Diagnostic Imaging of Peripheral Arterial Disease with Multi-Detector Row Computed Tomography Angiography

Marc Kock

Diagnostic Imaging of Peripheral Arterial Disease with Multi-Detector Row Computed Tomography Angiography

Beeldvormende diagnostiek van perifeer arterieel vaatlijden met multidetector computertomografie angiografie

Proefschrift

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X-actly So!

The Roentgen Rays, the Roentgen Rays,
What is this craze?
The town's ablaze
With the new phase
of X-Ray's ways.

I'm full of daze,
shock and amaze;
For nowadays
I hear they'll gaze
Thro' cloak and gown--and even stays,
Those naughty, naughty Roentgen Rays.

Wilhelma, Electrical Review, April 17, 1896

Aan opa van Haperen.

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Chapter 1
General Introduction

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Peripheral arterial disease

Peripheral arterial disease (PAD) is in the majority of patients caused by atherosclerosis in the lower extremities distal to the aortic bifurcation. Atherosclerosis is a complex systemic, progressive and degenerative disease of the intima of the arterial wall, which affects both large and medium-sized arteries. The prevalence of symptomatic PAD is 3-5% in older adults in different Western populations (1-2). Atherosclerosis has a pre-clinical course with absence of clinical symptoms for several decades. PAD generally becomes evident with symptoms of intermittent claudication. Intermittent claudication is defined as muscle cramps in the lower limb that occur following exercise and are relieved with rest. In a minority (a quarter) of patients, the disease progresses to critical limb ischemia i.e. rest pain or tissue necrosis (3-5). The diagnosis of PAD is based on patient history and physical examination. The severity of PAD is generally classified by measuring the ankle-brachial indices (Table 1).

Table 1. *Classification of peripheral arterial disease: Rutherford's categories and Fontaine's stages*

Rutherford			Fontaine	
Grade	Category	Clinical Description	Stage	Clinical Description
0	0	Asymptomatic	I	Asymptomatic
I	1	Mild claudication	IIa	Mild claudication
I	2	Moderate claudication	IIb	Moderate claudication
I	3	Severe claudication		Severe claudication
II	4	Ischemic rest pain	III	Ischemic rest pain
III	5	Minor tissue loss	IV	Ulceration or gangrene
III	6	Major tissue loss		

Note. - Chronic critical limb ischemia is defined by grades II and III, categories 4, 5, and 6 according to Rutherford (60) and stages III and IV according to Fontaine.

Patients suffering from PAD have a poor prognosis because they have an increased risk of fatal cerebrovascular and cardiovascular events (6-14). These patients have on average an age of 64 years and an average mortality ratio of 2.5, which corresponds to an average ten-year mortality of 38%.

The goal of treatment is to improve the symptoms of patients with claudication whose daily activities are limited, who are unresponsive to risk factor modification and exercise therapy, or to prevent amputation. The choice for endovascular and/or surgical revascularization is decided upon the results of diagnostic imaging. Digital subtrac-

tion angiography is considered to be the reference standard to characterize the level, multiplicity, and severity of stenoses (15-18).

Digital subtraction angiography

Traditionally, the standard reference for imaging PAD has been acquisition of X-ray images during intra-arterial injection of iodinated contrast media. For the peripheral runoff arteries, the translumbar puncture of the abdominal aorta was a routine procedure to accomplish this (19).
There was a great change in 1953 when Sven Seldinger described his percutaneous approach to the vascular system (20). He developed the transfemoral approach, where more secure arterial access was gained through the superficial or common femoral artery. Further refinement of the catheters and the lower iodine doses have led to significant reductions in morbidity (21, 22).
In 1953, Ziedses Des Plantes developed another important element of angiography: film subtraction to eliminate potentially confusing anatomical background (23). With the techniques of real-time digital fluoroscopic image processing and real-time subtraction, the catheterization time, and therefore, complications associated with the procedure, could be decreased considerably (21, 24). To this moment, intra-arterial digital subtraction angiography (DSA) is accepted as the reference (gold) standard for the evaluation of the peripheral vasculature due to its high spatial and temporal resolution. Another advantage is that hemodynamic information can be obtained by measuring the pressure gradient over a diseased arterial segment (25).

Due to its invasiveness, however, DSA is associated with local and systemic procedure related complications. The most frequent complication is minor hematoma (10%) but major hematoma requiring change of management is rare (26). Other complications that are routinely encountered are pseudoaneurysm and arterial wall dissection (22). DSA is based on injection of a considerable amount of iodinated contrast agent which is associated with a small but substantial risk of transient renal dysfunction (0.2%) and allergic contrast reactions (0.04-0.9%) (27-29). Therefore, this technique requires post-procedural observation and sometimes hospitalization, which makes the procedure expensive. In addition, it requires ionizing radiation, which can be a potential limitation, especially in younger patients. Conversely, these risks need to be considered in the perspective of the poor prognosis of these patients.

Contrast-enhanced magnetic resonance angiography

During the past 15 years, a wide variety of MR techniques have been developed for non-contrast-enhanced angiography. These are primarily based on inflow-enhanced (time-of-flight) and phase contrast techniques. While the phase contrast technique provides quantitative velocity and flow information, contrast-enhanced MR angiography (CEMRA) is currently the most clinically applied method because it can avoid artifacts inherent to the other methods and allow fast data acquisition (30). Gadolinium, which is injected intravenously, is the most frequent MR contrast agent which shortens the T1 of surrounding blood, resulting in a bright intravascular signal when

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a strong T1-weighted pulse sequence is used. Literature on the evaluation of the peripheral arteries using CEMRA became available in the nineties (31-32). CEMRA is currently widespread implemented in clinical practice for evaluating the entire peripheral run-off (31-33). CEMRA is a non-invasive technique that can be performed in an outpatient setting. Gadolinium is chelated to a carrier molecule and is excreted essentially through the kidneys. Because only very small amounts are used in CEMRA it can be used in patients with impaired renal function. The risk of a moderate or severe adverse event to intravenous injection of gadolinium chelates is 1.1% and 0.06%, respectively (34). Additionally, there is no ionizing radiation involved in CEMRA. A published meta-analysis showed that the pooled sensitivity and specificity for MR angiography is 97.5% and 96.2%, respectively (35). However, due to the high investment costs, CEMRA is an expensive imaging test for the evaluation of PAD.

Multi-detector CT angiography

A sequence of CT scanner generations has been developed. From a narrow "pencil" beam to a fan shaped beam and to scanners where the tube was positioned to rotate within a 360° stationary detector ring around the patient. The introduction of helical CT in the early 1990s laid the foundation for a fundamental improvement in CT imaging (36). This CT scanner was able to move the patient through the scanner while simultaneously acquiring a three-dimensional (3D) volume of data of a continuous rotating X-ray tube and detectors (37). This significant step in CT scanning finally allowed true 3D image acquisition within a single breath hold. The first studies that reported data on CT angiography of peripheral arterial disease were based on these helical CT scanners. Lawrence et al. described in 1995 that the acquisition was limited to two spiral sets of 60 seconds each to cover the upper and lower leg subsequently were necessary with an interscan delay of 9 seconds. Rieker et al. published in 1995 a study using a single continuous acquisition of CT for depiction of the lower extremities in 70 seconds. Because of the very slow scan speed, they noticed venous enhancement in 13% of the patients. In addition, they reported a limitation of poor longitudinal resolution to evaluate the proximal anterior tibial artery. Thus, single-slice helical CT angiography was limited to display only a portion of the peripheral arteries with adequate spatial resolution. Literature on CT angiography in peripheral arterial disease using the single helical CT scanners reported an average sensitivity and specificity, for the evaluation of significant stenosis, of 92% and 96%, respectively (38-45).

The next technological advancement was the introduction of the seventh generation CT scanners, better known as multi-detector row CT scanners. This CT scanner is similar to the helical CT, but it uses multiple rows of detectors in the longitudinal direction. With the simultaneous acquisition of several cross-sections the coverage within a given period of time can be increased. In 1992 a dual-slice CT scanner (Elscint TWIN) was introduced, which permitted a possible scan length, reaching from the aortic bifurcation down to about 10 cm below the crural trifurcation (43). The first four-detector row units were introduced in 1998 (46). With the 4-detector row CT, a complete coverage of the lower extremity inflow and runoff arteries became possible

with one acquisition using a single contrast bolus. Recent publications reported a high accuracy of 4- and 16-detector CT angiography in the evaluation of peripheral arterial disease (47-59). In 2004, 64-detector CT makes a further increase to a true isotropic high spatial resolution of the entire volume reality. At this moment, there are no reports of the assessment of peripheral arterial disease using the 64-detector CT.

These developments allowed multi-detector CT angiography (MDCTA) to become an alternative to the reference test, DSA, for the assessment of the entire peripheral arterial tree. MDCTA is a non-invasive technique that can be performed in an out-patient setting. However, like in DSA, a considerable amount of iodinated contrast agent is necessary with the associated risks of nephrotoxicity and idiosyncratic contrast reactions and it requires ionizing radiation. Not unimportant, in an ever more cost-conscious health-care system, is that it demands a proven added value for every euro spent. By means of lower investment costs and short patient room time, MDCTA could be considerably less expensive than DSA or CEMRA.

Aim and outline of this thesis

The aim of this thesis was to evaluate non-invasive MDCTA in the diagnostic work-up of patients with PAD.

The development of new imaging tests is ongoing. When starting this study, preliminary results of new imaging techniques in the work-up of PAD, such as MDCTA, were promising but parameters such as sensitivity, specificity, and interpretability were not published. Using a decision model we estimated the target values, such as sensitivity and the proportion of uninterpretable test results, for which a new alternative would be cost-effective when compared with the current work-up (Chapter 2).

In the assessment of radiological techniques, the evaluation of the performance of a new test has always been essential. Therefore, we compared the reproducibility of MDCTA, measured as the interobserver agreement for reporting degree of stenosis, with that of DSA and CEMRA in the work-up of PAD (Chapter 3 and 4).

In Chapter 5 and 6 the effects and associated costs after clinical implementation of MDCTA in the work-up of PAD were evaluated in the randomized controlled trial 'Diagnostic Imaging of Peripheral Arterial Disease' (DIPAD). With this trial, clinical utility, in terms of therapeutic confidence, the number of additional imaging tests performed, patient outcome in terms of quality of life, and costs of diagnosis, therapy, and hospital visit and admission were assessed during 6 months follow-up.

In addition, we need to address the potential limitations of this new non-invasive imaging test in the assessment of PAD. An important drawback of MDCTA is the depiction of extensively calcified arteries, which constrains the assessment of arterial lumen stenosis. Chapter 7 evaluates the impact of arterial wall calcifications on the clinical utility of MDCTA and identifies clinical predictors of arterial wall calcifications in order to identify those patients for whom MDCTA would be less useful as the initial

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imaging test in the work-up.

In Chapter 8 we evaluated whether current radiation doses from MDCTA and DSA can safely be given to patients in the evaluation of PAD. The measured radiation exposure of MDCTA and DSA and the calculated effective dose to the patient were evaluated. We modified the multiplicative model of the International Commission on Radiological Protection in order to estimate the excess risk from radiation accounted for the reduced life expectancy of patients suffering from PAD.

The technical review (Chapter 9) explains the principles of scanning and injection technique, the properties of image postprocessing for effective evaluation and communication, discusses the clinical value of MDCTA and summarizes the strengths and limitations of MDCTA in PAD.

The systematic literature review (Chapter 10) summarizes the diagnostic performance of MDCTA for the detection of significant stenoses using a summary receiver operator characteristic analysis.

