement in the CTA group compared to the MRA group.

Table 5. Differences in Improvement of Patient Outcomes between the groups.

Measure of Patient Outcome[†]	Adjusted Mean Difference (95% CI)[*]		
	MRA vs. DUS[‡]	MRA vs. CTA[‡]	DUS vs. CTA[§]
ABI at rest	0.01 (-0.04 to 0.05)	-0.04 (-0.11 to 0.02)	-0.05 (-0.13 to 0.03)
ABI after exercise	0.01 (-0.04 to 0.07)	0 (-0.08 to 0.08)	-0.01 (-0.11 to 0.08)
Maximum Walking Distance	-4 (-19 to 10)	-14 (-36 to 8)	-10 (-36 to 17)
Change in Clinical Status[‖]	7 (-8 to 22)	-7 (-17 to 4)	14 (-5 to 32)

Paired observations in MRA group were 244, in DUS group 170, and in CTA group 74. In MRA group 46% completed the maximum walking time (mean 273 meter), in Duplex group 57%, and in CTA group 53% (p=0.1). Data are means.

* Adjusted for baseline scores of ABI or maximum walking distance, severity of disease (critical ischemia vs claudication), renal disease, cerebrovascular disease, cardiac disease, diabetes mellitus at baseline, hospital, and rank order.

† Only measured for the treated leg during 6 months follow-up.

‡ Negative difference indicates that the MRA group has less improvement than the DUS or CTA group and vice versa.

§ Negative difference indicates that the DUS group has less improvement than the CTA group and vice versa.

‖ Data are percentages.

Discussion

We performed a multicenter randomized controlled trial to evaluate the costs and effects of non-invasive imaging strategies. Both MRA and CTA provided similar improvement in quality of life and functional patient outcomes as DUS, but provided higher confidence and less additional vascular imaging tests compared to DUS. Furthermore, the total costs were similar for MRA and DUS, but CTA incurred lower total costs during 6 months follow-up compared to MRA and DUS. The results suggest that both MRA and CTA are clinically more useful than DUS and that CTA leads to cost-savings compared to both MRA and DUS in the initial imaging evaluation of patients with peripheral arterial disease. The final decision which test should be implemented in routine clinical practise in a particular setting also depends on local expertise, availability of equipment, and considerations concerning ionizing radiation and renal insufficiency.

The mean diagnostic costs were significantly higher in the MRA group compared to the DUS and CTA group which is explained by the higher costs of the initial imaging test. MRA is more expensive than DUS and CTA due to higher investment costs, construction costs, costs for the contrast agent, and personnel costs. A reduction in the investment costs of MR equipment would make the difference in total diagnostic costs of MRA compared to the DUS strategy insignificant, but the CTA strategy would still be cost-saving compared to MRA. Furthermore, the total costs in the CTA group were significantly lower than in the MRA and DUS group.

We found that the therapeutic confidence for MRA and CTA was higher than for DUS. A probable explanation is that both MRA and CTA provide a precise roadmap for planning treatment whereas DUS provides interpreted data on a schematic drawing. Probably due to the lower confidence in DUS, the physicians requested additional vascular imaging tests more frequently in the DUS group than in the MRA and CTA group.

A cohort study has traditionally been used for the evaluation of new diagnostic imaging tests by performing both the new test and the reference test in all patients to determine the sensitivity and specificity. For DUS a sensitivity of 88% and a specificity of 95% have been reported (3). For both MRA and CTA a sensitivity between 91-98% and a specificity between 92-99% have been reported (4-11). These results are, however difficult to translate into a meaningful clinical decision with respect to which diagnostic strategy should actually be implemented. A decision about the usefulness of a diagnostic strategy requires either a decision analysis or a randomized controlled trial (12). Although randomized controlled trials are not frequently used to evaluate diagnostic tests, we found our pragmatic randomized trial to be both feasible and inexpensive (13,30-33).

We acknowledge several limitations of our study. Although eligible patients were randomized between MRA and DUS in three hospitals and between MRA and CTA in one hospital we also compared the DUS group with the CTA group. CTA is a relatively new test and was only performed in one hospital. We feel that the comparison between DUS and CTA is valid because both groups were randomized in one study with the same inclusion and exclusion criteria. Furthermore, the baseline characteristics were comparable between these two groups and we adjusted for predictive variables.

Another limitation of the study was that although patients were randomized, there were differences between the MRA group and the other two groups at baseline in EQ-5D and the dimension general health of SF-36. To calculate the difference in improvement of quality of life we adjusted for the baseline quality of life scores. There were minor differences between the groups at baseline in diabetes mellitus, cardiac disease, renal disease, and critical ischemia. These baseline differences were not statistically significant, but we felt it would be prudent to adjust for predictive baseline variables that may lead to differences in outcomes (34,35). Therefore, adjustment for potentially predictive variables in a multivariable or logistic regression was used to correct the estimates of the outcomes for any imbalance that by chance may have occurred between the randomized groups. Furthermore, imaging techniques were different between the hospitals. For this reason we adjusted for hospital setting in the regression analysis.

A possible limitation was that patients and physicians were not blinded for group allocation. At the same time, the goal of our study was to evaluate the outcomes of the diagnostic tests as they are used in routine clinical practice. Patients could not be blinded and blinding of the treating physicians by for example, transferring the diagnostic information to a schematic drawing would have introduced an artificial step that could have affected diagnostic interpretation and therapeutic planning. Furthermore, although schematic drawings are used in routine clinical practice as adjunct, they are not used solely when the imaging test provides a good roadmap.

Finally, the costs were calculated from a hospital perspective instead of a societal perspective. There is international consensus that an economic evaluation should be performed from the societal perspective (36). A societal perspective implies that not only the costs within the healthcare sector, but also the direct (i.e. patient costs) and indirect costs (i.e. costs of production losses) outside the healthcare sector have to be included in the cost analysis (25). In our study we chose for the hospital perspective because other studies which assessed the costs related to the management of PAD showed that patient costs were low in both the Dutch and US settings (37,38). Furthermore, in the setting of PAD the costs of production losses are negligible since most patients are retired (39).

In conclusion, the results suggest that both MRA and CTA are clinically more useful than DUS and that CTA leads to cost-savings compared to both MRA and DUS in the initial imaging evaluation of patients with peripheral arterial disease.

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Vessel Wall Calcifications on Multi-Detector Row CT Angiography in Patients with Peripheral Arterial Disease: Impact on Clinical Utility and Clinical Predictors

Chapter 7

Abstract

Purpose

To evaluate the impact of vessel wall calcifications on the clinical utility of multi-detector row computed tomographic angiography (CTA) in patients with peripheral arterial disease, and to identify clinical predictors for the presence of vessel wall calcifications.

Materials and Methods

For this study we included 145 patients from two randomized controlled trials that measured the costs and effects of diagnostic imaging in patients with peripheral arterial disease. All patients underwent a CTA and were followed for 6 months. Clinical utility was measured with therapeutic confidence (0-10) in the initial CTA and the need for additional vascular imaging. Univariable and multivariable logistic and linear regression analysis and the area under the receiver operating characteristic curve (AUC) were used to evaluate the impact of vessel wall calcifications on clinical utility, and patient characteristics for their ability to predict the number of calcified segments on CTA.

Results

We found that the number of calcified segments was a significant predictor of the need for additional imaging and of the confidence scores. Furthermore, the number of calcified segments discriminated between patients requiring additional imaging following CTA from those who did not need additional imaging (AUC=0.66; 95%CI 0.54 to 0.77). Age, diabetes mellitus, and cardiac disease were significant predictors of the number of calcified segments in both the univariable and multivariable analysis (p<0.05).

Conclusion

Vessel wall calcifications decrease the clinical utility of CTA in patients with peripheral arterial disease. Diabetes mellitus, cardiac disease, and elderly age are independently predictive for the presence of vessel wall calcifications.

Introduction

Computed tomographic angiography (CTA) is increasingly used for diagnostic imaging in patients with peripheral arterial disease. With the introduction of multi-detector row CT scanners, CTA has been substantially improved for peripheral arterial disease. The use of multi-detector row technology has resulted in shorter acquisition time, increased volume coverage, lower dose of contrast medium, and improved spatial resolution for assessing small arterial branches (1, 2). The number of studies showing that multi-detector row CTA is accurate for imaging peripheral arteries is still increasing (3-10). Furthermore, we showed in our institution that patient outcomes and clinical utility of CTA was comparable with both digital subtraction angiography (DSA) and MRA, but CTA incurred lower diagnostic costs compared to both DSA and MRA (11, 12). These results suggest that CTA is the optimal strategy for the initial diagnostic work-up of PAD.

A major drawback of CTA is the difficulty in assessing arterial luminal stenosis in extensively calcified vessels. Several studies reported that calcified plaques were the main reason for misinterpretations on CTA (3, 5, 10). In the presence of extensive vessel wall calcifications, especially in small arteries, it is difficult to produce MIP images with high diagnostic value. Continuous calcification of the vessel wall may cause false-negative findings of patency, whereas high-density artifacts, known as "blooming" of calcification on axial images may result in a false-positive diagnosis of significant stenosis or occlusion. Two studies reported significantly lower diagnostic accuracy and interobserver agreement in arterial segments with calcifications compared to segments without calcifications (6, 13). Furthermore, some authors stated that when extensive calcifications are present, the end product of CTA is of no, or questionable, diagnostic value and that these cases could not be managed without digital substraction angiography for accurate evaluation (5, 6).