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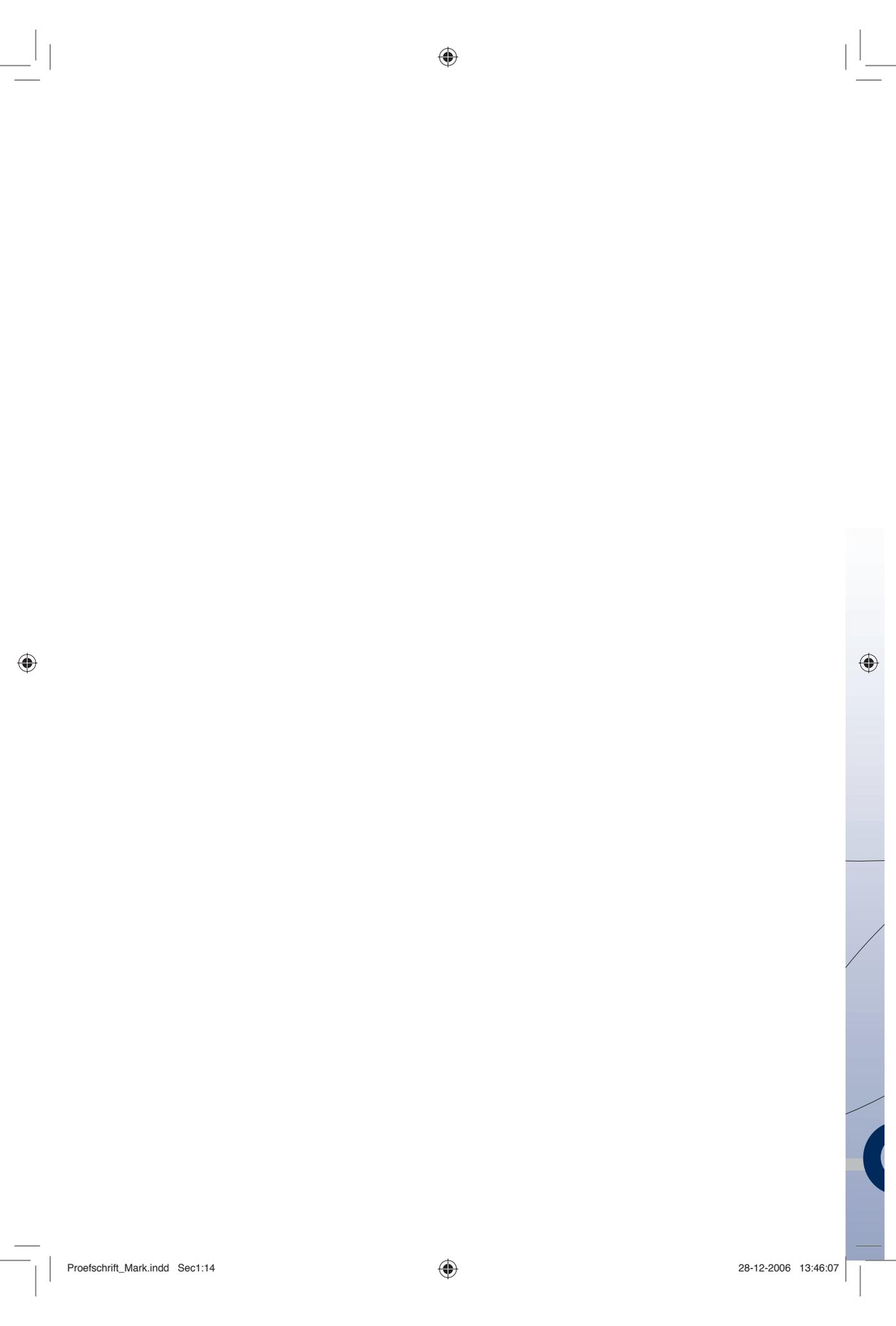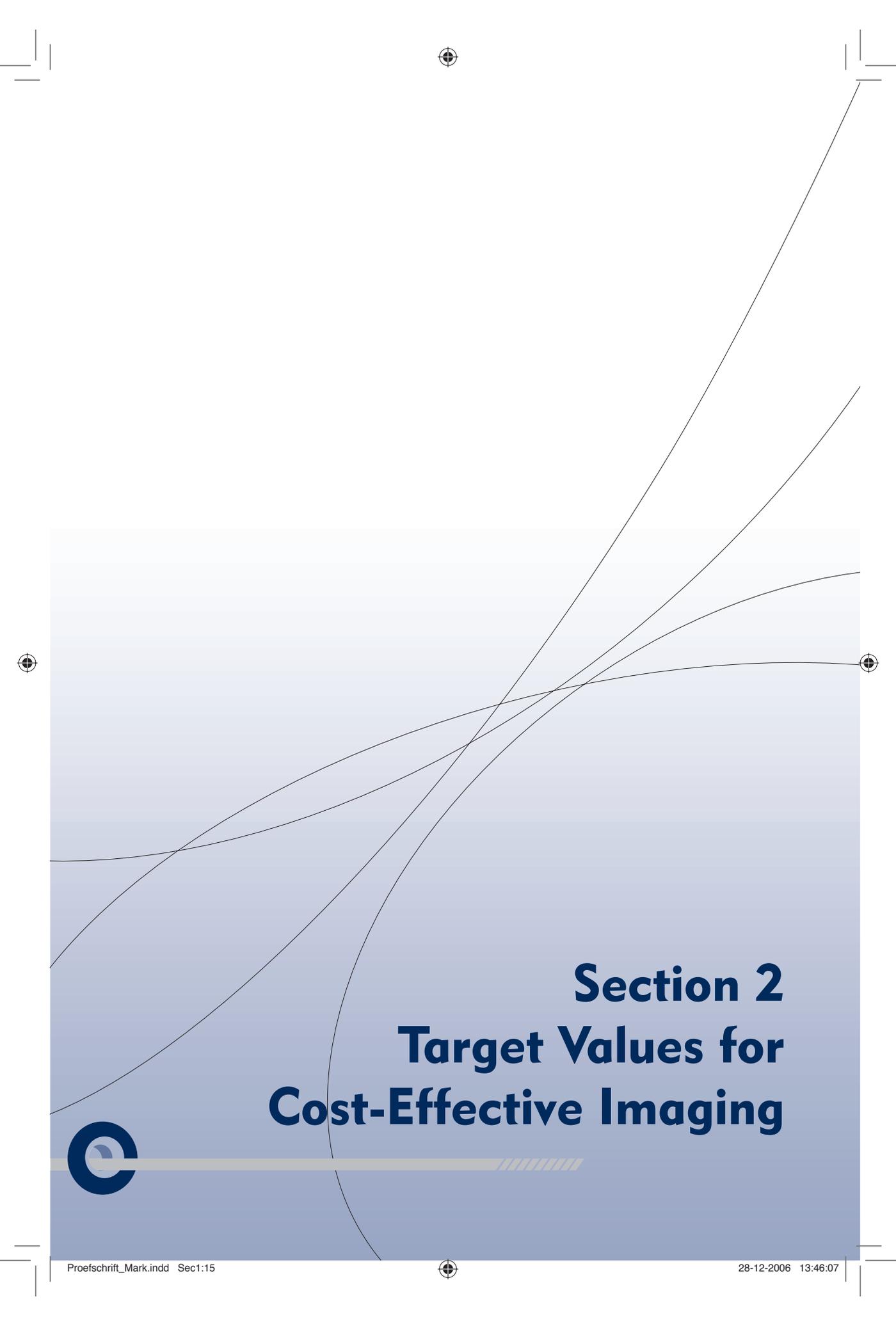
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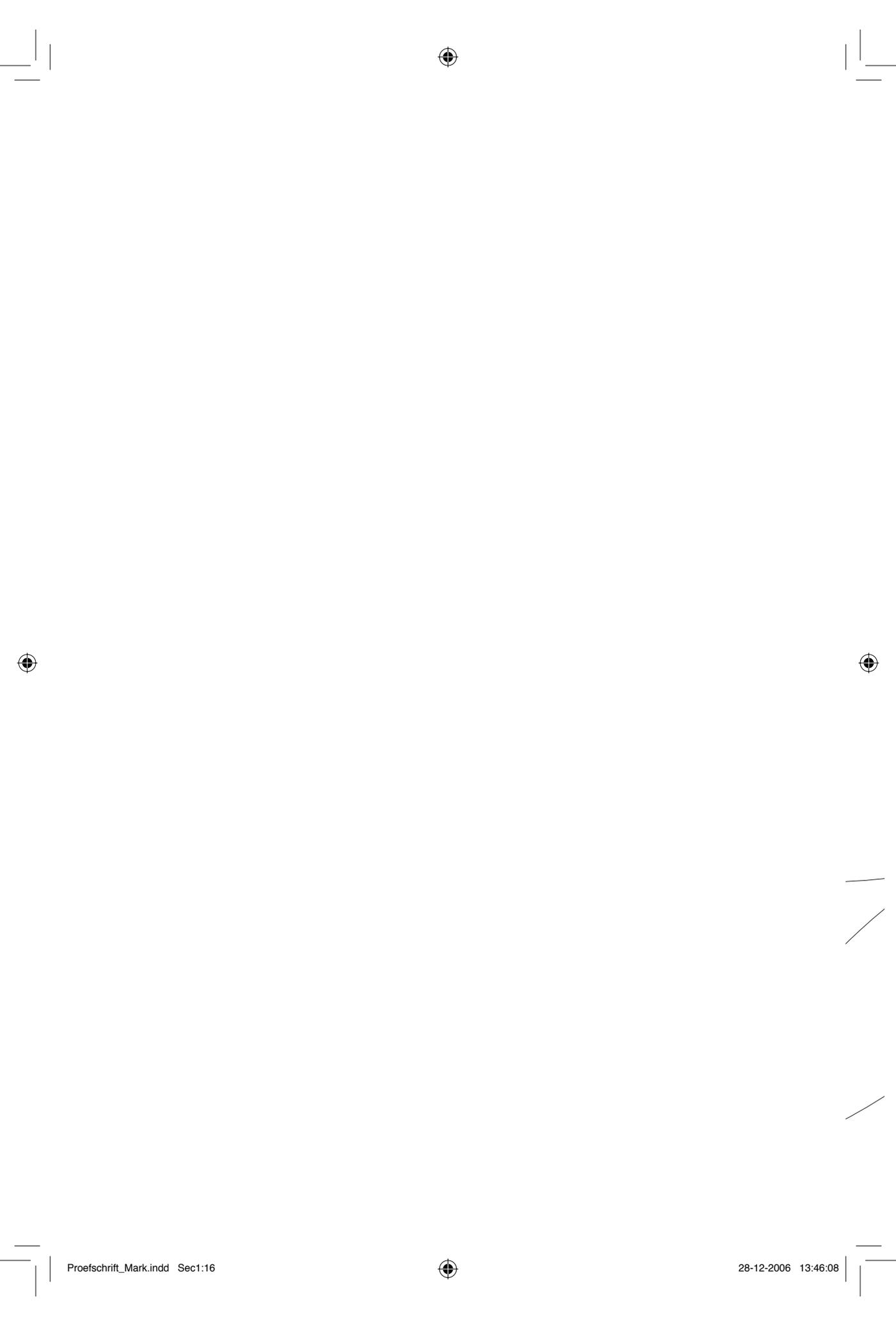
Chapter 2
Targets for a New Diagnostic Imaging Modality in the Work-Up of Peripheral Arterial Disease

Visser K, Kock MCJM, Kuntz KM, Donaldson MC, Gazelle GS, Hunink MGM.

Target Values for Cost-Effective Imaging

Abstract

Purpose: To determine the costs, sensitivity for detection of significant stenoses, and proportion of equivocal multi-detector row computed tomographic angiography (MDCTA) results in the work-up of patients with intermittent claudication that would make this imaging examination cost-effective compared with gadolinium-enhanced magnetic resonance angiography (CEMRA).

Materials and methods: A decision model was used to compare the societal cost-effectiveness of a new imaging modality with that of CEMRA. Main outcome measures were quality-adjusted life years (QALYs) and lifetime costs. By using threshold analysis of a given willingness to pay per QALY, target values for costs, sensitivity for detection of significant stenoses, and proportion of cases requiring additional work-up with intra-arterial digital subtraction angiography owing to equivocal results of the new modality were determined. The base case evaluated was that of 60-year-old men with severe intermittent claudication and assumed an incremental cost-effectiveness threshold of $100,000 per QALY.

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

Conclusion: MDCTA, as compared with currently used imaging modalities such as CEMRA, has the potential to be cost-effective in the evaluation of patients with intermittent claudication.

Introduction

The development of new diagnostic imaging modalities for the evaluation of peripheral arterial disease (PAD) is ongoing. Intra-arterial digital subtraction angiography (DSA) has been used as the sole preinterventional imaging modality for the detection of PAD. DSA is still considered the reference standard and is associated with a small degree of risk of mortality (1, 2). In the 1980s, duplex ultrasonography (US) was introduced into clinical practice (3, 4). The addition of color guidance improved the diagnostic accuracy of this non-invasive modality (5), and US became a useful diagnostic tool that has the potential to replace a number of the DSA examinations performed (6). In the early 1990s, magnetic resonance (MR) angiography was developed for the work-up of PAD (7–9). MR angiography is minimally invasive and with gadolinium enhancement is highly accurate (10–12). Gadolinium-enhanced MR angiography (CEMRA) can be used as the sole imaging examination in the planning of treatment for PAD (13–15).

Multi-detector row computed tomographic angiography (MDCTA) has recently been developed as a potential imaging modality for the diagnosis of PAD. The preliminary results of studies to evaluate CT angiography are promising (16,17). Also, other examinations such as MR angiography with blood pool agents (18), MR angiography (19) or DSA with carbon dioxide as the contrast material (20), and duplex US with contrast material (21) have been suggested as new imaging modalities for the detection of PAD.

Currently, the future role of these imaging modalities is speculative. To determine whether a new imaging modality has the potential to be cost-effective, as compared with the modalities currently used in practice, the diagnostic accuracy, costs, and complications associated with the new modality should be known. In the early development of new technologies, these parameters are generally unknown and it is difficult to predict what the exact values for these parameters will be. However, because these values are known for the currently used modalities, it is possible to calculate the target values that a new modality should meet to be cost-effective compared with the modalities currently used for diagnostic work-up (22–24). Calculations of this kind can help focus not only the development of new modalities for the diagnostic work-up of PAD but also the development of new technologies in health care in general.

The purpose of our study was to determine the target values for diagnostic accuracy that would make MDCTA, as compared with CEMRA, cost-effective in terms of the following parameters: the sensitivity for detection of significant stenoses, the proportion of cases requiring additional work-up with DSA because of equivocal results, and the costs of MDCTA, in the work-up of patients with intermittent claudication.

Methods and materials

Decision Model

For the current study, we used a decision-analytic model that was developed to evaluate the societal cost-effectiveness of diagnostic imaging strategies for the work-up of patients with intermittent claudication (25). In this model, patients presented to the vascular surgery department with severe unilateral intermittent claudication (i.e., ability to walk a maximum distance of <250 m), and on the basis of their medical history, physical examination results, and ankle-brachial index were referred for diagnostic imaging work-up. The probability of having at least one significant stenosis (i.e., luminal diameter reduction >50%) for patients with an ankle-brachial index of less than 0.90 is higher than 0.99 (26); therefore, we assumed that all patients had at least one significant stenosis in the suprainguinal or infrainguinal arterial tract. Patients with isolated infrapopliteal disease were not considered.

Diagnostic work-up with CEMRA consisted of localizing the lesion (i.e., suprainguinal or infrainguinal) and determining the treatment plan (percutaneous angioplasty, bypass surgery, or supervised exercise program). Results were defined as equivocal when the examination was technically inadequate (eg, because of poor vessel opacification, incorrect timing, artifacts, or early venous filling) or for some other reason the examination did not enable formulation of a treatment plan (eg, discrepancy between symptoms and CEMRA findings or doubt about the hemodynamic significance of a stenosis). Intra-arterial DSA was performed when the CEMRA result was equivocal or could not be performed because of a contraindication (e.g., claustrophobia). DSA was also performed when no significant lesion was localized at CEMRA; this outcome was considered to be a false result. Furthermore, we recognized that MR angiography could yield incorrect information, and, as a result, patients could be treated incorrectly.

For percutaneous treatment, we assumed that the DSA examination performed just prior to the procedure would correctly depict the findings that had been incorrectly depicted at MR angiography. If the percutaneous intervention procedure was then canceled, the costs were considered to be equal to the costs of performing DSA plus some extra expenses for the inefficient use of personnel, housing, and equipment. The rates of complication associated with planned but not performed angioplasty were considered to be equal to the rates of complication associated with diagnostic DSA. For bypass surgery, we assumed that an incorrect CEMRA result would not be detected unless the wrong arterial segment was bypassed, in which case the patient would still have symptoms and thus return to the hospital for DSA followed by repeat intervention. Figure 1 is a flowchart of the decision tree.
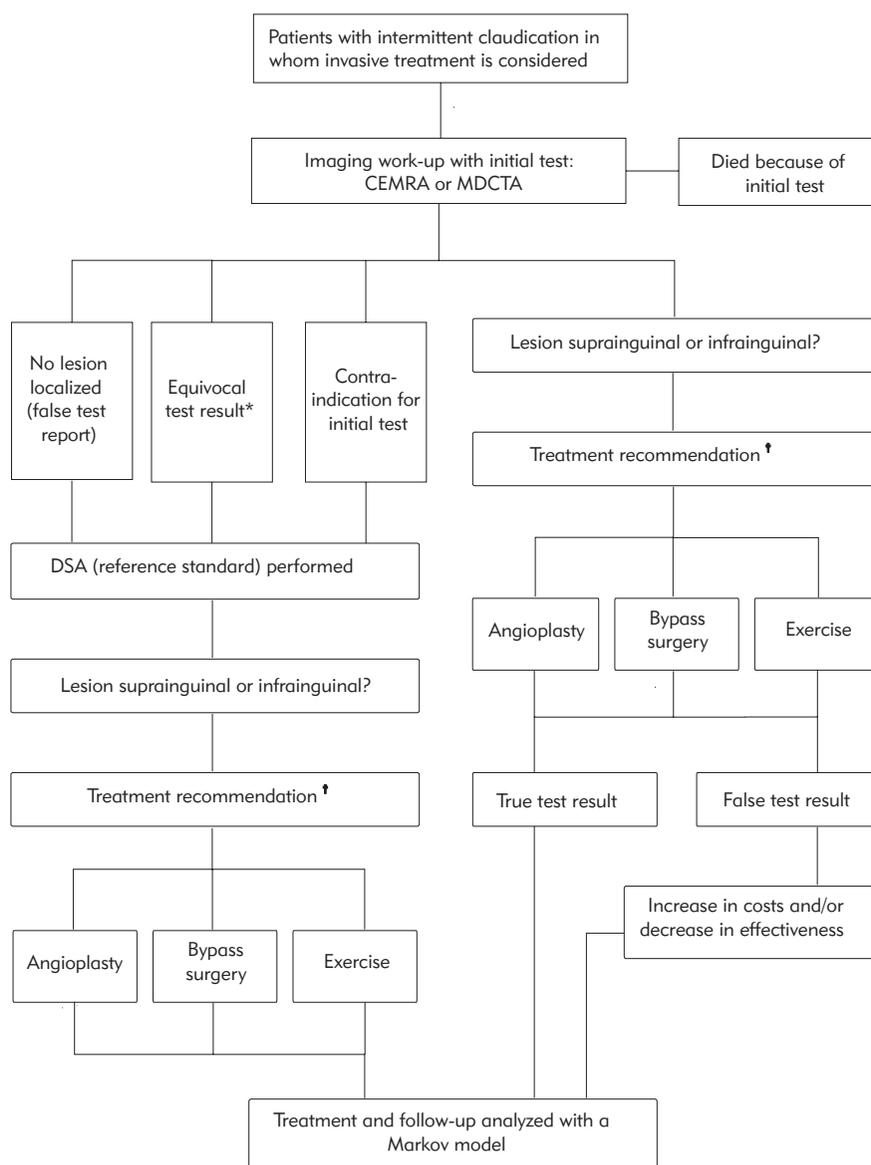
Figure 1. *Flow diagram of decision tree*
Equivocal test result (*) was defined as a technically inadequate imaging examination or an imaging result that did not enable a treatment plan to be formulated because of the depiction of calcified arterial walls. Two treatment scenarios (†) were considered: In the first scenario, that of minimally invasive treatment, patients underwent angioplasty if it was feasible; otherwise, they were started on a supervised exercise program. In the second scenario, that of more invasive treatment, patients underwent angioplasty if it was feasible; otherwise they underwent bypass surgery.

In clinical practice, bypass surgery is sometimes considered too invasive for the treatment of intermittent claudication and patients in whom angioplasty is not feasible are treated conservatively. To reflect clinical practice, we evaluated two scenarios of treatment after initial imaging work-up. In the first scenario, that of minimally invasive treatment, percutaneous treatment was performed in those patients in whom a lesion suitable for percutaneous treatment had been detected at imaging work-up; otherwise, the patients were started on a supervised exercise program. The feasibility of percutaneous treatment for lesions in the aortoiliac or femoropopliteal segment was consistent with published guidelines (27). During follow-up, the patients could have developed recurrent symptoms of intermittent claudication or critical limb ischemia, in which case a second percutaneous treatment was performed if feasible. Bypass surgery was performed in only those patients with critical limb ischemia in whom angioplasty was not feasible.

In the second scenario, that of more invasive treatment, bypass surgery was performed in those patients who did not have lesions that were suitable for angioplasty. For recurrent symptoms of intermittent claudication or critical limb ischemia, a second treatment was considered: percutaneous treatment, if feasible; otherwise bypass surgery was performed. For those patients with a history of coronary artery disease, it was assumed, because of the higher complication rates for these individuals, that bypass surgery could be performed only if the patient developed critical limb ischemia. Finally, there are always some patients (5%, assumption) who have imaging results indicating that no revascularization would be considered unless the patient developed critical limb ischemia.

Data Sources
Diagnostic examination characteristics.—Values for the sensitivity of CEMRA in the detection of significant stenoses were available from a previously performed meta-analysis (12). The probabilities of treatment recommendations based on CEMRA findings were derived from the literature (15). The examination characteristics of CEMRA were available from studies in which MR angiography was compared with DSA, which was considered the reference standard (12,15,28). We incorporated the risks of morbidity and mortality associated with DSA (1,2) and assumed that CEMRA did not involve risks. The diagnostic DSA examinations were planned in such a way that angioplasty could be performed immediately afterward if the patient had a suitable lesion. The examination characteristics of CEMRA and DSA are presented in Table 1.

Table 1. *Test characteristics for Gd-enhanced MR angiography and intraarterial DSA*

Parameter	CEMRA		DSA	
	Value*	Source†	Value*	Source†
Senstvity for detection of stenosis > 50%	0.96	12	1	Assumption
Probability that examination will facilitate recommendation of angioplasty given that lesion is suitable	0.79	15	1	Assumption
Probability that examination will facilitate recommendation of angioplasty given the lesion is suitable for bypass surgery	0.03	15	0	Assumption
Probability that examination will facilitate recommendation of angioplasty given lesion is not suitable for invasive treatment	0	15	0	Assumption
Probability that examination will facilitate recommendation of bypass surgery given that lesion is suitable	0.97	15	1	Assumption
Probability that examination will facilitate recommendation of bypass surgery given that lesion is suitable for angioplasty	0.14	15	0	Assumption
Probability that examination will facilitate recommendation of bypass surgery given that lesion is not suitable for invasive treatment	0	15	0	Assumption
Morbidity	0	Assumption	0.03	2
Morbidity	0	Assumption	3.3×10^{-4}	1
Probability that additional diagnostic work-up is required	0.07‡	12, 15, 28	0	Assumption

* Data are probability values.
† Unless otherwise stated, data are reference numbers.
‡ Additional work-up with DSA was required if the given imaging examination yielded a technically inadequate result, no treatment plan could be formulated on the basis of the result, or the examination could not be performed because of a contraindication.

Treatment and follow-up

Data on treatment and follow-up were derived from a Monte Carlo Markov model in which 100,000 patients for each possible diagnostic outcome were simulated (29). In this decision-analytic model the cost-effectiveness of supervised exercise versus that of invasive treatment options such as angioplasty and bypass surgery was evaluated. The Markov model allowed for treatment of recurrent symptoms and for treatment of symptoms involving the contralateral limb. The lesions were predominantly suprainguinal or infrainguinal (56% vs. 44%, respectively); 51% of the suprainguinal lesions versus 18% of the infrainguinal lesions were suitable for percutaneous treatment. These data were available from a series of 722 patients from the Brigham and Women's Hospital in Boston (29).

Invasive treatment for suprainguinal lesions consisted of angioplasty with selective stent placement and aortic bifurcation surgery. Invasive treatment for infrainguinal lesions consisted of angioplasty and either femoropopliteal or femoroinfrapopliteal bypass surgery. Patency rates were available from published meta-analyses (30–32). The annual rate of critical limb ischemia in patients with intermittent claudication was 0.017 for patients younger than 65 years (33) and 0.036 for patients aged 65 years and older (33–36). Limb amputation was performed if treatment for critical limb ischemia failed and three invasive interventions had already been performed in the diseased limb.

Costs

Medicare reimbursement rates were used for the costs of CEMRA and DSA and yielded estimates of $574 and $1,183, respectively (Table 2). Costs for revascularization vary more widely among patients than do costs for diagnostic work-up; therefore, we decided to use the costs available from a study that was performed to assess the costs of revascularization procedures for PAD as a function of patient characteristics (37). These costs were adjusted for the age, sex, history of coronary artery disease, and presenting symptoms (intermittent claudication vs. critical limb ischemia) of patients. The estimated costs were $25,790 for aortic bifurcation surgery, $8,290 for suprainguinal angioplasty, $18,110 for infrainguinal bypass surgery, and $4,480 for infrainguinal angioplasty (Table 2). Although the costs of amputations vary widely among patients, we used Medicare reimbursement rates because amputations are rare among patients with intermittent claudication—and, thus, cost estimates have little effect on the results—and a more elaborate cost-accounting analysis was not within the scope of this study.

The costs of below-the-knee amputation, including transmetatarsal amputations, and above-the-knee amputation were $8,550 and $15,830, respectively (Table 2). The estimated cost of a supervised exercise program was $4,417 per year and comprised mainly the expenses for the patient time spent walking, and follow-up visits in the hospital were included (29). The extra costs incurred for 1 hour of inefficient use of personnel, housing, and equipment in the case of a planned but not performed angioplasty were estimated to be $316 (38), which was added to the costs of a diagnostic DSA examination. All costs were converted to 1998 U.S. dollars by using the consumer price index (United States Bureau of Labor Statistics data) (41).

Target Values for Cost-Effective Imaging

Table 2. *Costs and health-related quality of life*

Factor	Value	Source*
Costs†		
CEMRA	574	Medicare reimbursement rate
DSA	1,183	Medicare reimbursement rate
Aortic bifurcation surgery	25,790	37
Suprainguinal angioplasty with selective stent placement	8,290	37
Infrainguinal bypass surgery	18,110	37
Infrainguinal angioplasty	4,480	37
Amputation below knee	8,550	Medicare reimbursement rate
Amputation above knee	15,830	Medicare reimbursement rate
One year supervised exercise	4,417	29
Planned but not performed angioplasty	1,499	
DSA	1,183	Medicare reimbursement rate
Inefficient use of personnel, room, and equipment	316	38
Health-related quality of life‡		
No or mild intermittent claudication	0.79	39
Severe intermittent claudication	0.71	39
Critical limb ischemia	0.35	40
Amputation below knee	0.61	40
Amputation above knee	0.20	40

* Unless otherwise stated, data are reference numbers.
† Data in the value column are 1998 US dollars.
‡ Data in the value column are time trade-off values.

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Health-related quality of life

Estimated health values for patients with intermittent claudication were available from a study performed with participants in an exercise program in the Netherlands (39). These values were derived from responses to the EuroQol-5D (a generic questionnaire on quality of life), which were converted to time trade-off values. The values were 0.79 for patients with no or mild claudication and 0.71 for those with severe claudication (Table 2). The estimated health values for patients with critical limb ischemia, amputation below the knee (including transmetatarsal amputations), and amputation above the knee were available from a study conducted among the general public (40). Scenarios describing these three health states were presented, and time trade-off estimates were calculated. For patients with critical limb ischemia, the utility estimate was 0.35 (40) (Table 2). The estimated health value for patients who had undergone below-the-knee amputation was 0.61, whereas that for patients who had undergone above-the-knee amputation was 0.20 (40) (Table 2).

Determination of Thresholds

Cost-effectiveness analysis was performed to determine whether MDCTA, as compared with CEMRA, would be cost-effective in the work-up of patients with intermittent claudication. Lifetime costs and quality-adjusted life years (QALYs) were calculated (with a discount rate of 3%) (42), and a strategy was considered to be cost-effective if the additional cost per QALY did not exceed the society's willingness to pay—that is, the amount of money that society is willing to pay for one additional QALY. For these analyses, we varied the cost-effectiveness threshold between $50,000 and $250,000 per QALY gained and used a threshold of $100,000 per QALY gained for the baseline analysis.

On the basis of the analysis, we determined what combinations of costs, sensitivity for detection of significant stenosis, and proportion of patients requiring additional work-up with DSA owing to equivocal MDCTA results (eg, because of technically failed examinations, artifacts, or vessel wall calcifications) would be required for MDCTA to be cost-effective compared with CEMRA. To determine these thresholds for a new imaging modality, we had to make assumptions about the risks involved and about the treatment recommendations based on MDCTA findings. In terms of the mortality- and morbidity-related risks associated with MDCTA, we assumed that these risks equaled those that are associated with the use of a low-osmolality contrast agent: probabilities of 9.0×10^{-6} for mortality risk and 3.1×10^{-4} for morbidity risk (43). Furthermore, the probabilities of a given treatment being recommended on the basis of MDCTA findings were assumed to be the same as those for MR angiography (Table 1). For sensitivity analysis, we assumed that the probabilities of a given treatment being recommended on the basis of MDCTA findings were the same as those recommended on the basis of duplex US (44) or DSA findings.

In a base-case analysis, cohorts of 60-year-old men with symptoms of severe unilateral claudication for 1 year, an ankle-brachial index of 0.70, and no history of coronary artery disease were evaluated. Target values for MDCTA in both the minimally invasive scenario and the more invasive treatment scenario were determined. Two other

patient cohorts were considered: 40-year-old men with characteristics similar to those in the base case and 70-year-old men with a history of coronary artery disease and other characteristics similar to those in the base case. Women were not considered in this analysis because the results of previous analyses showed that the results of treatment for women were similar to the results of treatment for men (29). In the sensitivity analysis, the target criteria for MDCTA that would make this examination, as compared with DSA, cost-effective were determined. Also, sensitivity analyses were performed to determine the estimated health value with no or mild claudication (range, 0.75–0.83) and the costs of revascularization (50% and 150% of baseline estimates), because previous analyses have shown that the results of evaluating treatment for patients with intermittent claudication were sensitive for these parameters (29).

Results

Minimally Invasive Treatment Scenario

In the minimally invasive treatment scenario, CEMRA yielded 6.1487 QALYs at a cost of $21,942. With use of a societal willingness to pay of $100,000 per QALY, a new imaging modality was equivalent to CEMRA in terms of cost-effectiveness if the cost of the modality was $420, the sensitivity for detection of significant stenosis was 90%, and 20% of the patients required additional work-up owing to equivocal MDCTA results. With these conditions and with the assumption of a threshold incremental cost-effectiveness ratio of $100,000 per QALY, the strategy with the new imaging modality yielded 6.1490 QALYs at a cost of $21,965. The distribution of events and treatment after the initial examination are presented in Table 3.

Target values for the costs and sensitivity of a new modality that would make it cost-effective compared with CEMRA are shown in figure 2. For example, if MDCTA cost $300 or less and had a sensitivity of at least 85%, it would be cost-effective compared with CEMRA, even if up to 35% of patients needed additional work-up after undergoing the new modality. If the proportion of patients who required additional work-up with DSA decreased, a higher cost for MDCTA would be acceptable.

Table 3. *Distribution of events after initial diagnostic work-up for base-case analysis*

	Initial Imaging Examination	
Event	CEMRA	MDCTA*
Diagnostic work-up		
Contraindications for initial examination	0.050	0
Equivocal examination result	0.020	0.20
No lesion localized, false examination result	0.021/0.021[†]	0.040/0.020[†]
Patient died owing to initial examination complications	0	9.0×10^{-6}
Initial treatment: minimally invasive scenario		
PTA	0.281	0.292
Bypass surgery	0	0
Supervised exercise	0.719	0.708
Initial treatment: more invasive scenario		
PTA	0.281	0.290
Bypass surgery	0.647	0.641
Supervised exercise	0.075	0.065

Note. - Data are probability values.

* Values calculated for the strategy in which multi-detector CT angiography (MDCTA) was cost-effective, as compared with MR angiography, with regard to a society's willingness to pay for health care interventions costing \$100,000 per QALY. Minimally invasive treatment scenario: costs of MDCTA, \$420; sensitivity for detection of significant stenoses, 90%; and 20% of patients would need to undergo additional DSA for equivocal results. More invasive treatment scenario: costs of MDCTA, \$673; sensitivity for detection of significant stenoses, 95%; and 20% of patients would need to undergo additional DSA for equivocal MDCTA results.