The impact of vessel wall calcifications on the clinical utility of CTA in terms of therapeutic confidence and the number of additional imaging tests performed remains to be clarified. Furthermore, it would be useful to identify clinical predictors of vessel wall calcifications to select patients for whom CTA is less clinically useful. The purpose of this study was to evaluate the impact of vessel wall calcifications on the clinical utility of CTA, and to identify clinical predictors of vessel wall calcifications.

Materials and methods

Study design
The patient population recruited for this study are patients included in two randomized controlled trials that measured the costs and effects of initial imaging tests in the diagnostic work-up of PAD. Both studies were performed in the same university hospital. In the first study (12) between April 2000 and August 2001 patients with PAD were randomly assigned to undergo CTA or DSA as the initial imaging test. In a second study (11) between December 2001 and September 2003 patients with PAD were randomized between CTA and MRA.

Inclusion criteria for participation in both studies were age older than 18 years, symptomatic PAD, an ankle-brachial index of less than 0.90, and referral for diagnostic imaging work-up to evaluate the feasibility of a revascularization procedure. Exclusion criteria included contraindications for MRA (eg, pacemaker or claustrophobia) or CTA and DSA (eg, severe renal insufficiency or adverse reactions to iodinated contrast agents), and the necessity of an acute intervention. Both studies were approved by the institutional review board and informed consent for both studies and all manuscripts deriving from the studies was obtained from all patients.

Imaging Technique and Evaluation
Multi-detector CTA was performed on a Somatom Plus 4 Volume Zoom or a Sensation 16 scanner (Siemens Medical Systems, Forchheim, Germany).

After obtaining an initial scout image (120 kV, 100 mAs), the scanning range was planned to encompass the entire vascular system from the diaphragm to the level of the ankles. For optimal intraluminal contrast enhancement, the delay time between start of contrast material administration and start of scanning was obtained for each patient individually by using a bolus-tracking technique (CARE-Bolus, Siemens). Each patient received 120 ml of contrast agent intravenously (Visipaque 320 mgI/ ml; Amersham Health, Buckinghamshire, UK) at a flow rate of 3 ml/sec.

Data acquisition was performed craniocaudally with the following parameters: collimation, 0.75/ 2.5 mm; number of detector rows, 16/ 4; pitch, 1.5/ 1.6; X-ray tube voltage setting, 120/ 120kV; current, 140/ 110 mAs for the 16-slice and 4-slice CT scanner, respectively.

Transverse sections were reconstructed with a 2-3 mm slice thickness at an interval of 1-1.5 mm. Postprocessing resulted in orthogonal curved planar reformations through the aortoiliac tract and rotating volume maximal intensity projections (MIPs) for aortoiliac, femoropopliteal, and crural arteries.

Two readers with extensive experience in interpreting CTA, a vascular radiologist and a dedicated researcher, evaluated all images for arterial stenosis or other pathology. For image interpretation, the readers used the curved planar reformations, the rotating volume MIPs, and the source data on a workstation. For analysis purposes, the arterial vascular system was divided into 31 segments, namely the distal aorta, the paired common iliac arteries, the external iliac arteries, the common femoral arteries, the deep femoral arteries, the superficial femoral arteries (proximal and distal part), the popliteal arteries (above and below the knee), the anterior tibial arteries (proximal and distal part), the tibial peroneal trunk, the posterior tibial arteries (proximal and distal part), and the peroneal arteries (proximal and distal part). The following five point ordinal scale was used to grade stenotic or occlusive disease: 0 for 0-19% stenosis, 1 for 20-49% stenosis, 2 for 50-74% stenosis, 3 for 75-99% stenosis, and 4 for occlusion. When two or more stenotic luminal lesions were detected in the same vessel segment, the most severe lesion was used for grading. Furthermore, the readers recorded the presence of vessel

wall calcifications. The presence of calcifications in each segment was counted as 1 and its absence as 0. The final calcification score was the sum of all the segments ranging from 0 to 31. The images were first evaluated independently and subsequently all by a consensus reading. These consensus readings were used for the data analysis. All images were evaluated without knowledge of further workup.

Measurement of Clinical Utility

In both studies we assessed the therapeutic confidence of vascular radiologists and surgeons during the weekly vascular conference (11, 12, 14). In addition to patient history and physical examination, the findings of the initial imaging test were discussed and each clinician was asked to rate his/her individual confidence in making a well-founded therapeutic choice on a ten-point rating scale. Furthermore, we measured the recommendations for additional imaging (duplex ultrasound, DSA, MRA, or CTA) during the vascular conference. Any additional vascular imaging test performed within 6 months after the initial test was noted.

Measurement of Clinical Predictors

In both studies we collected information concerning patient characteristics. Baseline data included information on history of cardiovascular disease and cardiovascular risk factors. The stage of PAD (intermittent claudication or critical ischemia) was assessed by the vascular surgeon. Smoking was dichotomized in ever smokers (current and former) and those who never smoked. Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 100 mmHg or over, or current use of antihypertensive drugs for the indication of hypertension. Diabetes mellitus was defined as the current use of antidiabetic drugs. Hyperlipidemia was defined as the current use of lipid lowering drugs. History of cardiac disease (including chest pain, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, and myocardial infarction), cerebrovascular disease (including transient ischemic attack and stroke), renal disease (including renal insufficiency, haemodialysis, and renal transplantation), and previous vascular interventions (including percutaneous transluminal angioplasty and vascular surgery) were obtained through direct questioning and using the medical records.

Statistical Analysis

With univariable and multivariable logistic and linear regression the predictive ability of the number of calcified segments in predicting the need for additional imaging and the confidence scores, respectively, was assessed. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to assess the discriminatory power of the number of calcified segments in distinguishing patients requiring additional imaging from those who do not require additional imaging. To evaluate which variables were predictive for the number of calcified segments we first assessed each variable separately using univariable linear regression analysis and calculated the regression coefficient and the 95% confidence interval (CI). Subsequently, we performed multivariable linear regression analysis including all variables that had a p-value of less than 0.10 in the univariable analysis. The final multivariable model was obtained using a stepwise backward selection with a significance level of 0.05. All calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il).

Results

In both studies a total of 152 patients were randomized to CTA (*Figure 1*). Finally, 145 patients were analyzed because seven patients participated in both studies (at different points in time, ie. they returned with recurrent symptoms) and were excluded from the analysis. The baseline characteristics of the study population are shown in *Table 1*. The distribution of the number of calcified segments was slightly skewed, with a median of 10 and a range of 0 to 28. During the follow-up period 40 patients underwent additional vascular imaging.
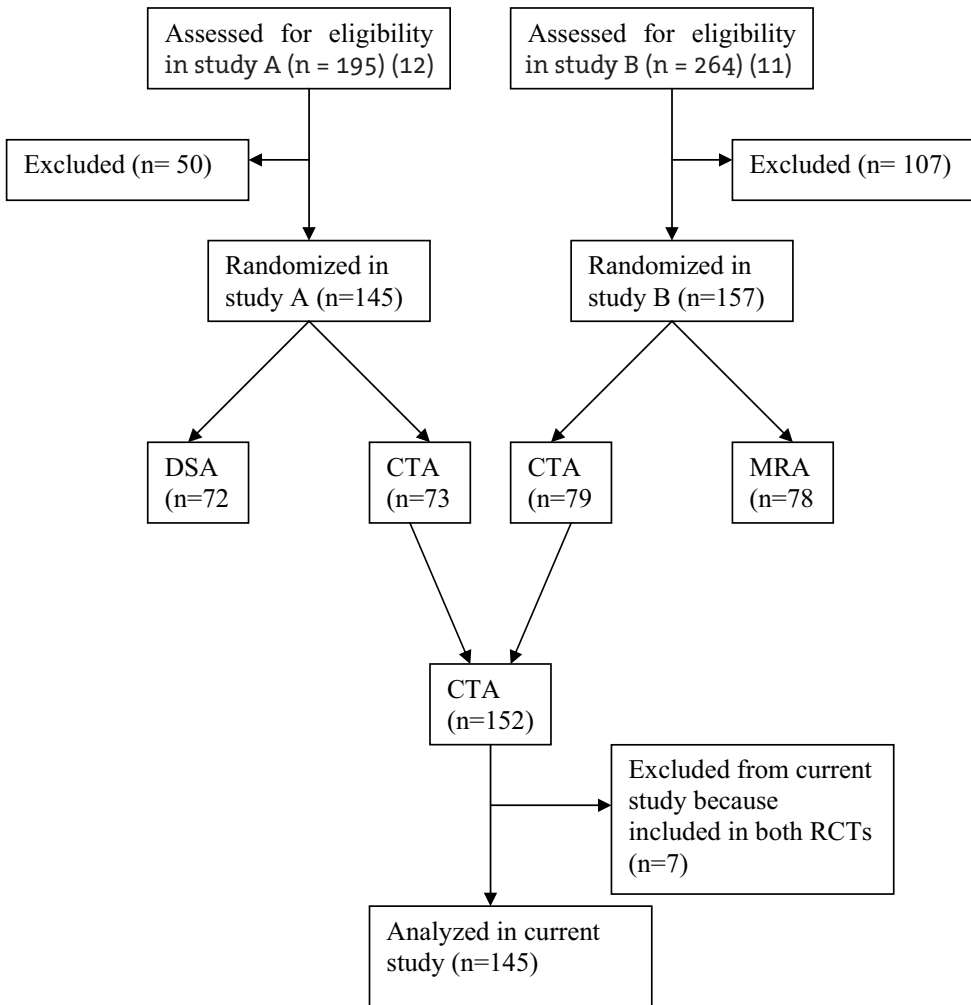
Figure 1. Flow diagram of patients passing through both randomized controlled trials (RCTs) and those included in the current study.