† Proportion calculated for the minimally invasive treatment scenario/proportion calculated for the more invasive treatment scenario. The sensitivities of MDCTA in the minimally invasive and more invasive treatment scenarios were different because of the threshold analysis, and, consequently, the proportions of false results in the two treatment scenarios were different.

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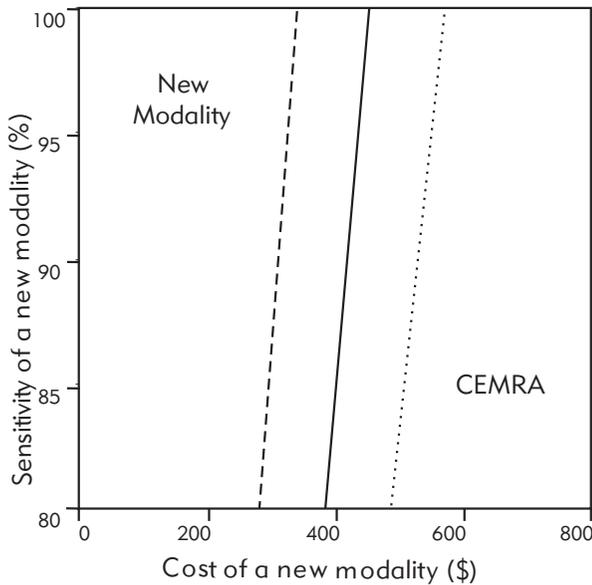
Figure 2. *Graph illustrates results of base-case analysis: a 60-year-old man in the **minimally invasive** treatment scenario.*
Target values of the costs and sensitivity for detection of significant stenosis of a new imaging modality in the minimally invasive treatment scenario and with a threshold for society's willingness to pay of $100,000 per QALY gained are plotted. The lines of plotted values represent combinations of costs and sensitivity that would make a new modality cost-effective compared with CEMRA, based on the proportion of patients who would require additional work-up. -- = 35% of patients requiring additional work-up, — = 20% of patients requiring additional work-up, •• = 5% of patients requiring additional work-up. MDCTA would be cost-effective compared with CEMRA if the combination of costs and sensitivity for a new modality was to the left of the line. If, however, the combination of costs and sensitivity for MDCTA was to the right of the line, then CEMRA would be more cost-effective.

More Invasive Treatment Scenario

In the more invasive treatment scenario, the MR angiography strategy yielded 6.2137 QALYs at a cost of $48,965. With the assumption of a threshold incremental cost-effectiveness ratio of $100,000 per QALY, the new imaging modality would be equivalent to MR angiography in terms of cost-effectiveness if the costs were $673, the sensitivity for detection of significant stenosis was 95%, and 20% of the patients required an additional DSA examination owing to equivocal MDCTA results. With these conditions, the strategy involving a new imaging modality would yield 6.2151 QALYs at a cost of $49,102. Target values for the costs and sensitivity of a new imaging modality are presented in figure 3. If, for example, MDCTA cost only $300 and 20% of patients required an additional DSA examination, then MDCTA would still need to have a sensitivity of 94% or higher to be cost-effective compared with CEMRA. The distribution of events and treatment after the initial examination in the more invasive treatment scenario also are presented in Table 3.
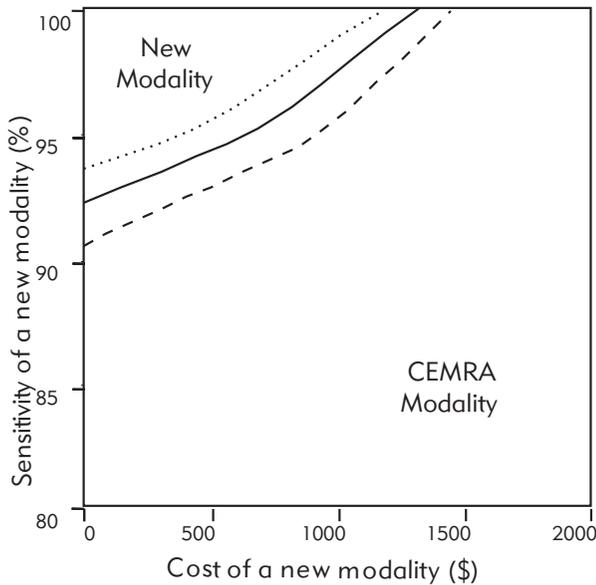
Figure 3. *Graph illustrates results of base-case analysis: a 60-year-old man in the **more invasive** treatment scenario.*
Target values of the costs and sensitivity for detection of significant stenosis of a new imaging modality in the more invasive treatment scenario and with a threshold for society's willingness to pay of $100,000 per QALY gained are plotted.
The lines of plotted values represent combinations of costs and sensitivity that would make a new modality cost-effective compared with CEMRA, based on the proportion of patients who would require additional work-up. -- = 35% of patients requiring additional work-up, — = 20% of patients requiring additional work-up, •• = 5% of patients requiring additional work-up. MDCTA would be cost-effective compared with CEMRA if the combination of costs and sensitivity of MDCTA was above the line. If, however, the combination of costs and sensitivity of MDCTA was below the line, then the new modality would not be cost-effective.

Sensitivity Analysis

The target values for a new imaging modality did not change substantially when society's willingness to pay was varied (Table 4). For 40-year-old men, the target criterion for the cost of a new imaging modality was more lenient (Figures 4, 5), whereas for 70-year-old men with a history of coronary artery disease, the target criterion was stricter—that is, only the minimally invasive treatment scenario was considered (Figure 6). If it was assumed that the capabilities of a new imaging modality in facilitating the selection of a treatment plan were the same as those of duplex US, then either the target values for the new imaging modality would be stricter—that is, the minimally invasive treatment scenario would be considered—or the new imaging modality would not be cost-effective compared with CEMRA—that is, the more invasive treatment scenario would be considered. Assuming that a new imaging modality would have the same capabilities as DSA in facilitating the selection of a treatment made the target criteria more lenient (Table 4).
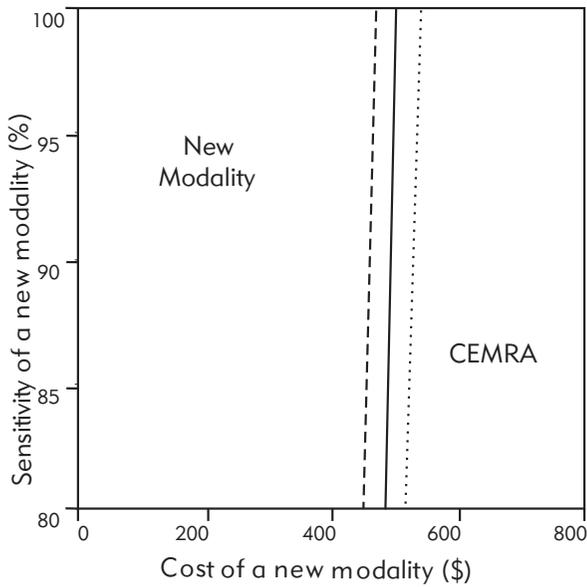
Figure 4. *Alternative case: a 40-year-old man modality in the **minimally invasive** treatment scenario.*

Target values of the costs and sensitivity for detection of significant stenosis of a new imaging modality in the minimally invasive treatment scenario and with a threshold for society's willingness to pay of $100,000 per QALY gained are plotted.

*The lines of plotted values represent combinations of costs and sensitivity that would make a new modality cost-effective compared with gadolinium CEMRA, based on the proportion of patients who would require additional work-up. **--** = 35% of patients requiring additional work-up, **—** = 20% of patients requiring additional work-up, •• = 5% of patients requiring additional work-up.*

MDCTA would be cost-effective compared with CEMRA the combination of costs and sensitivity of the new modality was to the left of the line. If, however, the combination of costs and sensitivity of MDCTA was to the right of the line, then CEMRA would be more cost-effective.

Figure 5. *Alternative case: a 40-year-old man in the **more invasive** treatment scenario.*

Target values of the costs and sensitivity for detection of significant stenosis of a new imaging modality in the more invasive treatment scenario and with a threshold for society's willingness to pay of $100,000 per QALY gained are plotted.

*The lines of plotted values represent combinations of costs and sensitivity that would make a new modality cost-effective compared with gadolinium CEMRA, based on the proportion of patients who would require additional work-up. **--** = 35% of patients requiring additional work-up, **—** = 20% of patients requiring additional work-up, •• = 5% of patients requiring addi-*

tional work-up. MDCTA would be cost-effective compared with CEMRA the combination of costs and sensitivity of the new modality was to the left of the line. If, however, thecombination of costs and sensitivity of MDCTA was to the right of the line, then CEMRA would be more cost-effective.

Figure 6. *Alternative case: a 70-year-old man with a history of coronary artery disease modality in the **minimally invasive** treatment scenario.*
Target values of the costs and sensitivity for detection of significant stenosis of a new imaging modality in the minimally invasive treatment scenario and with a threshold for society's willingness to pay of $100,000 per QALY gained are plotted. The lines of plotted values represent combinations of costs and sensitivity that would make a new modality cost-effective compared with gadolinium CEMRA, based on the proportion of patients who would require additional work-up. -- = 35% of patients requiring additional work-up, — = 20% of patients requiring additional work-up, •• = 5% of patients requiring additional work-up. MDCTA would be cost-effective compared with CEMRA if the combination of costs and sensitivity of the new modality was to the left of the line. If, however, the combination of costs and sensitivity of MDCTA was to the right of the line, then the new imaging modality would not be cost-effective.

In the sensitivity analysis, we compared a new imaging modality with DSA (Table 4). In the minimally invasive treatment scenario, the target criterion for the cost of a new modality was more lenient. In the more invasive treatment scenario, a new modality would not be cost-effective compared with DSA with the assumptions that we made, even if the sensitivity was 100% and no patients required additional work-up with DSA. If, in addition, we assumed that a new imaging modality had the same capabilities as DSA in facilitating the recommendation of a treatment and involved no risks, the new modality, regardless of its costs, would be more cost-effective than DSA.

Table 4. *Combinations of target values for a new imaging examination to be cost-effective, as compared with CEMRA, for a threshold of a society's willingness to pay of $100,000 per QALY gained*

Factor	Minimally Invasive Treatment Scenario			More Invasive Treatment Scenario		
	Cost ($)	Sensitivity (%)	Additional Work-up (%)	Cost ($)	Sensitivity (%)	Additional Work-up (%)
Base case: 60-year-old man with history of CAD						
	420	90	20	673	95	20
	551	95	5	729	97	5
WTP ($/QALY)						
50,000	409	90	20	604	95	20
250,000	454	90	20	877	95	20
40-year old man	495	90	20	836	95	20
70-year old man with CAD	367	90	20	NA	NA	NA
Quality of life with no or mild intermittent claudication						
0.75	391	90	20	654	95	20
0.83	341	90	20	637	95	20
Costs of revascularization						
50% of baseline estimate	410	90	20	642	95	20
150% of baseline estimate	430	90	20	703	95	20
Treatment-planning capability of new imaging examination						
Similar to that of duplex US	0	95	5	NC	NC	NC
Similar to that of DSA	825	90	20	2,357	95	20
New imaging modality compared with DSA						
	584	90	20	NC	NC	NC

Note. - CEMRA = Gd-enhanced MR angiography, CAD = coronary artery disease, NA = not applicable, NC = not cost-effective, QALY = quality adjusted life-years, WTP = society's willingness-to-pay for gain of 1 QALY.

Target Values for Cost-Effective Imaging

There was an inverse relationship between the health-related quality of life with no or mild intermittent claudication and the estimated costs of a new imaging modality. The costs for the new imaging modality would need to be lower if the quality of life was higher. If the costs for the revascularization were higher than our baseline estimate, the new modality would potentially have a higher cost. However, the differences in estimated target values for the range in health-related quality of life estimates and the range in cost of revascularization were modest (Table 4).

Discussion

In the current study, we determined target values for MDCTA in the pretreatment work-up of patients with intermittent claudication. When we compared MDCTA with CEMRA, the current imaging examination performed for work-up, the observed target values seemed possible to achieve. Compared with the target values for DSA, the target values for MDCTA would be attainable if angioplasty was considered as the only treatment option. With the assumptions that we made about MDCTA—namely, that it involves minimal risks and could lead to incorrect recommendations for treatment—DSA would always be more cost-effective than MDCTA if both angioplasty and bypass surgery were considered as treatment options. If, however, we assumed that MDCTA involved no risks and had diagnostic accuracy that was comparable to that of DSA, the reference standard, then MDCTA would be more cost-effective than DSA. In terms of developing new imaging modalities, it is important that the new modality has a fairly low cost and high sensitivity for the detection of significant stenoses.

Our study was limited by the fact that we used various data sources and made a number of assumptions to keep the model tractable. Such limitations are inherent to decision models and cost-effectiveness analyses. For instance, in our model we considered DSA the reference-standard examination; this precedent is well established in the literature on the diagnostic work-up of patients with PAD (12). Assuming that DSA is the reference standard implies that the new imaging modalities that are potentially more effective than DSA could not be evaluated with the model that we used.

Furthermore, with the described model it was assumed that CEMRA and CT angiography were clinically interchangeable; however, this assumption may not be realistic. Patients with renal insufficiency might be better served by undergoing CEMRA to avoid the nephrotoxicity of iodinated contrast agents, whereas patients with contraindications to CEMRA, such as those who have a pacemaker or are claustrophobic, might be better served by undergoing MDCTA. However, patients with renal insufficiency, pacemakers, or claustrophobia constitute the minority of PAD cases, whereas the described model addresses what the primary choice of imaging should be and allows for secondary imaging examinations, if necessary. For example, the model took into account that a proportion of patients cannot undergo MR angiography because of contraindications, in which case the patients undergo DSA.

Another limitation of the study was that we did not consider regional health care circumstances such as the expertise of the radiologists and the availability of equip-

ment. In an earlier study (25), it was found that differences in quality-adjusted life expectancy and lifetime costs among diagnostic imaging modalities were small, and a new imaging modality that enabled the target values to be met would be in the same range as CEMRA, duplex US, and DSA.

To determine the cost-effectiveness of a new imaging modality that fulfills the target criteria assessed in the current study, it might be better to compare MDCTA with the currently used work-up modality in a pragmatic empirical setting. Such a comparison could be made in a randomized controlled trial in which patients are randomly placed in either the new imaging modality group or the currently used work-up modality group (45) and followed up for a certain time. Possible outcome measures would be the quality of life of the patients, the costs incurred by performing the work-up imaging examination, including those for supplementary imaging and treatment, the confidence of the physician in the examination result, and the patients' and/or the physicians' preferred imaging modalities. This suggested study design would also take into account local expertise, physicians' preferences, and equipment availability.

A final limitation was that we assumed that the society's willingness to pay (i.e., amount of money society is willing to pay for one additional QALY) could be defined. The amount society is willing to pay depends on many variables, such as the characteristics of the health care system, the general economy, and the decision context. The actual value is always hypothetical. Recently, an attempt to estimate society's willingness to pay was made by converting estimates of value of life, which were available from various sources, to dollars per QALY gained (46). A range of willingness-to-pay values, from $25,000 to $428,000 per QALY (in 1997 U.S. dollars), was observed (46).

In our base-case analysis, we used $100,000 per QALY as an estimate of society's willingness to pay. We performed an extensive sensitivity analysis and found that the results did not change substantially when society's willingness to pay was varied (from $50,000 to $250,000/QALY gained). We chose $100,000 per QALY as a baseline value instead of the commonly quoted $50,000 per QALY for various reasons: First, the incremental cost-effectiveness ratios for generally accepted interventions vary between $10,000 and $100,000 per QALY gained (47), indicating that the threshold should be $100,000 per QALY. Second, a willingness to pay of $50,000 per QALY has been quoted for well over 10 years and to our knowledge has not been adjusted for either inflation or increasing levels of welfare use. Third, we wanted to determine the least stringent target values that would need to be met for a new technology, and the use of a high threshold value yields the least stringent target criteria.

Currently, several new imaging techniques have been suggested for use in the work-up of patients with PAD (16–21,48–50). The most promising of these techniques seems to be MDCTA which is simple to perform, fast, and quickly becoming widely available. Preliminary results indicate that MDCTA has high diagnostic accuracy and the sensitivity was close to our estimated target value (17,48–50). The cost of a contrast material–enhanced MDCTA examination was estimated to be $237 (in 1997 U.S. dollars) (51), which were below the target cost. The fact that MDCTA depicts

the calcified vessel wall is a disadvantage because the appearance of calcium interferes with the accurate interpretation of stenosis severity and thus may necessitate additional work-up.

On the other hand, contraindications to MDCTA are rare. Usually, a low-osmolality contrast material is used to perform MDCTA, and a small degree of risk associated with the use of contrast material was incorporated into our analysis. The long-term risks of radiation were not considered in our analysis. However, the risk of a one-time exposure is low, and the life expectancy of most patients who have PAD is shorter than the time it typically takes to develop long-term harmful effects from radiation.

In conclusion, compared with currently used imaging examinations such as CEMRA, MDCTA, has the potential to be cost-effective in the evaluation of patients with intermittent claudication. The role of new imaging modalities that have fairly good preliminary results can be assessed by performing a pragmatic randomized controlled trial in which the new modality is compared with the imaging modality that is currently being used for diagnostic work-up.

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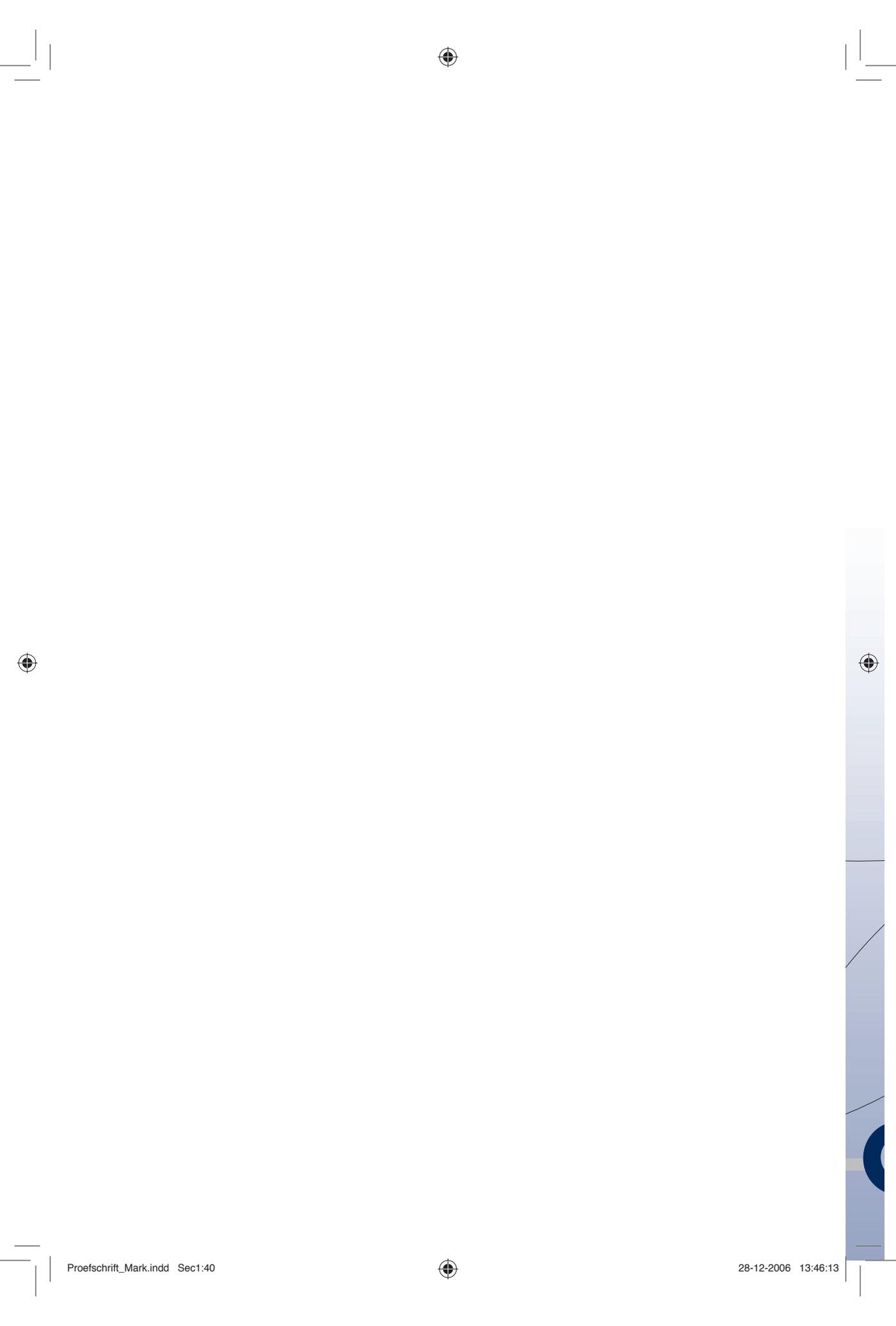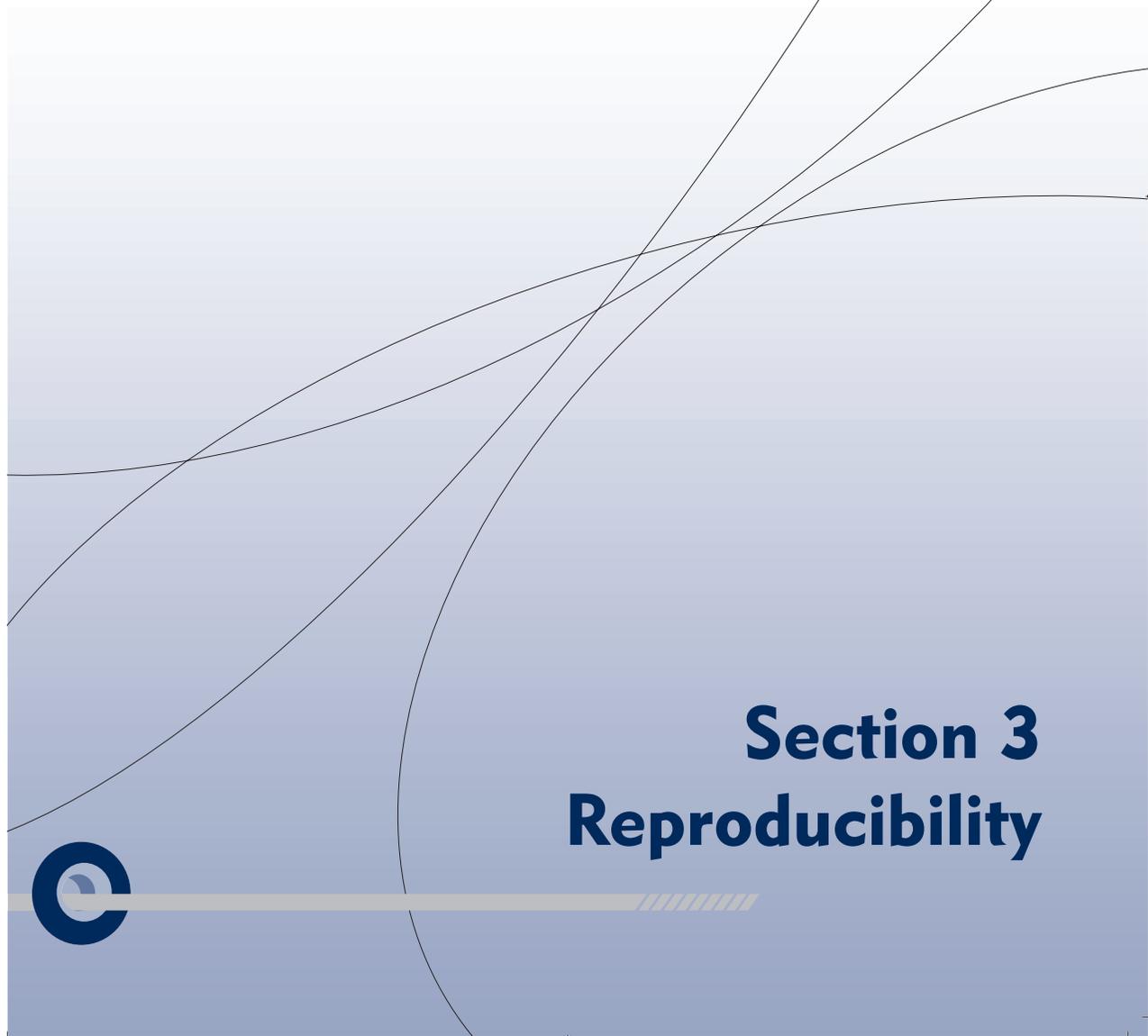
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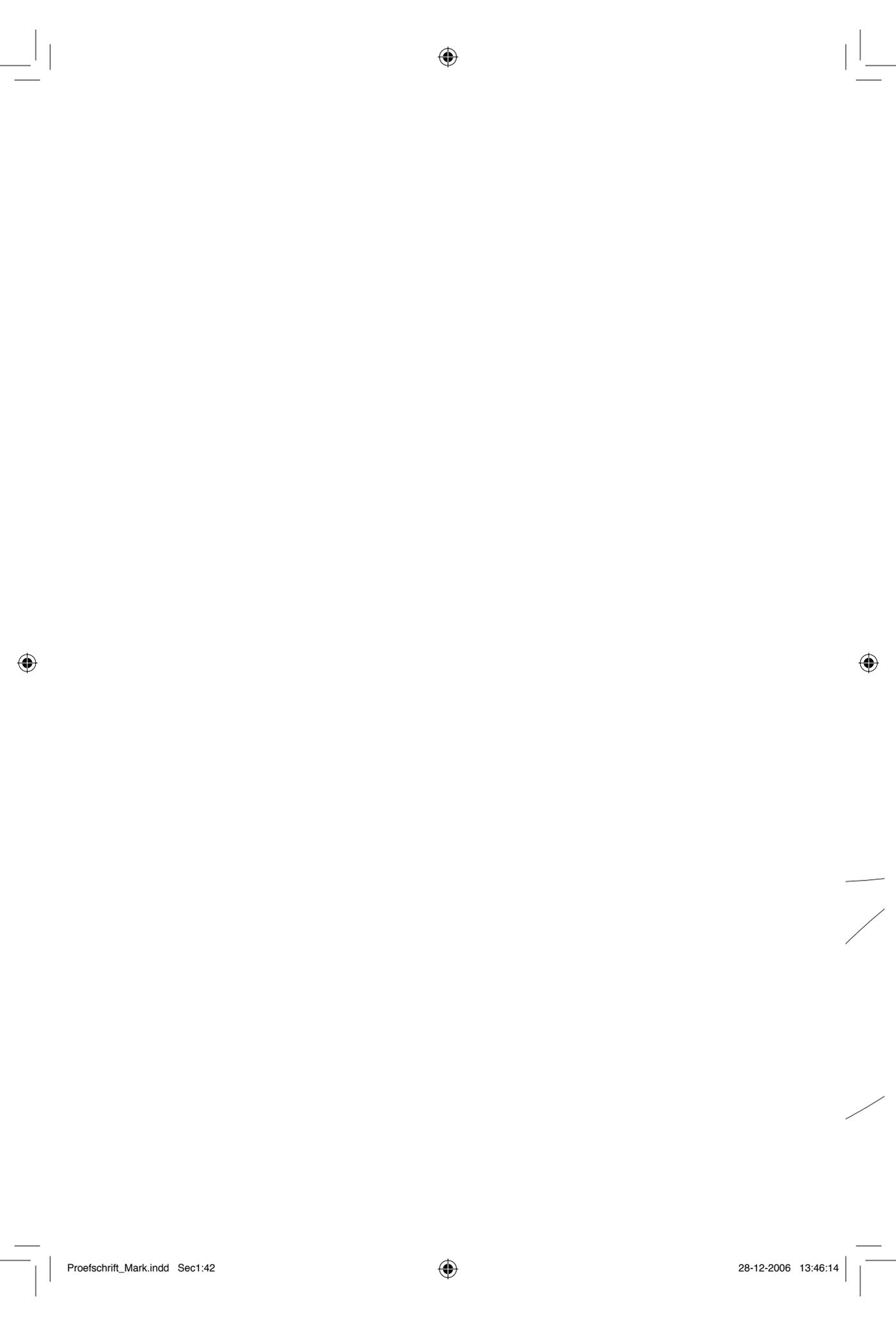
Chapter 3
Interobserver Agreement for Interpretation of Multi-Detector CT Angiography Compared with Digital Subtraction Angiography

Kock MCJM, Kuiper JW, Pattynama PMT, Hunink, MGM.
Submitted.

Reproducibility

Abstract

Purpose: To compare interobserver agreement in reading 4-detector row CT angiography (MDCTA) with that of reading digital subtraction angiography (DSA) in the evaluation of peripheral arterial disease.

Materials and methods: One-hundred-and-forty-one consecutive patients with peripheral arterial disease were prospectively randomized to either DSA (n = 68) or MDCTA (n = 73). Two readers independently evaluated arterial stenosis on DSA (2006 segments) and MDCTA (2268 segments) using a five-point ordinal scale. The presence of arterial wall calcifications was noted per segment. Interobserver agreement for each test was evaluated using the linear weighted kappa (K_w) statistic.

Results: We found excellent interobserver agreement of DSA (K_w = 0.83) and MDCTA (K_w = 0.84) for reporting the degree of stenosis in all segments. The interobserver agreement of DSA vs. MDCTA in the aortoiliac segment was K_w = 0.78 vs. K_w = 0.84, in the femoropopliteal segment K_w = 0.88 vs. K_w = 0.86, and in the crural segment K_w = 0.78 vs. K_w = 0.82, respectively. The interobserver agreement of MDCTA decreased in the presence of calcifications but was still good for all anatomic stations. The lowest agreement of MDCTA was found for crural segments in the presence of calcifications (K_w = 0.79).