Table 1. Baseline Characteristics of Study Population (n=145).

Characteristics	Mean or percentage*
Age, mean (SD)	64.0 (11.6)
Male sex, (%)	69.7
Diabetes mellitus, (%)	29.7
Hyperlipidemia, (%)	49.7
Smoking[†], (%)	76.6
Arterial hypertension, (%)	49.7
Cardiac disease, (%)	29.0
Cerebrovascular disease, (%)	22.1
Renal Disease[‡], (%)	11.7
Previous revascularization, (%)	41.4
Critical Ischemia, (%)	29.0

* Dichotomous variables are expressed as percentage. Values of continuous variables are expressed as mean, SD in parentheses.
† Include current and former smokers.
‡ Mild renal insuffiency or hemodialysis with permission of the nephrologist to undergo a CTA.

With univariable logistic and linear regression the number of calcified segments was a significant predictor of the need for additional imaging (odds ratio 1.09; 95% CI 1.03 to 1.14; p=0.001) and of the confidence scores (regression coefficient −0.08; 95% CI −0.10 to −0.05; p<0.0001; R square = 0.21). When controlling for all baseline characteristics in a multivariable model the number of calcified segments still significantly contributed to the prediction of both the need for additional imaging and confidence scores. Furthermore, the number of calcified segments discriminated well between patients requiring additional imaging following CTA from those who did not need additional imaging (AUC=0.66; 95%CI 0.54 to 0.77; *Figure 2*).

The regression coefficients and 95% CIs of all clinical variables that were
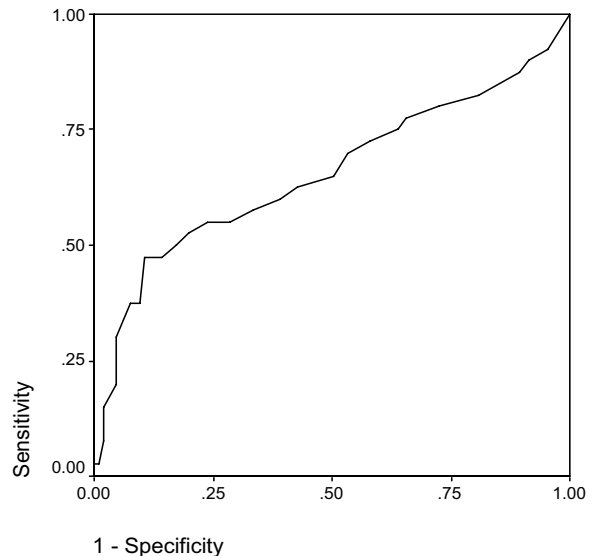
Figure 2. Receiver operating characteristic curve for the number of calcified segments for prediction of the need for additional vascular imaging.

Table 2. Performance of clinical variables in predicting the number of calcified segments – univariable linear regression analysis

Clinical variables	Regression coefficient (95% CI)	p-value*
Age (continuous)	3.34 (1.28 to 5.40)[†]	0.002
Male sex	2.00 (-0.66 to 4.66)	0.14
Diabetes mellitus	3.70 (1.07 to 6.33)	0.006
Hyperlipidemia	-1.02 (-3.48 to 1.44)	0.41
Smoking[‡]	-0.26 (-3.17 to 2.65)	0.86
Arterial hypertension	1.46 (-0.99 to 3.92)	0.24
Cardiac disease	4.05 (1.42 to 6.69)	0.003
Cerebrovascular disease	1.64 (-1.32 to 4.60)	0.28
Renal Disease[§]	4.82 (1.07 to 8.57)	0.01
Previous revascularization	1.09 (-1.41 to 3.58)	0.39
Critical Ischemia	2.95 (0.27 to 5.62)	0.03

* Variables with p-value<0.10 were included in the multivariable analysis.
† Per 20-year increase.
‡ Include current and former smokers.
§ Mild renal insuffiency or hemodialysis with permission of the nephrologist to undergo a CTA.

Table 3. Performance of clinical variables in predicting the number of calcified segments – multivariable linear regression analysis

Clinical variables	Regression coefficient (95% CI)	p-value
Age (continuous)	3.40 (1.44 to 5.38)*	0.001
Diabetes mellitus	3.07 (0.54 to 5.59)	0.02
Cardiac disease	3.58 (1.03 to 6.13)	0.006

* Per 20-year increase. R-square = 0.17.

assessed in the univariable linear regression analysis are presented in *Table 2*. Age, diabetes mellitus, cardiac disease, renal disease, and critical ischemia had a p-value of less than 0.10 and were subsequently used in the multivariable linear regression analysis (*Table 3*). We found that diabetes mellitus, cardiac disease, and age were independently predictive for the presence of vessel wall calcifications (all p-values<0.05).

Discussion

Multi-detector row CTA is increasingly used for clinical decision-making in patients with suspected arterial occlusive disease. Because interpretation of CTA images is difficult in extensively calcified vessels, it is important to evaluate the impact of vessel wall calcifications on the clinical utility of CTA. Subsequently, if vessel wall calcifications

decrease clinical utility of CTA, it would be useful to identify clinical predictors of calcifications in peripheral arteries to select patients for whom CTA is less clinically useful. Using the data from two randomized controlled trials we found that the number of calcified segments was a significant predictor for both the need of additional imaging and lower confidence scores. Furthermore, we showed that diabetes mellitus, cardiac disease, and elderly age were independently predictive for the presence of vessel wall calcifications.

Our results imply that for elderly patients (age above 84 years), patients with diabetes mellitus, and those with cardiac disease a CTA is less clinically useful due to decreased clinical utility. In these patients MRA should be considered as initial imaging test. Although renal disease was only a significant predictor for calcified segments in the univariable analysis and not an independent predictor in the multivariable analysis, patients with renal disease will generally undergo MRA instead of CTA because of the nephrotoxicity of iodinated contrast agents. Furthermore, in patients with critical ischemia the choice of test depends larger on availability of imaging equipment and the need for urgent revascularization. If a percutaneous intervention is deemed urgent and possible one should consider proceeding to the angiography suite directly where a DSA can be performed as initial test followed by an intervention. In contrast to the literature about prediction of coronary calcification, articles about prediction of calcifications in the arteries to the lower extremities are scarce. One article evaluated calcifications in plain radiographic films of the pelvis and hands in haemodialysis patients (15).They reported that diabetes mellitus, male sex, age, duration of haemodialysis, and mean arterial pressure were independently associated with vessel wall calcifications in the arteries of the pelvis and hands. They did not, however, evaluate a history of cardiac disease as a predictor.

We acknowledge several limitations of this study. For this study we used a limited sample size of 145 patients. A larger sample size would be better to identify predictors of vessel wall calcifications.

Another limitation is that we used data from two different studies. Although these studies were performed almost consecutively in the same center with the same inclusion and exclusion criteria this may have led to misclassification of baseline characteristics. Different researchers were involved in the studies and they may have applied the definitions for the baseline characteristics just slightly differently. Furthermore, diabetes mellitus was defined as the current use of antidiabetic drugs and hyperlipidemia was defined as the current use of lipid lowering drugs. These definitions could have led to misclassification because patients may have had undiagnosed diabetes or hyperlipidemia at the time of inclusion. Finally, the score of vessel wall calcifications was not performed quantitatively as with calcium volume or Agatston scores (16). Quantitative measurement is a more accurate measure of the amount of calcification then the method we used and could lead to more precise prediction of vessel wall calcifications.

To the best of our knowledge this was the first study evaluating the impact of vessel wall calcifications on the clinical usefulness of CTA in patients with peripheral arterial

disease. We showed that vessel wall calcifications on CTA are associated with the need for additional vascular imaging and lower confidence in the imaging findings. This result implies that it would be useful to identify patients in advance for whom the initial CTA is not conclusive due to vessel wall calcifications and refer these patients to another imaging modality. Despite several limitations we performed an initial evaluation of clinical predictors of vessel wall calcifications on CTA. A future study is needed to develop and validate a clinical prediction rule for this problem. The results from the current study can help design such a future study and restrict the data collection to the most relevant variables.

In conclusion, the results of our study demonstrated that vessel wall calcifications decrease the clinical utility of CTA in patients with peripheral arterial disease and that diabetes mellitus, cardiac disease, and elderly age are independently predictive for the presence of vessel wall calcifications.

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Guiding Future Clinical Cost-Effectiveness Studies of Non-Invasive Diagnostic Imaging Tests for Peripheral Arterial Disease

Chapter 8

Abstract

Purpose
To guide future clinical cost-effectiveness research concerning the use of non-invasive imaging tests for peripheral arterial disease.

Materials and Methods
We performed value of information analysis to estimate the benefit of future clinical cost-effectiveness research, using data from a randomized controlled trial of the costs and effectiveness of non-invasive diagnostic imaging for peripheral arterial disease. The primary outcomes of interest for the imaging tests were costs from the hospital perspective and quality of life. For the value of information analysis these two outcomes were combined into one outcome: the net monetary benefit (NMB), assuming a societal willingness-to-pay of 20,000 euro/QALY. The expected benefit of future research was expressed in euros per patient and euros for the Dutch patient population, assuming a 5-year effective lifetime of the imaging technologies.

Results
The total expected value of perfect information (EVPI) was 4.5 euro per patient, resulting in a population EVPI of 276,000 euro for the Netherlands. This population benefit did not exceed conservative estimates for the costs of future research. Exploration of the partial EVPI demonstrated that uncertainty about the therapeutic costs was more important than uncertainty about diagnostic costs.