Conclusion: In unselected patients with PAD, the interobserver agreement for MDCTA is in the same order as that of DSA. Interobserver agreement is lower in calcified arterial segments.

Reproducibility

Introduction

The introduction of multidetector row CT scanners has substantially improved CT angiography due to increased volume coverage, shorter acquisition times, and improved spatial resolution (1-3). Results of several studies have shown that multidetector row CT angiography (MDCTA) is accurate for imaging peripheral arteries (4-6). Compared to DSA, the advantages of MDCTA are the substantially reduced risk of morbidity and mortality, lower costs, and less patient discomfort (7-10). Main disadvantages of MDCTA are the time-consuming 3D reconstruction techniques and the difficulty in assessing arterial luminal stenosis in the presence of arterial wall calcifications (5,11). The interobserver agreement plays an important role in the evaluation of new diagnostic tests (12). This measure provides information about the reproducibility of the classification of disease using the test. A high reproducibility of the test results is a necessary condition to make a test valid and useful in clinical practice.

The purpose of this study was to compare interobserver agreement in reading 4-slice MDCTA with that of DSA in the evaluation of peripheral arterial disease.

Materials and methods

Patients
The patients included in this study are the patients of a randomized controlled trial that compared DSA with MDCTA 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 revascularization procedure. Exclusion criteria were contraindications for angiography, for iodinated contrast agents, and for revascularization. The subjects were randomized across two diagnostic strategies consisting of DSA and MDCTA. A computer generated list for the strategy assignment was used. Block randomization was used with a block size of 6 to obtain equal numbers in both strategies. The trial nurses or the researchers, who were unaware of the randomization sequence, consecutively opened the numbered sealed opaque envelopes containing the allocation of the participant. The study was approved by the hospital institutional review board and informed consent was obtained from all patients.

Digital Subtraction Angiography
DSA was performed using either an Integris V3000 (Philips Medical Systems, Best, the Netherlands) or an Angiostar Plus (Siemens Medical Systems, Forchheim, Germany).
All patients were catheterized from a trans-femoral approach. For evaluation of the abdominal aorta, the 4-French pigtail catheter was positioned with its tip between the 12th thoracic and first lumbar vertebral body and 20 mL of a nonionic iodinated contrast material (Iomeron 300; Altana Pharma, Hoofddorp, the Netherlands; iodine concentration = 300 g/L) was injected at a rate of 15 mL/sec. Subsequently, the catheter tip was positioned above the aortic bifurcation to inject 10 mL of contrast

material at a rate of 15 mL/sec to obtain DSA images of the pelvic and lower-extremity arteries. At contiguous anatomic levels from the abdominal aorta (at the level just above the renal arteries) down to the level of the ankles, images were obtained in the anteroposterior projection and were supplemented with additional oblique views if considered necessary. All angiographic procedures were performed by radiology residents in training with the supervision of one of three interventional radiologists (including J.W.K. and P.M.T.P.), each with at least 3 years of post-residency experience. Since the angiography suite was not connected to a PACS, images from catheter DSA were printed on hardcopies with customized window width and level settings and pixel shift settings to allow clear delineation of the enhanced lumen.

Multidetector Row CT Angiography

MDCTA was performed on a Somatom Plus 4 Volume Zoom (Siemens Medical Systems, Forchheim, Germany). Patients were in the supine position on the CT table with their legs held together and stabilized with padding but without strapping around the patient's legs.

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. The scan parameters were a pitch of 1.6, 120 kV, 110 effective mA, and a collimation of 4 x 2.5 mm.

Patients were asked to hold their breath for approximately 15 sec at the start of scanning and then to breathe shallowly to minimize movement of the lower extremities during the rest of the scanning procedure. Before scanning was started, 120 mL of nonionic contrast material (Visipaque 320 mgI/ ml, Amersham Health, Buckinghamshire, UK) was injected via an antecubital vein at a rate of 4 mL/sec. The scanning was started at a fixed delay of 25 seconds after the start of contrast material injection with an average acquisition time of 35 seconds to obtain a robust protocol. In patients with a history of decreased cardiac output, a longer delay time was used. The images were reconstructed with an effective section width of 3 mm and an increment of 1.5 mm using the smooth algorithm (B20; Siemens). Three data sets with an overlap of approximately 10 cm were created (approximately 250 images each).

Image reconstruction

The images were transferred to two online workstations (Easy-Vision, Philips; and Volume Wizard, Siemens) for the preparation of reconstructions. For all patients all reconstructions were created according to our standard protocol by an independent 3-D technologist who was blinded to detailed clinical information and follow-up and outcome data. Sliding maximum intensity projections were obtained with transverse, coronal, and sagittal projections of each dataset. Two orthogonal curved planar re-formations (CPR) were created along the longitudinal axis of the aorta through both common and external iliac arteries and the common femoral artery. To obtain angiogram-like images, whole-volume maximum intensity projection images with segmentation (ie. removal) of bone and arterial wall calcifications were constructed (Figure 1). To remove bone and arterial wall calcifications a threshold technique was used in combination with a region-growing algorithm. Subsequently, oblique radially reformatted maximum intensity projection images of the segmented volumes were obtained, parallel
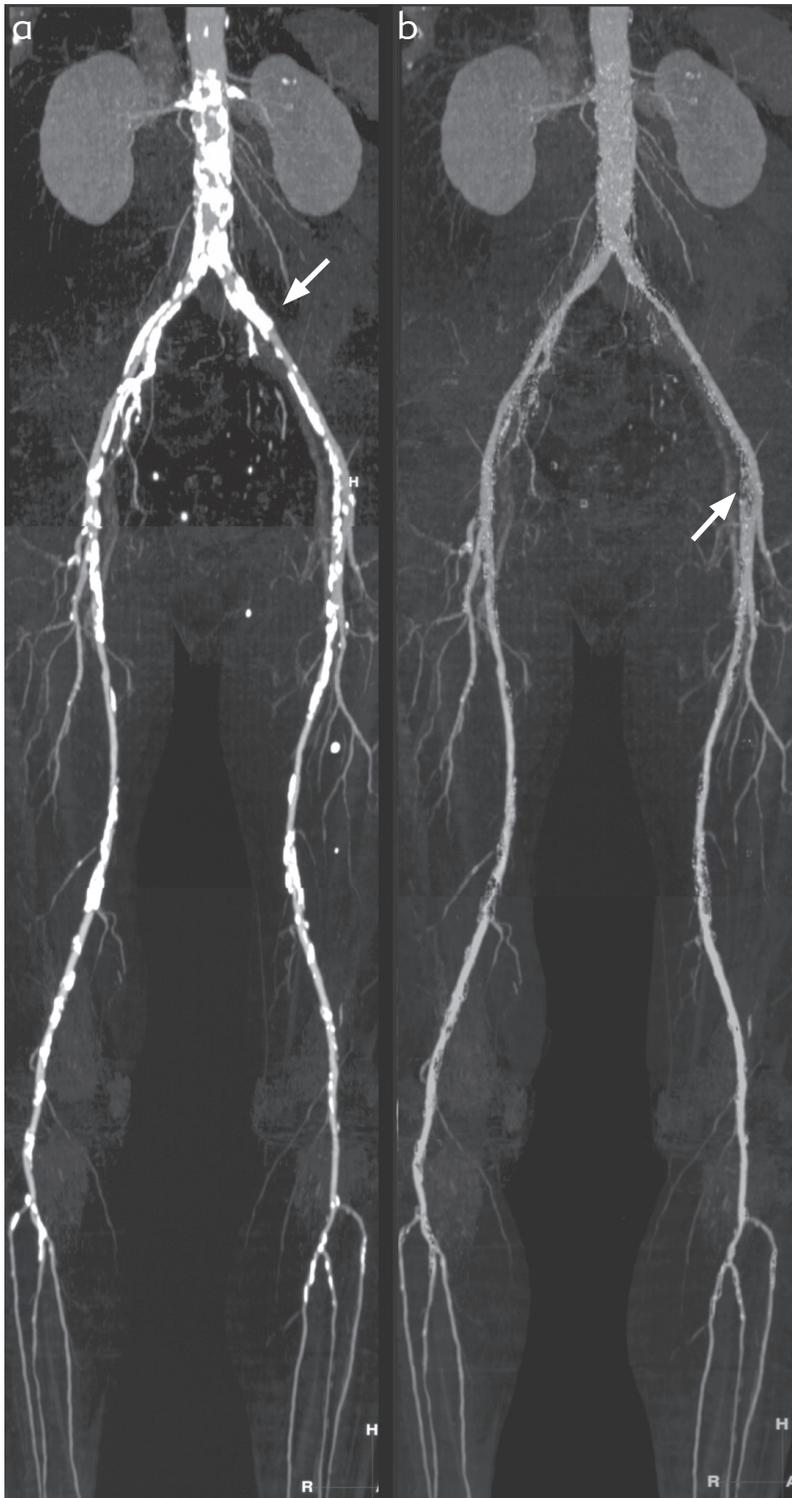
Figure 1. *Images in a 55-year-old man with claudication in both legs. (a) Whole-volume MIP image (frontal view) of MDCTA after segmentation of the bones. The angiogram shows arterial tree with extensive arterial wall calcifications and a stent in the left common iliac artery (arrow). (b) Whole-volume MIP image (frontal view) after segmentation of the bones and the arterial wall calcifications including the stent. The image shows remaining voxels (arrow) of the high density structures which were intentionally not removed from the dataset to prevent introducing pseudostenosis.*

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Reproducibility
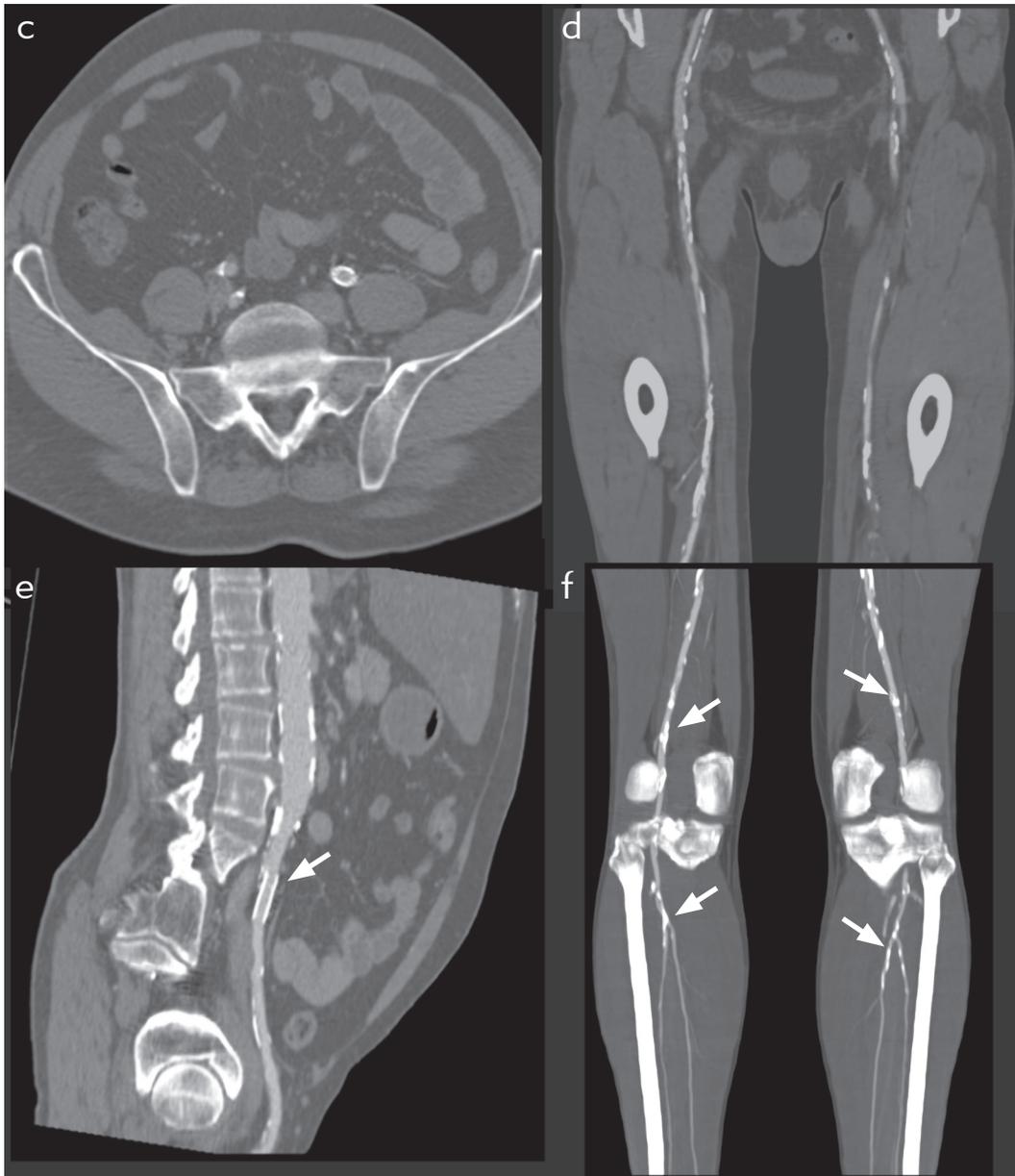
Continuing figure 1. *(c) Axial source images always need to be considered during interpretation and verify that there is less tapering of the lumen than displayed with the MIP after segmentation technique. (d and e) Curved planar reformat is able to display the interior of the artery (arrow) even when there are arterial wall calcifications or stents. (f) In small caliber vessels such as the crural arteries, the evaluation of the lumen is hampered by mural calcifications (arrows).*

Reproducibility

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to the aorta and using the aorta as the centre, with a slice thickness of the total volume and a 14° angle between every view over 180°. This resulted in 12 rotational MIP images showing the vascular enhanced tree with and without arterial wall calcifications (Figure 1 a and b).

Image Analysis
All DSA and MDCTA images were interpreted independently by two readers. The readers were blind for results of treatment, proposed treatment, and clinical follow-up of the patient, but they were aware of age, sex, the side of the symptoms and whether the patient had claudication or critical ischemia. Both reader 1 (M.G.M.H.) who interpreted the MDCTA images, and reader 2 (J.W.K.), who interpreted the DSA images, are vascular radiologists, with at least three years vascular interventional and CT angiography experience. Reader 3 (M.C.J.M.K.), who interpreted both the DSA and MDCTA images, is a dedicated researcher with two years of general radiology residency training including vascular interventional and CT angiography experience (M.C.J.M.K.). For interpretation of the DSA images the readers used the hard copies. For interpretation of the MDCTA images the reconstructed slab MIPs and the transverse CT images (source data), along with the volume MIPs and curved planar reconstructions were available for readers on dedicated workstations. The angiogram-like volume MIPs and the curved planar reconstructions of the MDCTA were also printed on hardcopy, and readers used both the hard copies and the source data on the workstations for image interpretation.

For analysis purposes, the arterial vascular system was divided into 3 anatomic stations of in total 32 segments, namely the aortoiliac arteries consisting of the suprarenal and infrarenal abdominal aorta, the common iliac artery, and the external iliac artery; the femoropopliteal arteries consisting of the common femoral artery, the deep femoral artery, the superficial femoral artery (proximal and distal part), and the popliteal artery (above and below the knee); the crural arteries consisting of the anterior tibial artery (proximal and distal part), the tibial peroneal trunk, the posterior tibial artery (proximal and distal part), and the peroneal artery (proximal and distal part).

Segments not contained within the imaging volume or not interpretable because of poor 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 also recorded nondiagnostic segments on both DSA and MDCTA. The presence of arterial wall calcifications was recorded when any calcification was present on whole-volume MIP images of MDCTA (Figure 2).

Reproducibility
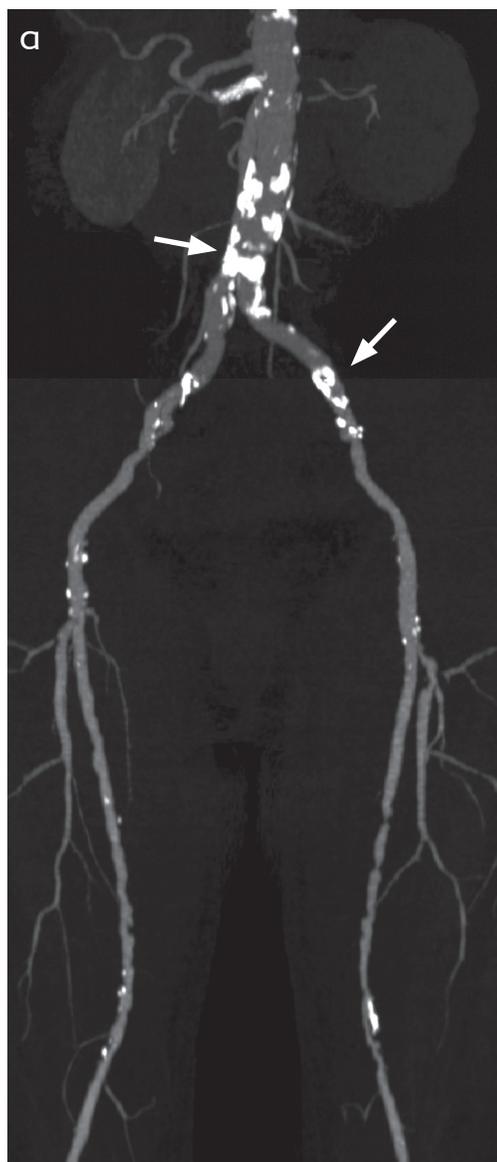
Figure 2. *Whole-volume MIP images (frontal view) after segmentation of the bones of MDCTA of two different patients showing the multiple arterial wall calcifications. (a) Image in 68-year-old man with claudication in the left leg shows multiple arterial wall calcifications (arrows) which hamper accurate lumen assessment. (b) Image in a 62-year-old man with claudication in the right leg since one year showing a few small arterial wall calcifications. All vessel segments can be evaluated.*

Statistical Analysis

To evaluate the agreement of stenotic grading, which is data from an ordered scale, we used a linear weighted kappa (K_w) statistic (13). The linear weighted kappa assigns different weights depending on the degree of disagreement. The weight (*w*) in the linear weighted kappa is given by

$$W_i = 1 - \frac{i}{k-1}$$

where i is the number of categories of disagreement and k is the total number of categories. We used 5 categories (k), so that the weights in the linear set are 1, 0.75, 0.50, 0.25 and 0 when there is a difference of 0 (= total agreement) or 1, 2, 3 and 4 categories respectively. A K-value of 0-0.20 indicates poor agreement, 0.21-0.40 indicates fair agreement, 0.41-0.60 indicates moderate agreement, 0.61-0.80 indicates good agreement, and 0.81-1.00 indicates excellent agreement (14). If a segment was classified as nondiagnostic by one of the two observers the segment was omitted from the K-calculations. 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 secondary 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. First, all the segments of the selected symptomatic leg were included in the analysis. Subsequently, we redid the analysis selecting at random one segment per anatomic station from the selected leg. Thus, in the latter secondary analysis the number of segments analyzed was reduced from 32 to 3 segments per patient (i.e. one aortoiliac, one femoropopliteal, and one crural segment).

Additionally analyses were performed to examine the effect of arterial 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 versus significant arterial stenosis and for determination of patent versus occluded arteries. Calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il) and Medcalc v8.1.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

From April 2000 to August 2001, we approached consecutive patients who were referred from the Department of Vascular Surgery at our university hospital. From a total of 195 patients who were potentially eligible we randomized 145 patients (Figure 3). Fifty patients did not fulfill all inclusion criteria. Fifteen patients were excluded because they needed an acute intervention, 6 patients were excluded because there was a language barrier, 6 patients were not randomized due to logistical problems, and 2 patients were not randomized for unknown reasons. Six patients refused to participate in the study and in 15 patients the clinician refused to allow the patient

to be randomized. Seventy-two patients were assigned to DSA and seventy-three to MDCTA. Of the 72 patients assigned to DSA 68 actually underwent DSA. Two patients underwent MDCTA due to the absence of arterial femoral pulsations (n = 2). One patient underwent Duplex Ultrasound because the clinician explicitly requested this. One patient moved abroad and underwent no other diagnostic test and no data was available for this patient. Of the 73 patients allocated to MDCTA all underwent MDCTA. The baseline characteristics are described in Table 1.
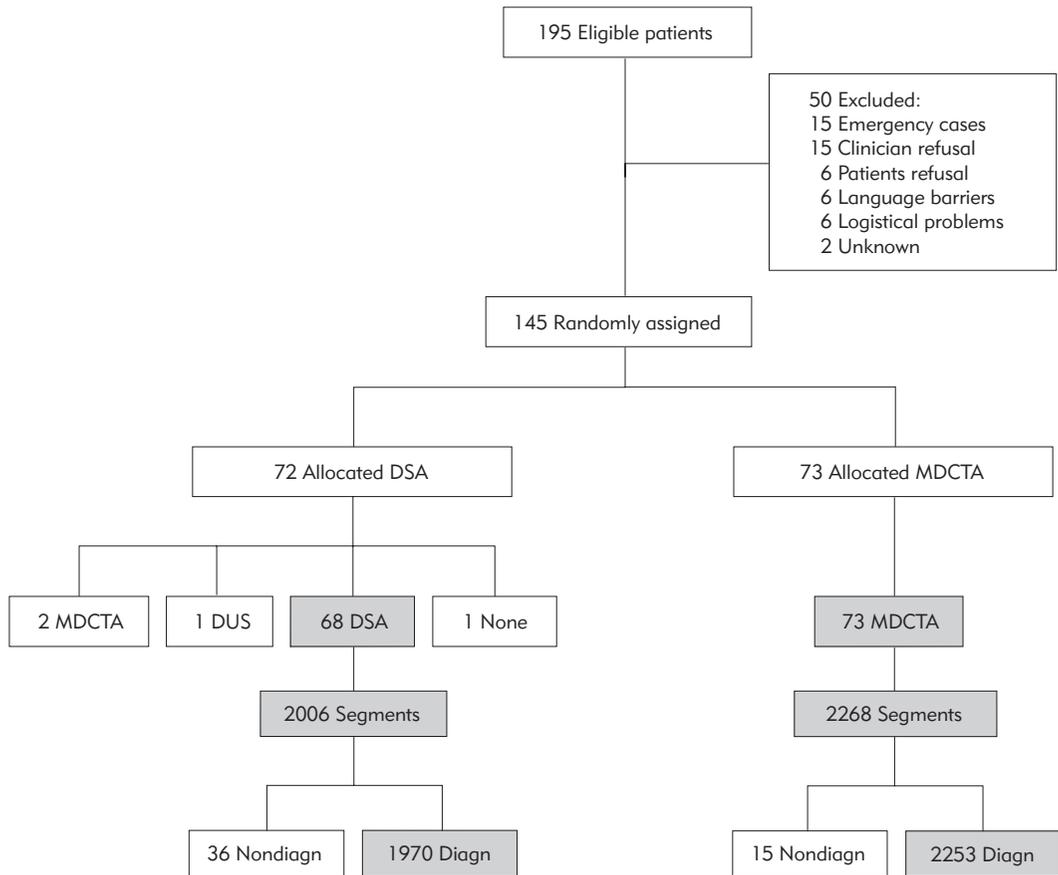
Figure 3. *Flow diagram illustrates the reasons for exclusion, random assignment of patients to diagnostic test groups, and the diagnostic tests that the patients actually underwent.*

Reproducibility

Table 1. *Baseline characteristics of patients*

Characteristics	DSA group* (n = 72)	MDCTA group* (n = 73)
Age, average years (SD) †	63 (10)	64 (11)
Male/female	47 (66)	58 (79)
Smoking	49 (78)	59 (84)
Diabetes mellitus	15 (25)	26 (38)
Hypertension	39 (57)	43 (63)
Cerebrovascular disease	10 (18)	18 (28)
Cardiac disease	23 (38)	23 (37)
Renal insufficiency	11 (17)	18 (26)
Hyperlipidemia	40 (62)	33 (53)
Critical ischemia	24 (34)	28 (38)

Note. - Data are numbers of patients and percentages in parentheses.
* The denominator has been adjusted for missing data.
† Data are given as mean (SD).

In the DSA group 2006 segments were imaged. One hundred-seventy segments were not imaged because of lower leg amputation (n = 95), congenital agenesis of the tibioperoneal trunk (n = 5), and limited range of imaging in the z-axis (suprarenal aorta, n = 4; distal crural arteries, n = 66). On DSA 36 segments were nondiagnostic, which were mainly crural segments and mainly due to poor enhancement. This leaves 1970 segments in the DSA group on which the analyses are based. In the MDCTA group 2268 segments were imaged. Sixty-eight segments were not imaged because of lower leg amputation (n = 66) and congenital agenesis of the tibioperoneal trunk (n = 2). On MDCTA 15 segments were nondiagnostic, which were due to poor enhancement of small caliber arteries with arterial wall calcifications, leaving 2253 segments on which the analyses are based.

There was excellent interobserver agreement of both DSA (K_w = 0.83; 95% CI: 0.80-0.85) and of MDCTA (K_w = 0.84; 95% CI: 0.83-0.86) for reporting the degree of stenosis in all segments (Tables 2 and 3). The results of the primary analysis including all segments and the two secondary analyses of only the symptomatic leg were similar within the different anatomic stations (Tables 5 and 6). The interobserver agreement of MDCTA was lower for arterial segments with arterial wall calcifications than for segments without arterial wall calcifications (Table 7). In the presence of arterial wall calcifications there was still good interobserver agreement in all anatomic stations. The lowest agreement was found for crural segments in the presence of calcifications (K_w = 0.79: 95% CI: 0.74-0.83).

3

Reproducibility

Table 2. *Interobserver agreement of digital subtraction angiography for grading stenosis in all segments*

Reader 2	Reader 1						
	0-19%	20-49%	50-74%	75-99%	Occlusion	Nondiagn	Total
0-19%	1274	48	10	4	14	4	1354
20-49%	52	63	16	5	3	0	139
50-74%	13	19	36	16	1	0	85
75-99%	8	7	10	37	13	0	75
Occlusion	26	3	0	12	280	9	330
Nondiagn	2	1	0	1	3	16	23
Total	1375	141	72	75	314	29	2006

Note. - Linear weighted K = 0.83 (95%-CI, 0.80-0.85) of all categories without nondiagnostic segments (n = 1970). Data are the number of segments.
Nondiagn = nondiagnostic.

Table 3. Interobserver agreement of 4-detector row CT angiography for grading stenosis in all segments

Reader 2	Reader 1						
	0-19%	20-49%	50-74%	75-99%	Occlusion	Nondiagn	Total
0-19%	1112	96	15	1	3	1	1228
20-49%	114	217	58	7	3	0	399
50-74%	15	48	128	18	2	0	211
75-99%	4	5	17	68	14	2	110
Occlusion	2	0	1	17	288	1	309
Nondiagn	2	2	0	0	1	6	11
Total	1249	368	219	111	311	10	2268

Note. - Linear weighted K = 0.84 (95%-CI, 0.83-0.86) of all categories without nondiagnostic segments (n = 2253). Data are the number of segments.
Nondiagn = nondiagnostic.

Table 4. *Interobserver agreement of the different anatomic stations including both legs (primary analysis)*

Anatomic station	Interobserver agreement in digital subtraction angiography		Interobserver agreement in 4-detector row CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
All stations	1970	0.83 (0.80-0.85)	2253	0.84 (0.83-0.86)
Aortoiliac	397	0.78 (0.72-0.84)	438	0.84 (0.80-0.87)
Femoropopliteal	789	0.88 (0.86-0.91)	861	0.86 (0.84-0.89)
Crural	784	0.78 (0.74-0.82)	954	0.82 (0.79-0.85)

Table 5. Interobserver agreement of the different anatomic stations including all segments of only the symptomatic leg (secondary analysis)

Anatomic station	Interobserver agreement in digital subtraction angiography		Interobserver agreement in 4-detector row CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
All stations	1032	0.84 (0.81-0.87)	1181	0.86 (0.83-0.88)
Aortoiliac	246	0.81 (0.74-0.88)	277	0.86 (0.81-0.90)
Femoropopliteal	390	0.90 (0.87-0.93)	418	0.88 (0.85-0.91)
Crural	396	0.79 (0.73-0.85)	486	0.83 (0.79-0.86)

Table 6. Interobserver agreement of the different anatomic stations including all segments of only the symptomatic leg (secondary analysis)

Anatomic station	Interobserver agreement in digital subtraction angiography		Interobserver agreement in 4-detector row CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
All stations	182	0.85 (0.78-0.92)	213	0.86 (0.81-0.91)
Aortoiliac	61	0.80 (0.63-0.97)	73	0.82 (0.71-0.92)
Femoropopliteal	68	0.90 (0.84-0.96)	71	0.87 (0.79-0.96)
Crural	53	0.79 (0.63-0.95)	68	0.86 (0.79-0.93)

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

Reproducibility

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Subgroup analysis for disease severity (claudication vs. critical ischemia) showed no difference in interobserver agreement of DSA (K = 0.81; 95% CI: 0.79-0.86 vs. K = 0.86; 95% CI: 0.83-0.90) and MDCTA (K = 0.82; 95% CI: 0.80-0.84 vs. K = 0.86; 95% CI: 0.84-0.89). Subgroup analysis for trial period (first half vs. second half) showed lower, but not significantly different, interobserver agreement of both DSA and MDCTA (K_w = 0.84; 95% CI: 0.81-0.87 vs. K_w = 0.81; 95% CI: 0.77-0.84 for DSA and K_w = 0.85; 95% CI: 0.83-0.88 vs. K_w = 0.83; 95% CI: 0.81-0.85 for MDCTA). Interobserver agreement for diagnosing hemodynamically insignificant versus significant arterial stenosis was excellent for both DSA (K = 0.82; 95% CI: 0.79-0.85) and MDCTA (K = 0.82; 95% CI: 0.80-0.85). Interobserver agreement for determination of patent versus occluded arteries was excellent for both DSA (K = 0.86; 95% CI: 0.83-0.90) and MDCTA (K = 0.92; 95% CI: 0.90-0.95).