Conclusion
More clinical cost-effectiveness research concerning the use of non-invasive imaging tests for peripheral arterial disease is not justified.

Introduction

Peripheral arterial disease (PAD) is the expression of atherosclerosis in the lower limb distal to the aortic bifurcation, which is a major problem in the population of 55 years and older (1). The first manifestation of symptomatic PAD is usually intermittent claudication. In a minority of patients, the disease progresses to critical limb ischemia, i.e. rest pain and tissue necrosis. Diagnostic imaging is performed when PAD becomes lifestyle limiting and a revascularization procedure is considered.

In a previous study we performed a randomized controlled trial (RCT) of the costs and effectiveness of non-invasive diagnostic imaging for peripheral arterial disease (PAD), and found that initial imaging with multi-detector computed tomographic angiography (CTA) was the optimal strategy. CTA incurred significantly lower total costs compared to contrast-enhanced magnetic resonance angiography (MRA) and duplex ultrasound scanning (DUS) and the effectiveness was comparable.

The RCT identified the optimal strategy but, as with every trial of finite sample size, it did not give a definitive answer. Thus, if we implement CTA as standard care, we may still make the wrong decision. The question arises whether more research is justified to decrease the remaining uncertainty. More research is not justified if the expected costs of a future study exceed the expected benefit of that study. Value of information analysis (VOI) can explicitly estimate the expected benefit of a future study by considering both the probability and the consequences of making the wrong decision based on currently available evidence (2, 3). Moreover, VOI analysis can guide the design of a future study by identifying key parameters.

The purpose of this study was to guide future clinical cost-effectiveness research concerning the use of non-invasive imaging tests for peripheral arterial disease.

Materials and methods

Randomized Controlled Trial

In a pragmatic multicenter randomized controlled trial we enrolled consecutive patients between December 2001 and September 2003 with symptomatic PAD who were referred from the Department of Vascular Surgery for diagnostic imaging. Patients were randomly assigned to undergo MRA or DUS in three hospitals and MRA or CTA in one hospital as the initial imaging test.

During 6 months follow-up, quality of life was measured using the EuroQol-5D (EQ-5D). A self-administered questionnaire was sent to all patients at the time of randomization and 2 weeks, 3 months, and 6 months after the initial imaging test. The EQ-5D covers five different health dimensions including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, which together give a total of 243 different health states. Using a published population-based utility function, a single index score was calculated for each patient (4). Subsequently, we calculated the quality-adjusted life years (QALYs) experienced per patient over the course of the 6-month follow-up period.

For the cost analysis, we collected information concerning all relevant items of medical care (i.e. diagnostic and therapeutic) used by each patient during a follow-up period of 6 months following randomization to calculate the mean cost per imaging strategy per patient. The cost of diagnostic imaging included the initial imaging test (i.e MRA, CTA, or DUS), all additional vascular imaging (i.e MRA, CTA, DUS, and digital subtraction angiography (DSA)), and the associated hospital admissions. The therapeutic costs included costs for percutaneous vascular interventions (i.e. percutaneous angioplasty, stent placement, and thrombolysis), vascular surgery (i.e. aortic bifurcation reconstruction, bypass surgery, endarterectomy, and amputation), and associated hospital admissions during 6 months follow-up. Futhermore, we assessed the costs for outpatient visits. All costs were computed from the hospital perspective according to the Dutch guidelines for cost calculations in health care (5).

Medical costs can be divided in directly and non-directly assignable costs. Directly assignable costs include personnel costs, material costs, and equipment costs. For the personnel costs, the time spent on a diagnostic or percutaneous intervention procedure was measured and multiplied with the mean wage rates from our hospital. Social security of 37% of the wage was included in accordance with national guidelines. Costs of materials used in diagnostic or percutaneous intervention procedures were based on cost prices and summed. The annuitized costs(6) of the radiological equipment and the annual equipment servicing costs were summed and divided by the proportion of the total available room time (80% of a 40 hour work-week) (5, 6). Costs were discounted at a rate of 3% per annum (7). Non-directly assignable costs include costs of supporting departments, housing costs, and overhead costs. Information on costs of supporting departments was obtained from records of our Financial and Economics Department. The costs for housing were computed for the used radiological rooms by multiplying the surface space with the housing costs of 204 euros per m2 per year. The overhead costs for MRA and CTA were estimated to be 15% of directly assignable costs (5).

We obtained unit costs of surgical procedures from another study with a comparable study domain and setting (8). For a limited number of surgical procedures performed in our study, the unit costs were not available from this article and we had to estimate these costs using the published values as starting point (personal communication van Sambeek, MD, PhD, 2002). The costs of hospital admission and outpatient visits were calculated using national estimates for hospital stay, intensive care unit admission, and outpatient visits (5). All costs were reported in euros for the year 2002 (the exchange rate was 0.82 euro per US dollar, September 2004).

In our RCT, the mean total cost and QALY per patient were adjusted for potentially predictive variables using multivariable linear regression. These baseline characteristics were comparable between the groups, but based on previous studies (9) and clinical experience we assumed that severity of disease (critical ischemia vs claudication), renal disease (i.e. renal insufficiency and renal transplantation), cerebrovascular disease, cardiac disease, and diabetes mellitus at baseline were potentially predictive for the outcomes. Furthermore, we adjusted for hospital setting because the imaging techniques were different between the hospitals. For the cost outcomes we applied a log

transformation before adjustment and after adjustment the data was transformed back to the original scale (i.e. euro).

All statistical analyses of the RCT were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il).

Value of Information Analysis

The primary outcomes of the RCT were total costs and effectiveness. We transformed this two-dimensional outcome into one composite outcome: net monetary benefit (NMB) (10). The NMB is expressed as the monetary equivalent of effectiveness, which is QALY times the societal willingness-to-pay (WTP) minus the costs. For example, if the effectiveness is 0.3 QALY, the costs are 5000 euro, and the WTP is 20,000 euro per QALY, then the NMB is (0.3 * 20,000) – 5000 = 1000 euro. To calculate the NMB we used a WTP of 20,000 and 50,000 euro/QALY.

To estimate the total expected value of perfect information (EVPI), we calculated the mean NMB and the standard error of the mean for each strategy. The uncertainty around de "true" values of the mean NMB for each strategy was represented by a normal distribution with mean equal to the calculated mean and standard deviation equal to the calculated standard error of the mean (11). The total EVPI per patient was estimated by applying Monte Carlo simulation (65,000 iterations) to the strategy-specific distributions of the mean NMB. At each iteration we observed whether CTA, which was the estimated optimal strategy from the clinical trial, was the best. If not, the gain was calculated of interchanging CTA with the best strategy in that iteration (3, 12-14). The average gain over all iterations yielded the total EVPI. It can be interpreted as the expected benefit per patient of an infinitely large RCT, eliminating all uncertainty around the mean outcomes. VOI results are always expressed in the same units as the outcome of the strategies and thus, in our analysis, this was euros.

Next we estimated the population EVPI, which is the total EVPI per patient multiplied by both the annual number of future patients expected to benefit from more research and the effective lifetime of the optimal strategy (3). For the calculation of the population EVPI we took a discount rate of 3% into account. Because there is uncertainty about the effective lifetime of a diagnostic strategy and the population that could benefit we performed a sensitivity analysis for these variables. Expressing the population EVPI in euros enables comparison with the research costs. If the population EVPI is less than the estimated costs of future research, more research is not justified.

The overall decision uncertainty in our study arose from uncertainty about 10 individual cost parameters (total cost, therapeutic cost, diagnostic cost, cost of MRA, CTA, DUS, DSA, percutaneous interventions, surgical procedures, and outpatient visits) and the effectiveness (QALY) parameter. The partial EVPI estimates the expected value of knowing the "true" values of only one or more of these parameters, instead of all parameters simultaneously, as was estimated with the total EVPI. The uncertainty in the true values of the 11 parameters was represented by a multivariate normal distribution with means equal to the calculated means and standarddeviations equal to the calculated standard

errors. Next we calculated partial EVPI's per patient by applying Monte Carlo simulation to the strategy-specific distributions of the individual cost parameters as well as the effectiveness parameter. Collecting information on the parameters with the highest partial EVPI yields the highest benefit per patient and these parameters are therefore the most important parameters to measure in future studies. Subsequently, the partial EVPI was estimated for the entire population. All VOI analyses were performed with Excel 2000 (Microsoft Corporation).

Results

Randomized Controlled Trial

A total of 514 patients were randomized, of whom 258 were allocated to MRA, 177 to DUS, and 79 to CTA. The mean QALYs per patient over the course of a follow-up period of 6 months was 0.27 (95%CI 0.26 to 0.28) for the MRA group, 0.28 (95%CI 0.26 to 0.29) for the DUS group, and 0.29 (95%CI 0.27 to 0.31) for the CTA group, which was not a statistically significant difference (*Table 1*). The mean total costs per patient were 4139 euro (95%CI 3471 to 4808) for the MRA group, 3872 euro (95%CI 3457 to 4287) for the DUS group, and 1604 (95%CI 613 to 2595) for the CTA group (Table 1). The total costs were significantly lower in the CTA group compared to the MRA and DUS group (p<0.01). Cost for surgical procedures and percutaneous interventions were responsible for most of the total costs. Combining QALYs and total costs using a WTP of 20,000 euro/QALY resulted in a significantly higher mean NMB per patient for the CTA group (4165 euro; 95%CI 3097 to 5233) compared to the MRA group (1313 euro; 95%CI 581 to 2044) and the DUS group (1667 euro; 95%CI 1153 to 2180) (*Table 1*).

Table 1. Results of the randomized controlled trial.

	MRA (n=255) [†]	DUS (n=174)[‡]	CTA (n=79)
Quality-adjusted life years	0.27 (0.26 to 0.28)	0.28 (0.26 to 0.29)	0.29 (0.27 to 0.31)
Total costs	4139 (3471 to 4808)	3872 (3457 to 4287)	1604 (613 to 2595)
Net monetary benefit[*]	1313 (581 to 2044)	1667 (1153 to 2180)	4165 (3097 to 5233)

Data are mean scores, 95% confidence intervals in parentheses.
* Calculated using a willingness-to-pay of 20,000 euro per quality-adjusted life year.
† In the MRA group three patients were excluded from the analysis because they received no test.
‡ In the DUS group three patients were excluded from the analysis because they received no test.

Expected Value of Perfect Information

Using a WTP of 20,000 euro/QALY, CTA had the highest mean NMB per patient and was the optimal strategy in 98% of the Monte Carlo simulations. Using a WTP of 50,000 euro/QALY, the CTA strategy was the optimal strategy in 96% of the Monte Carlo simulations. Put in other words, if based on this RCT CTA was implemented as standard care, there

would be a probability of 2 to 4% that the wrong strategy is introduced, i.e. that a strategy is introduced which does not optimize NMB.

The total EVPI for NMB was 4.5 euro per patient. This implies that an infinitely large future RCT is expected to increase the NMB per patient with PAD with 4.5 euro on the current mean of 4165 euro per patient for the optimal strategy. Using a WTP of 50,000 euro/QALY, the total EVPI for NMB was 11 euro per patient.

Based on the literature, we estimated the number of patients with PAD that undergo a diagnostic work-up to be 13,000 per year for the Netherlands (15). These 13,000 patients are expected to benefit from future clinical cost-effectiveness research. We assumed that the effective lifetime of a diagnostic strategy as used in the RCT was 5 years. With a discount rate of 3% this resulted in a population EVPI of 276,000 euro. Using a WTP of 50,000 euro/QALY, the population EVPI was 695,000 euro. Performing a sensitivity analysis by increasing the effective lifetime to 10 years and the population to benefit to 20,000/year, we observed a total EVPI of 800,000 euro for a WTP of 20,000/QALY and almost 2 million euro for a WTP of 50,000/QALY (*Figure 1*).

The population partial EVPI of the individual effectiveness and cost parameters is presented in *figure 2*. For a WTP of 20,000 euro/QALY, effectiveness had a negligible partial EVPI whereas the total cost was responsible for 49% (136,000 euro) of the expected benefit to gain with more research. Subdividing the total cost in therapeutic and diagnostic cost, we observed that the therapeutic cost was responsible for 95% of the partial EVPI of the total cost. The cost for surgical procedures was responsible for 44% of the partial EVPI of therapeutic cost (*Figure 2*). Using a WTP of 50,000/QALY, the effectiveness parameter
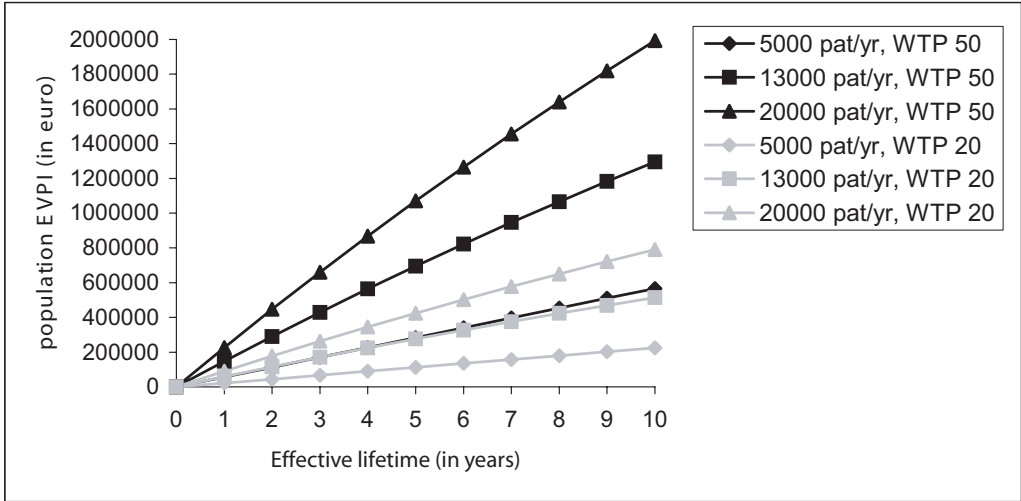
Note: WTP 20 is willingness-to-pay of 20000 euro/QALY and WTP 50 is willingness-to-pay of 50000 euro/QALY

Figure 1. Population EVPI as a function of effective lifetime for different willingness-to-pay thresholds and populations to benefit.
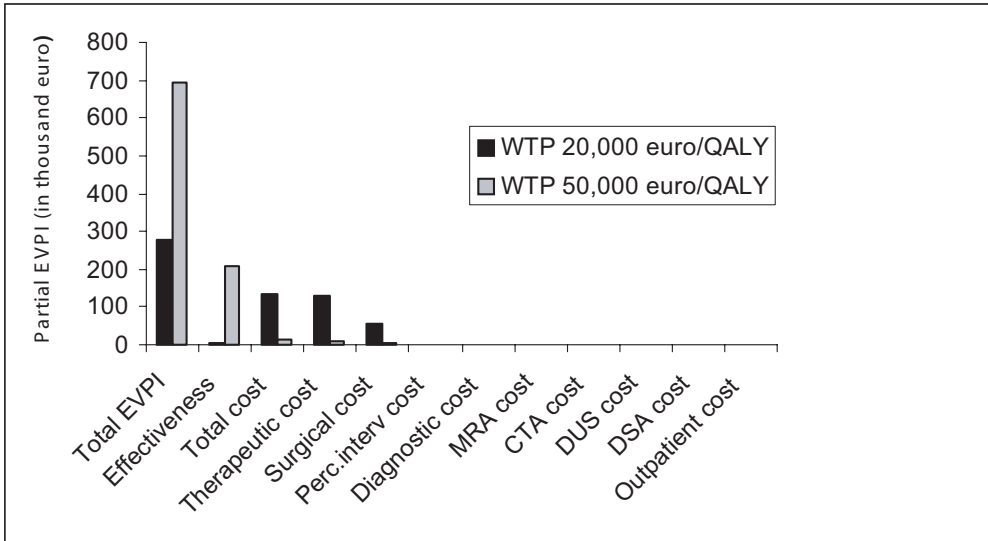
Note: Perc. interv. cost is cost of percutaneous interventions

Figure 2. Population partial EVPI for all individual effectiveness and cost parameters.

contributed more to the total EVPI than the total cost parameter (30% vs. 2%). With both the WTP thresholds the partial EVPI of the diagnostic costs was zero.

An interesting (and generally acknowledged) result was that the partial EVPI of a subset of parameters was not the same as the sum of the partial EVPI of each parameter separately. For example, the partial EVPI for the therapeutic costs was 136,000 euro, which exceeds the sum of the partial EVPI of its components (i.e. cost of surgery and cost of percutaneous interventions) (*Figure 2*).

Discussion

In an economic RCT, we compared three non-invasive imaging tests for the diagnosis of PAD. During 6 months follow-up, the CTA group had a significantly higher NMB compared to the MRA group and the DUS group. Regardless of the statistical significance, MRA or DUS could still be the "true" optimal test. To assess whether the remaining decision uncertainty justifies future research, we performed value of information analysis. The total EVPI was 4.5 euro per patient, resulting in an estimated population EVPI of 276,000 euro for the Netherlands. This implies, that if future research would eliminate all uncertainty about costs and effects, we can expect a population benefit of 276,000 euro. Exploration of the partial EVPI demonstrated that for a WTP of 20,000 euro/QALY the uncertainty about costs was more important whereas for a WTP of 50,000 euro/QALY the uncertainty about effects was most important. Uncertainty about the therapeutic costs was more important than uncertainty about diagnostic costs.

Our results imply that more research is justified if we could get perfectly accurate estimates of the relevant parameters in a research project that would cost less than 276,000 euro. Compared to other published values for the population EVPI, the value we found is very small (13). Considering the fact that the performed RCT cost more than 1 million euro, it is very unlikely that a new study to estimate perfectly accurate total cost would be cost-effective. Even with a WTP of 50,000 euro/QALY resulting in a population EVPI of 695,000 euro, the costs of research exceed the expected benefit of a new study. Based on this value of information analysis more research on the costs and effectiveness of non-invasive imaging for patients with PAD is not justified. This conclusion is only valid as long as the costs and effects of the imaging tests and the treatment remain unchanged. Moreover, the expected benefit of research as calculated with VOI analysis does not take the improvement of imaging tests and treatment into account.

We acknowledge several limitations of our analyses. The performed VOI analysis considered perfect information obtained in a future study with a hypothetical infinitely large sample size. Because research typically reduces uncertainty - instead of eliminating uncertainty - the population EVPI is a ceiling level for the benefit of future research. In practice an infinitely large sample size is not feasible and we actually want to estimate the expected value of future research with various finite sample sizes, which is possible with expected value of sample information (EVSI) analysis (12). However, the population EVPI provides a maximum of expected benefit and thus the EVSI will be lower than the already low population EVPI. Since the population EVPI was lower than the expected cost of a future study, calculating the EVSI was not useful.

Ideally one would want to calculate the EVPI using all available knowledge with uncertainty represented by a decision model. Instead we only used data from our RCT. This implies that we may have overestimated the EVPI. Since the estimated EVPI is low, taking into account our possible overestimate would only strengthen our conclusion that further research is not justified.

Another limitation also relates to using only data from a RCT. We assumed that beyond the follow-up of 6 months there is no difference in costs and effectiveness between the strategies. A decision model could overcome this assumption and extend the follow-up period to lifetime outcomes. However, in the clinical setting of peripheral arterial disease most patients will be treated within 6 months after the initial imaging test and given the similar effectiveness outcomes across the imaging strategies, we feel that the assumption is valid.

Finally, the number of patients expected to benefit from more research is an influential parameter in VOI analysis. It is not obvious whether one should use the worldwide or country-specific annual population to benefit. Moreover, VOI is influenced by the highly uncertain effective lifetime of diagnostic imaging technology. Both an increase in the number of patients to benefit and an increase in lifetime result in an increase in population EVPI. These influential uncertainties are inherent to all health care decisions, but need to be made explicit for VOI analyses. Furthermore, VOI is influenced by different thresholds of the WTP. That is the reason why we performed the VOI analysis with two

different WTP thresholds. For this purpose we used the generally accepted WTP of 20,000 and 50,000 euro per QALY gained.

Researchers commonly conclude that "more research is needed", especially when they failed to identify a significant difference between alternative interventions. Differences between reasonable alternatives, however, are often small. Implementing the second best intervention may therefore cause little harm to patients and/or have only a small budget impact. On the other hand, research is a costly investment, ultimately aimed at improving patient's health. The costs of a proposed research project may be better allocated to other quantitative research, to basic science, or to patient care. Choosing wisely amongst the available research options, where possible substantiated by value of information analysis, should be the health research policy maker's priority.

In conclusion, our results suggest that the expected cost of future clinical research on the costs and effectiveness of non-invasive imaging for PAD probably exceeds the benefit of such a study which implies that future research in this area is not justified.

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General discussion

Chapter 9

General discussion

The aim of the studies described in this thesis was to determine the optimal non-invasive imaging test for the initial evaluation of patients with peripheral arterial disease. This thesis describes the results of the DIPAD trial in which the costs and effects of three non-invasive imaging tests were compared. Furthermore, this thesis describes several other studies concerning the evaluation of non-invasive diagnostic imaging tests. The shortcomings and merits of the individual studies presented have been discussed in the previous chapters. In this discussion, the main findings are discussed and placed in a broader perspective. Subsequently, some methodological issues are discussed and finally, I will consider the implications for future research.

Main findings

The prevalence of symptomatic peripheral arterial disease (PAD) is 1.6% in the population of 55 years and older (1). Thus, nationwide the absolute prevalence of PAD is approximately 60,000. Annually, approximately 13,000 patients in the Netherlands undergo a diagnostic imaging workup for PAD with the goal of revascularization (2).

If revascularization is being considered, most centers perform duplex ultrasound (DUS) to localize the disease and determine the severity, and subsequently perform intra-arterial catheterization with X-ray digital subtraction angiography (DSA) to determine the best therapeutic approach (3, 4). In some centers DUS is not used as (first) imaging modality but (only) DSA. Others use multi-detector computed tomographic angiography (CTA) or contrast-enhanced magnetic resonance angiography (MRA).

Although DUS is commonly recommended as initial imaging study, it is has not been widely implemented because of its disadvantages. DUS is operator dependent (5), does not produce an easy-to-interpret image ("roadmap") for treatment, and is uninterpretable in about 10% of cases. Meta-analyses showed that sensitivity is in the order of 85-88% whereas specificity is about 95-97%, and these depend on the threshold velocity ratio used to make the diagnosis (6-8).

DSA has traditionally been used for anatomic assessment of PAD, but requires catheterization of the common femoral artery and intra-arterial injection of iodinated contrast with a morbidity risk of 1.7% and mortality risk of 3:10000 (9). Subsequently, a 4-6 hour period of bedrest and observation is required after the procedure and many patients undergoing angiography are admitted as inpatients for one day.

CTA using a multi-detector CT scanner has been shown to be a useful alternative to DSA for the initial evaluation of arterial disease. CTA is currently routinely used for various indications including the evaluation of abdominal aortic aneurysms, aneurysms and dissections of the thoracic aorta, and the pulmonary arteries for thrombo-embolic disease. Recent studies have also shown that it is a sensitive and specific technique for the evaluation of peripheral arteries (10-17). Pooling these data using a random effects

model demonstrated a sensitivity of 93% (95% CI; 90-96%) and a specificity of 92% (95% CI; 89-96%).

MRA is currently considered a good alternative for both DUS and for DSA for the initial workup prior to revascularization. MRA has shown an enormous improvement with the advent of intravenously administered Gadolinium contrast enhancement (18-22). The reported pooled sensitivity and specificity of contrast-enhanced MRA is 92-98% and 95-97%, respectively (4, 6, 23).

The previous results suggest that DSA could be replaced by non-invasive imaging tests. Visser et al. developed a decision model, integrating all available evidence, to evaluate the (societal) cost-effectiveness of DSA, MRA, DUS, combinations of tests, and a no-test strategy (24, 25). They assumed that patients were undergoing a workup to determine whether a revascularization procedure was feasible and which procedure would be preferable. Revascularization options included percutaneous treatment and bypass surgery, which were analyzed with a Monte Carlo Markov model. A positive test result was followed by revascularization. A non-invasive test that was unable to localize disease was followed by DSA. If the test suggested that revascularization was impossible, and in the no-test strategy, treatment was supervised exercise. The baseline case evaluated was a 60-year-old man. The results demonstrated that the range in effectiveness and costs across different diagnostic work-up strategies was small. Furthermore, the results suggested that the non-invasive imaging tests could replace DSA for the diagnostic imaging work-up of patients with PAD.

Subsequently, Visser et al. determined the cost-effectiveness targets for multi-detector CTA in patients with PAD (26). Compared to MRA they found that a new imaging modality would be cost-effective if the costs were $300, the sensitivity was higher than 94%, and 20% of patients required additional imaging. These results suggest that CTA, as compared with MRA, has the potential to be cost-effective in the evaluation of patients with PAD.

The previous cost-effectiveness analyses were based on decision-analytic models, which have their own advantages and disadvantages. Recently, a new design for the evaluation of diagnostic imaging technology has been suggested (27). This design includes an empirically based pragmatic randomized clinical trial and deals at the same time with the development, assessment, and implementation of a new diagnostic imaging test. Kock et al. used this design to determine the clinical and economical consequences of replacing DSA with CTA as the initial diagnostic imaging test in the work-up of PAD (28). They randomized patients between DSA and CTA and found lower therapeutic confidence, similar effectiveness, and less diagnostic costs for CTA compared to DSA. These results suggest that non-invasive imaging with CTA can replace DSA for the initial evaluation of peripheral arterial disease.

Both the decision-analytic models and the clinical trial showed that DSA could be replaced by non-invasive imaging tests, which by itself generates a new question: which

non-invasive imaging test is preferred in the diagnostic work-up of PAD. For this purpose we designed the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) randomized trial to compare outcomes following DUS, MRA, and CTA as the initial imaging test in the diagnostic workup of patients with peripheral arterial disease. Primary outcomes evaluated were quality of life and costs. Secondary outcomes evaluated were clinical utility and functional patient outcomes. The DIPAD trial described in this thesis (chapter 4-6) demonstrates that both MRA and CTA are clinically more useful than DUS and that CTA leads to cost-savings compared to both MRA and DUS in the initial imaging evaluation of patients with peripheral arterial disease. These results suggest that CTA is the optimal non-invasive imaging test for the work-up of PAD, but off course the final decision which test should be implemented in routine clinical practise in a particular setting also depends on local expertise, availability of equipment, and considerations concerning ionizing radiation and renal insufficiency.

Although, we identified CTA as the optimal imaging modality, it has the major drawback of hampered image interpretation in extensively calcified vessels. We found significantly lower interobserver agreement in arterial segments with calcifications compared to segments without calcifications (chapter 2). Furthermore, several studies reported that calcified plaques were the main reason for misinterpretations on CTA (11, 13, 14, 16). Also, in other vascular systems such as coronary arteries, vessel wall calcifications are a limitation for grading stenosis on CTA (29). Therefore, we evaluated the impact of vessel wall calcifications on the clinical utility of CTA using data from two randomized controlled trials (28, 30). We found that the number of calcified segments was a significant predictor for both the need of additional imaging and lower confidence scores (chapter 7). Subsequently, we identified diabetes mellitus, cardiac disease, and elderly age (age above 84 years) as independent predictors for the presence of vessel wall calcifications. These results imply that for elderly patients, patients with diabetes mellitus, and those with cardiac disease a CTA is less clinically useful due to decreased clinical utility. Based on the study population of the DIPAD trial, this would mean that for 48% of the patients a MRA instead of a CTA should be considered as initial imaging test. Although renal disease and critical ischemia were only a significant predictor for calcified segments in the univariable analysis and not an independent predictor in the multivariable analysis, patients with renal disease will generally undergo MRA instead of CTA because of the nephrotoxicity of iodinated contrast agents. For patients with critical ischemia the choice of test depends larger on availability of imaging equipment and the need for urgent revascularization.

Furthermore, as with every trial of finite sample size, the DIPAD trial did not give a definitive answer. Thus, if we implement CTA as standard care, we may still make the wrong decision. Value of information (VOI) analysis can explicitly estimate the expected benefit of a future study by considering both the probability and the consequences of making the wrong decision based on currently available evidence (31, 32). We performed a VOI analysis using data from the DIPAD trial. Therefore, the primary outcomes of the DIPAD trial (i.e. total costs and effectiveness) were transformed into one composite outcome: net monetary benefit (NMB) (33). The results showed that if based on the DIPAD

trial CTA was implemented as standard care, there would be a probability of 2 to 4% that the wrong strategy is introduced, i.e. that a strategy is introduced which does not optimize NMB (chapter 8). Furthermore, we found that the total EVPI for NMB was 4.5 euro per patient. This implies that an infinitely large future RCT is expected to increase the NMB per patient with PAD with 4.5 euro on the current mean of 4165 euro per patient for the optimal strategy. Based on the literature, we estimated the number of patients with PAD that undergo a diagnostic work-up to be 13,000 per year for the Netherlands (2). With the effective lifetime of a diagnostic strategy of 5 years and a discount rate of 3% this resulted in a population EVPI of 276,000 euro. These results imply that more research is justified if we could get perfectly accurate estimates of the relevant parameters in a research project that would cost less than 276,000 euro. Compared to other published values for the population EVPI, the value we found is very small (34). Considering the fact that the performed DIPAD trial cost more than 1 million euro, it is very unlikely that a new study to estimate perfectly accurate parameters would be cost-effective.

Methodological considerations

Traditionally the evaluation of new diagnostic imaging technologies has focussed on determining sensitivity and specificity of the new technology in comparison to a reference test. This entails performing both the new test and the reference test in all patients in a cohort study. Several problems with this approach exist.

First, the reference test is commonly not a perfect test. This problem applies to DSA in this setting. In fact, DSA has been shown to miss stenoses that can be identified with CTA or MRA (35, 36). In addition, DSA is invasive and on ethical grounds we cannot perform it in all patients. This implies that the new test will be verified in selected cases only, and may lead to biased estimates of sensitivity and specificity (37-39).

Second, a result indicating that sensitivity and specificity are both say 95% is difficult to translate into a meaningful clinical decision with respect to whether the new test should actually replace the old test. A definitive decision about the usefulness of the new test would require either a decision analysis or a randomized controlled trial (40).

Third, having performed a cohort study in which all studies are performed in all patients, which always will yield a less than perfect sensitivity and specificity for the non-reference test, we subsequently generally find ourselves performing both studies for a while because this is what the clinicians have gotten used to. Four out of five times implementation of new technology implies that instead of the new technique replacing the old technique, it gets performed in addition to the old technique.

Cost-effectiveness analysis can be performed using decision-analytic models (41-43). Decision-analytic models attempt to reflect reality but since reality is complex, assumptions have to be made to keep the model workable. Furthermore, assessment of subtle changes in the diagnostic work-up and treatment plan, determined by which initial imaging test was performed, is cumbersome to do in a decision model and indicate

the limitations of analyzing cost-effectiveness with a decision analysis alone. Another limitation of decision models is that the input variables come from multiple sources with potential confounding factors. Advantage of modeling studies is that many alternative strategies can be compared with lifetime follow-up, which cannot be done in a clinical study for ethical and practical reasons.

An alternative design would be a clinical trial. For the DIPAD trial an empirically based and pragmatic trial was used, that is, the trial was integrated into clinical practise rather than be implemented in a strictly controlled, but probably unrealistic, experimental setting. A RCT design was used to minimize bias introduced by extraneous factors and ensure an unbiased comparison between the groups. Patients were randomized after inclusion and prior to the initial diagnostic test, which is the most straightforward practical approach. However, it may not always be the most efficient approach, because a large proportion of the patients will not contribute to a difference in outcome. An alternative design is to study all patients with both tests and randomly assign only those patients with discordant test results, but the logistics of such a design are far more complicated, and the results may lead to interpretation problems. Randomization for evaluating diagnostic tests is not novel, but it has seldomly been used for comparing diagnostic imaging modalities (27, 44-47). Disadvantage of randomisation is reduced generalizability of study results due to the selected patient population and a perceived necessity to strictly control the experimental setting. We feel that the results of the DIPAD trial are generalizable to other settings because a wide range of patients (i.e. intermittent claudication and critical ischemia) was included. Furthermore, it was a multicenter study and by using an empirical and pragmatic design we in fact studied daily clinical practise, which increases generalizability. Another frequently mentioned disadvantage of randomization are the high costs. However, randomization between two diagnostic tests is less expensive than performing both tests in all patients.

We found the DIPAD trial to be both feasible and inexpensive, and enabled assessment of new non-invasive imaging technologies as they became available for clinical use.

Future directions
Based on our value of information analysis more research on the costs and effectiveness of non-invasive imaging for patients with PAD is not justified. This conclusion is only valid as long as the costs and effects of the imaging tests and the treatment remain unchanged. Moreover, the expected benefit of research as calculated with VOI analysis does not take the improvement of imaging tests and treatment into account.

MRA could be improved by reducing scan times to prevent venous enhancement in the lower legs. This can be achieved through parallel imaging techniques (22, 48). Signal-to-noise ratio (SNR) can be improved by the use of 3.0 Tesla MR scanners (49) or by increasing T1 relaxivity using contrast agents such as iron oxide compounds, protein binding gadolinium compounds, or 1.0 molar gadolinium chelates (50-53). Also dedicated peripheral vascular coils can improve SNR, which in turn can be used to achieve higher resolution and shorter scan time (54). In addition, shorter scan times could result in a cost reduction for MRA.

CTA could be improved by reducing the impact of vessel wall calcifications on image interpretation. With a 16-slice or recently introduced 64-slice MDCT scanner a higher resolution can be obtained compared to a 4-slice MDCT. This may result in less blooming of calcifications, which will improve image interpretation. However, the potential for radiation dose reduction with the 16- and 64-slice MDCT scanners, due to the differences in gantry geometry compared to a 4-slice MDCT, is lost when we obtain higher resolution images using thinner slices and lower pitch. Subtraction CTA is another approach to minimize the burden of vessel wall calcifications on image interpretation (55). However, this technique requires a high level of patient collaboration, is not feasible in 20% of the patients in spite of good collaboration, generates two times more images, and increases the radiation exposure. The possible solution for the calcification problem may be found in post-processing software or more likely in hardware improvements. A complete different solution lies not in the technique, but in selecting patients for whom CTA is contra-indicated due to extensive vessel wall calcifications. In this thesis we performed an initial evaluation of clinical predictors of vessel wall calcifications on CTA. A future study is needed to develop and validate a clinical prediction rule for this problem. The results from our study can help design such a future study and restrict the data collection to the most relevant variables.

In summary, CTA is the optimal non-invasive imaging test for the initial evaluation of patients with PAD. In elderly patients, patients with diabetes mellitus, and those with cardiac disease a CTA is contra-indicated due to decreased clinical utility. In these patients a MRA should be considered as initial imaging test. With the current knowledge of the DIPAD trial it is not useful to perform another study on the costs and effects of non-invasive imaging test for PAD.

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Summary

This thesis describes studies on the evaluation of non-invasive diagnostic imaging tests for patients with peripheral arterial disease (PAD). In **chapter 1**, the rationale for this research project is presented. Because PAD is a major problem in the population of 55 years and older, it is important to diagnose this disease accurately for planning adequate treatment. Digital subtraction angiography (DSA) has traditionally been used for the anatomic assessment of PAD, but carries a risk of morbidity and mortality. Therefore, non-invasive imaging tests such as duplex ultrasound (DUS), contrast-enhanced magnetic resonance imaging (MRA), and multi-detector computed angiography (CTA) are increasingly used for the diagnostic work-up of PAD. Because all these non-invasive imaging modalities have their own advantages and disadvantages, the question arises which non-invasive imaging test is preferred in the diagnostic work-up of PAD. Therefore, the aim of this thesis was to assess the optimal non-invasive diagnostic imaging test for the initial evaluation of patients with PAD.

Apart from evaluating accuracy of new diagnostic imaging techniques in comparison to a reference standard, it is important to evaluate the reproducibility, including interobserver agreement of a test. In **chapter 2** the interobserver agreement for the interpretation of MRA and CTA in patients with peripheral arterial disease was compared. It was found that interpretation of MRA and CTA for peripheral arterial disease has an excellent interobserver agreement, MRA has a higher interobserver agreement than CTA, and calcified segments on CTA significantly decrease the interobserver agreement.

Because clinical parameters such as Rutherford classification, ankle-brachial pressure index, and walking distance poorly reflect the perspective of the patient after diagnostic imaging and subsequent treatment, measurement of quality of life (QoL) is proposed as a primary endpoint in evaluating diagnostic imaging and subsequent treatment effects. It is still unclear which QoL questionnaire is preferred for this purpose. In **chapter 3** we compared the ability of generic with disease-specific questionnaires to assess QoL at baseline and to detect change in QoL after treatment in patients with PAD. We found that all three questionnaires VascuQol, SF-36 and Euroqol-5D performed equally well in assessing QoL at baseline in patients with PAD, but the disease-specific VascuQol is superior to the generic questionnaires SF–36 and Euroqol-5D with respect to the detection of changes in QoL after follow-up.

Non-invasive imaging tests, including MRA, DUS, and CTA have been shown to be sensitive and specific techniques for the evaluation of peripheral arteries. However, the clinical utility, patient outcomes, and the associated costs have not yet been evaluated, and therefore the decision which test should be used in the diagnostic work-up of PAD remains to be clarified. **Chapters 4**, **5**, and **6** describe the results of the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) multicenter randomised controlled trial (RCT) on the costs and effects of the various non-invasive imaging tests for PAD. We found that CTA and MRA had comparable clinical utility and patient outcomes, but CTA incurred

less total diagnostic costs compared to MRA (**chapter 4**). Furthermore, we found that the patient outcomes and total costs were comparable between MRA and DUS, but that the clinical utility was higher for MRA than for DUS (**chapter 5**). Finally, we found that CTA had higher clinical utility and incurred lower total costs compared to DUS (**chapter 6**). Overall, the results suggest that both MRA and CTA are clinically more useful than DUS and that CTA leads to cost-savings compared to both MRA and DUS in the initial imaging evaluation of patients with peripheral arterial disease.

From these results it seems that CTA is the optimal non-invasive imaging test for the initial evaluation of patients with peripheral arterial disease. However, there are some issues to take into consideration. A major drawback of CTA is the difficulty in assessing arterial luminal stenosis in extensively calcified vessels. So, it is important to evaluate the impact of vessel wall calcifications on the clinical utility of CTA in terms of therapeutic confidence and the number of additional imaging tests performed. Furthermore, it would be useful to identify clinical predictors of vessel wall calcifications to select patients for whom CTA is contra-indicated. It was found that vessel wall calcifications decrease the clinical utility of CTA in patients with peripheral arterial disease and that diabetes mellitus, cardiac disease, and elderly age are independently predictive for the presence of vessel wall calcifications (**chapter 7**). In these patients MRA should be considered as initial imaging test.

Another issue is that the RCT identified CTA as the optimal strategy but, as with every trial of finite sample size, it did not give a definitive answer. Thus, if we implement CTA as standard care, we may still make the wrong decision. The question arises whether more research is justified to decrease the remaining uncertainty. More research is not justified if the expected costs of a future study exceed the expected benefit of that study. In **chapter 8** we performed a value of information analysis (VOI), which can explicitly estimate the expected benefit of a future study by considering both the probability and the consequences of making the wrong decision based on currently available evidence. We found a total expected value of perfect information (EVPI) of 4.5 euro per patient, resulting in an estimated population EVPI of 276.000 euro for the Netherlands. Considering the fact that the currently performed DIPAD trial cost more than 1 million euro, more research on the costs and effectiveness of non-invasive imaging for patients with PAD is not justified.

In **chapter 9**, the general discussion, the main findings described in this thesis are placed in a broader context. In addition, relevant methodological aspects are discussed together with implications for future research.

Samenvatting

Dit proefschift beschrijft studies naar de evaluatie van niet-invasieve beeldvormende technieken voor patienten met perifeer arterieel vaatlijden (PAV). In **hoofdstuk 1** is de achtergrond van dit proefschrift beschreven. Omdat PAV een veel voorkomende ziekte is in de populatie van 55 jaar en ouder, is het belangrijk om de ziekte nauwkeurig in kaart te brengen zodat een adequate behandeling gestart kan worden. Digitale subtractie angiografie (DSA) is het traditionele onderzoek voor de anatomische beoordeling van PAV, maar is geassocieerd met een risico op morbiditeit en mortaliteit. Dit is de reden waarom niet-invasieve beeldvormende technieken zoals duplex ultrageluid (DUG), magnetische resonantie angiografie (MRA) en computertomografie angiografie (CTA) in toenemende mate worden gebruikt voor de diagnostische work-up van PAV. Al deze niet-invasieve beeldvormende technieken hebben hun eigen voor- en nadelen en de vraag is welke niet-invasieve test de voorkeur heeft in de diagnostische work-up van PAV. Daarom is de doelstelling van dit proefschrift om vast te stellen wat de optimale niet-invasieve beeldvormende test is in de diagnostische work-up van patiënten met PAV.

Naast het evalueren van de nauwkeurigheid van een nieuwe diagnostische test in vergelijking met een referentiestandaard, is het belangrijk om de reproduceerbaarheid van een test te evalueren. In **hoofdstuk 2** is de interobserver overeenstemming onderzocht van de beoordeling van perifere slagaders met MRA en CTA in patiënten met PAV. De resultaten lieten zien dat de interobserver overeenstemming excellent was voor zowel de beoordeling van MRA als CTA, de overeenstemming hoger was voor MRA dan voor CTA en dat verkalkte vaatsegmenten een significante lagere overeenstemming gaf voor de beoordeling van CTA.

Omdat klinische parameters zoals de Rutherford classificatie, enkel-arm index en loopafstand de toestand van de patiënt na het ondergaan van beeldvormde diagnostiek en behandeling vaak niet goed weergeven, wordt ook wel geopteerd om kwaliteit van leven als primaire uitkomstmaat te gebruiken bij de evaluatie van beeldvormende diagnostiek en behandeleffecten. Het is nog steeds onduidelijk welke kwaliteit van leven vragenlijst de voorkeur heeft als uitkomstmaat. In **hoofdstuk 3** hebben we bij patiënten met PAV generische en ziekte-specifieke vragenlijsten vergeleken in hun vermogen om de kwaliteit van leven te bepalen bij baseline en om verandering in kwaliteit van leven te detecteren na het ondergaan van behandeling. We vonden dat alle vragenlijsten vergelijkbaar waren bij het vaststellen van de kwaliteit van leven bij baseline, maar dat de ziekte-specifieke vragenlijst (VascuQol) superieur was in het detecteren van verandering in kwaliteit van leven gedurende de follow-up in vergelijking met de generische vragenlijsten (SF-36, Euroqol-5D).

Niet-invasieve testen zoals MRA, DUG en CTA hebben bewezen sensitieve en specifieke technieken te zijn voor de evaluatie van perifere slagaders. Echter de klinische bruikbaarheid, patiëntgerelateerde uitkomsten en de geassocieerde kosten zijn nog niet onderzocht en daarom blijft de vraag bestaan welke test we moeten gebruiken in de

diagnostische work-up van PAV. **Hoofdstuk 4**, **5** en **6** beschrijven de resultaten van de Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) multicenter gerandomiseerde gecontroleerde trial (RCT) naar de kosten en effecten van de verschillende niet-invasieve beeldvormende testen voor PAV. We vonden dat de klinische bruikbaarheid en patiëntgerelateerde uitkomsten gelijk waren voor MRA en CTA, maar dat CTA kostenbesparend was in vergelijking met MRA (**hoofdstuk 4**). Verder vonden we dat de patiëntgerelateerde uitkomsten en totale kosten gelijk waren voor MRA en DUG, maar dat de klinische bruikbaarheid groter was voor MRA dan voor DUG (**hoofdstuk 5**). Tot slot vonden we dat CTA een hogere klinische bruikbaarheid had en kostenbesparend was in vergelijking met DUG (**hoofdstuk 6**). Over het geheel genomen, suggereren de resultaten dat voor de initiële evaluatie van patiënten met PAV zowel MRA als CTA klinisch meer bruikbaar zijn dan DUG en dat CTA kostenbesparend is in vergelijking met MRA en DUG.

Uit deze resultaten blijkt dat CTA de optimale test is voor de initiële evaluatie van patiënten met PAV. Echter er moeten een aantal kanttekeningen gemaakt worden. Een groot nadeel van CTA is dat de beoordeling van de stenosegraad lastig is in ernstig verkalkte vaten. Daarom is het belangrijk om de invloed van vaatwandverkalkingen op de klinische bruikbaarheid van CTA te evalueren. Verder is het zinvol om klinische predictoren van vaatwandverkalkingen te identificeren om zo patiënten te selecteren voor wie CTA is gecontra-indiceerd. We vonden dat vaatwandverkalkingen zijn geassocieerd met een lagere klinische bruikbaarheid van CTA en dat diabetes mellitus, hartziekte en oudere leeftijd onafhankelijke voorspellers zijn voor de aanwezigheid van vaatwandverkalkingen (**hoofdstuk 7**). Bij deze patiënten moet een MRA als initiële test worden overwogen.

Een andere kanttekening is dat ondanks het feit dat de RCT CTA als optimale test heeft geïdentificeerd, de RCT net als iedere andere trial met eindige sample size geen definitief antwoord heeft opgeleverd. Dus als we CTA implementeren als standaard zorg kan dat nog steeds de verkeerde beslissing zijn. De vraag is of meer onderzoek om de overgebleven onzekerheid te verkleinen, gerechtvaardigd is. Meer onderzoek is niet gerechtvaardigd als de kosten van toekomstig onderzoek de verwachte opbrengst van datzelfde onderzoek overschrijden. In **hoofdstuk 8** hebben we een value-of-information (VOI) analyse uitgevoerd. VOI analyse maakt gebruik van de huidig beschikbare wetenschappelijke kennis om de verwachte opbrengst van toekomstig onderzoek te schatten, waarbij zowel de kans op het maken van een verkeerde beslissing als de consequenties van de verkeerde beslissing in beschouwing worden genomen. We vonden een totale expected-value-of-perfect-information (EVPI) van 4.5 euro per patiënt, wat resulteert in een populatie EVPI van 276.000 euro voor Nederland. In beschouwing genomen dat de huidig uitgevoerde DIPAD studie meer dan 1 miljoen euro heeft gekost, is meer onderzoek naar de kosten en effectiviteit van niet-invasieve beeldvorming bij patiënten met PAV niet gerechtvaardigd.

In **hoofdstuk 9**, de algemene discussie, worden de belangrijkste bevindingen van dit proefschrift geplaatst in een breder kader van huidige wetenschappelijke kennis. Daarnaast worden relevante methodologische aspecten van de studie besproken en ook de gevolgen voor toekomstig onderzoek.

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