Table 7. *Interobserver agreement of 4-detector row CT angiography in segments with and without vessel wall calcifications*

Anatomic station	Interobserver agreement in segments without vessel wall calcifications		Interobserver agreement in segments with vessel wall calcifications	
	n	K_w (95%-CI)	n	K_w (95%-CI)
All stations	1150	0.86 (0.83-0.88)	1103	0.81 (0.79-0.84)
Aortoiliac	110	0.87 (0.80-0.94)	328	0.82 (0.77-0.87)
Femoropopliteal	442	0.90 (0.87-0.93)	419	0.82 (0.78-0.85)
Crural	598	0.83 (0.79-0.86)	356	0.79 (0.74-0.83)

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

Reproducibility

Discussion

Over the last years the diagnostic approach to patients with suspected peripheral arterial disease has changed substantially. MDCTA is now increasingly used for the preoperative evaluation of peripheral arterial disease. Consequently, it is important that the image evaluation of new techniques is reproducible. Our results of a randomized controlled trial demonstrate that interobserver agreement for all segments and for the different anatomic stations for MDCTA in patients with peripheral arterial disease is as excellent as that for DSA but major calcified segments decrease the interobserver agreement.

Most reports about MDCTA in peripheral arterial disease describe agreement between two different modalities, such as between DSA and MDCTA, 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 linearly weighted kappa statistic as we did (6, 15, 16). For DSA an excellent interobserver agreement has been reported (weighted K-value of 0.87) (17), which is similar to our results. Romano et al. found excellent interobserver agreement for DSA (K = 0.82) and good interobserver agreement for 4 slice MDCTA (K_w = 0.80), which is consistent with our results (18). However, they divided the peripheral arterial tree into 81 segments.

We expected that dividing the arterial tree into multiple segments would result in the inclusion of multiple nondiseased segments and that the K-values would be overestimated. This was not confirmed by our 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 except for the crural station in MDCTA for which the values were even higher (Table 6). Also, including all segments of only the symptomatic leg of each patient resulted in K-values very similar to the K-values of the primary analysis. Furthermore, in both the primary and secondary analysis we found excellent interobserver agreement for DSA and MDCTA for all anatomic stations.

We anticipated that there might be a learning effect over time, which would result in an increase of the interobserver agreement during the trial period. To evaluate this effect we divided our data in two groups representing the first and second half of the trial period, which is a simple analysis to evaluate learning by experience. DSA and MDCTA showed a decreased interobserver agreement during the trial period. A possible explanation for these unpredicted findings may be that the observers became less thorough in categorizing between grade 0 and 1 or between grade 2 and 3 due to the routine and the realization that these distinctions have no substantial consequences in the clinical decision for treatment.

Our study showed that when major arterial wall calcifications are present in the peripheral arteries, evaluation of the arteries using MDCTA can be difficult. This is consistent with the literature which has reported underestimation as well as overestimation of arterial stenosis due to arterial wall calcifications (11,19,20). In particular, in small caliber vessels, circumferential mural calcifications have a relatively large effect

on lumen evaluation (16, 21) which is reflected in our study by the lowest agreement occurring in the crural arteries when arterial wall calcifications are present (Table 7). We found that only a few patients (12%) did not have any arterial wall calcifications and that in almost 50% of all segments in our study arterial wall calcifications were present. Therefore, arterial wall calcification is a frequent problem in the evaluation of the lumen using MDCTA.

Postprocessing techniques can be used to obtain images of the arteries that can facilitate interpretation. However, the axial source images always need to be considered during interpretation and can verify whether a stenosis is present or not (Figure 1c). Slab MIP images can be valuable by depicting arterial segments in one plane, however, when arterial wall calcifications are present the visualization of the real lumen can be very problematic. Also, if arteries are curved, which is especially relevant to the iliac arteries, slab MIP images are not suitable to display the arteries in the correct plane. The CPR technique can visualize the lumen of curved arteries very well (Figure 1 d-f). CPR projections display the interior of blood vessels and are, therefore, very practical in visualizing mural thrombus even in the presence of arterial wall calcification. Since one single CPR projection cannot adequately depict eccentric stenosis, two orthogonal projections of the vessel should always be created. A drawback is that CPR is an operator dependent technique and depends on the accuracy of placing the central lumen line. A pseudo-stenosis can be introduced when the central lumen line is inaccurately positioned.

In addition, we used MIP images of the whole volume to display the arterial tree as an angiogram after having removed all high density structures from the data. The removal of the bones and arterial wall calcifications was performed by using thresholding and a region-growing segmentation technique. This is an effective but time-consuming postprocessing technique. An important drawback of thresholding is that this technique is also operator dependent. When voxels that represent enhanced blood but have a Hounsfield value above the threshold value are inadvertently removed, a pseudo-stenosis can be introduced. To avoid this problem the threshold value was increased, with the downside that not all voxels with calcification were removed. The remaining voxels with calcification had a Hounsfield value close to the contrast enhanced lumen. The resulting angiogram showed these voxels as noise which was, however, preferable to introducing pseudo-stenoses (Figure 1b).

Our study had several limitations. First, we omitted the nondiagnostic segments from the calculations of the kappa values. This is consistent with daily clinical practice where when a relevant segment is nondiagnostic it will be re-imaged and when an irrelevant segment is nondiagnostic it will be ignored. A possible limitation is the method of evaluating the severity of stenosis. Subjective judgment could have been introduced since we used visual assessment. Dedicated software is commercially available for the semi-automatic quantitative analysis of vascular morphology in peripheral arteries of 3-dimensional datasets which reduces interobserver variability (19,22,23). On the other hand, the visual scoring assessment we used may well reflect daily clinical practice in which calipers and dedicated vascular software are not (yet) used on a routine

basis. Finally, although interesting, we did not evaluate the intra-observer agreement of DSA and MDCTA. Even so, since the interobserver agreement was excellent, it is likely that the intra-observer agreement would be excellent too (23,24).

In conclusion, the results of our study demonstrated that the interobserver agreement of MDCTA is as excellent as that of the reference standard DSA. Multiple calcified segments are frequently found in patients with peripheral arterial disease using MDCTA and decrease the interobserver agreement. To solve the drawback of arterial calcifications new acquisition and postprocessing techniques are necessary to increase performance of MDCTA.

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Reproducibility

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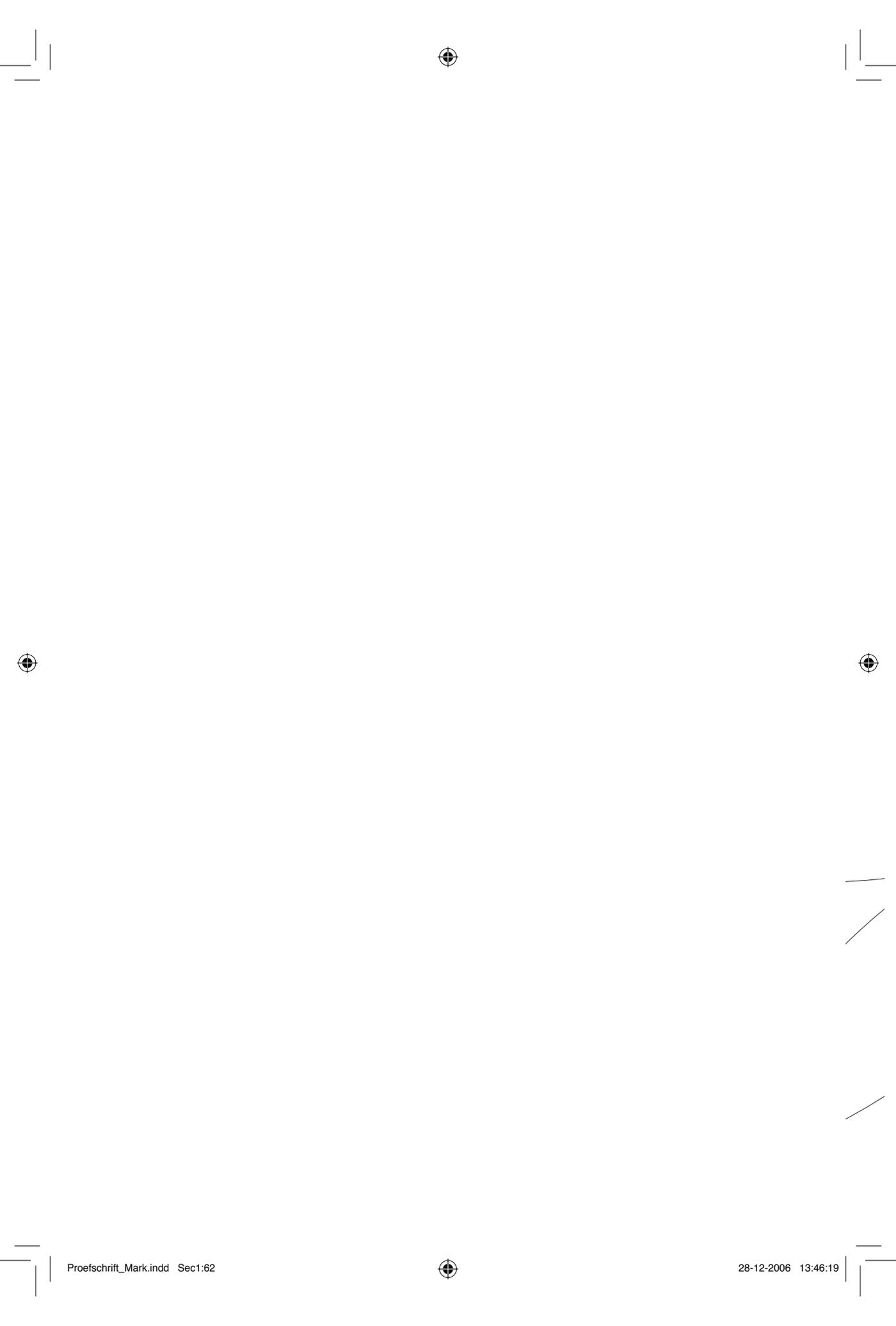
Chapter 4
Interobserver Agreement for Interpretation of Multi-Detector CT Angiography Compared with Contrast-Enhanced MR Angiography

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Reproducibility

Abstract

Purpose: The objective of our study was to compare interobserver agreement for interpretations of contrast-enhanced 3D MR angiography (CEMRA) and multi-detector row CT angiography (MDCTA) 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 CEMRA (n = 78) or MDCTA (n = 79). Two observers independently evaluated for arterial stenosis or occlusion on CEMRA (2,157 segments) and MDCTA (2,419 segments) using a 5-point ordinal scale. Vessel wall calcifications were noted. Interobserver agreement for each technique was evaluated with a weighted kappa (K_w) statistic.

Results: Although interobserver agreement for both was excellent, the interobserver agreement for CEMRA (K_w = 0.90; 95% confidence interval [CI], 0.89–0.92) was higher than that for MDCTA (K_w = 0.85; 95% CI, 0.83–0.86) for reporting the degree of arterial stenosis or occlusion in all segments. For the different anatomic locations, the interobserver agreement for MR angiography versus MDCT angiography was as follows: aortoiliac (K_w = 0.91 vs 0.84, respectively), femoropopliteal (K_w = 0.91 vs 0.87), and crural (K_w = 0.90 vs 0.83) segments. The interobserver agreement of MDCTA 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 CEMRA, there were 12 times more nondiagnostic segments than with MDCTA (81 vs 7, respectively).

Conclusion: Interpretations of CEMRA and MDCTA for peripheral arterial disease have an excellent interobserver agreement. MR angiography has a higher interobserver agreement than MDCTA, and the presence of calcified segments significantly decreases interobserver agreement for MDCTA.

Reproducibility

Introduction

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

Both contrast-enhanced 3D MR angiography (CEMRA) and multi-detector row CT angiography (MDCTA) used for non-invasive vascular imaging. CEMRA has gained widespread use for imaging peripheral arterial disease (5–7). Disadvantages of CEMRA 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 MDCT scanners have substantially improved MDCTA for peripheral arterial disease. The use of MDCT 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 MDCTA is accurate for imaging peripheral arteries (11–16). The main disadvantages of MDCTA are, the use of potentially nephrotoxic iodinated contrast medium, the time-consuming 3D reconstruction techniques, and the difficulty in assessing arterial lumen stenosis in the presence of vessel wall calcifications (17–19). In the evaluation of new diagnostic tests, the study of its interobserver agreements plays an important role (20). The accuracy of a test can never be perfect if assessments by different observers show significant variation. Furthermore, it is likely that poor interobserver agreement can cause variation in clinical decision making. Thus, apart from evaluating accuracy in comparison with a reference standard, it is important to evaluate reproducibility, including interobserver agreement for test results.

The purpose of this study was to compare the interobserver agreement for interpretations of CEMRA and 16-slice MDCTA in patients with peripheral arterial disease.

Subjects and Methods

Patients
The patient population recruited for this study is composed of the same patients who participated in a randomized controlled trial concerning patient outcomes and costs of CEMRA compared with MDCTA as the initial imaging test in the diagnostic work-up of peripheral arterial disease. Inclusion criteria for participation in the study were patient age of older than 18 years, symptomatic peripheral arterial disease, 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 in-

cluded contraindications for MR angiography (e.g., pacemaker or claustrophobia) or MDCTA (e.g., 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 MR angiography and MDCTA. The study was approved by the institutional review board, and informed consent for the study and all articles derived from the study was obtained from all patients.

Contrast-enhanced MR angiography
All examinations were performed with a 1.5-T imager (Signa, GE Healthcare) that was equipped with echo-speed gradients (40 mT/m, 150 mT/m/msec). A dedicated peripheral vascular phased-array coil was used for signal reception. For bolus-chase MR angiography, commercially available software (SmartStep, GE Healthcare) 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 segments. The parameters for the TOF sequence were as follows: TR/TE, 23/4.4; flip angle, 70°; bandwidth, 15.63 kHz; slice thickness, 8.0 mm; and matrix, 256 x 128. Acquisition times were between 1.31 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 3D 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 for imaging the aortoiliac location: TR/TE, 4.8/1.5; flip angle, 30°; field of view, 400 x 280 mm; slice thickness, 2.6 mm; matrix, 384 x 192; and phase-encoding, centric. The parameters for imaging the femoropopliteal location were as follows: TR/TE, 4.8/1.5; flip angle, 30°; field of view, 400 x 320; slice thickness, 2.0 mm; matrix, 384 x 192; and phase-encoding, centric. The parameters for imaging the crural location were as follows: TR/TE, 5.1/1.5; flip angle, 30°; field of view, 400 x 360 mm; slice thickness, 2.0 mm; matrix, 512 x 512; and phase-encoding, elliptic centric. 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 (Smart-Prep, GE Healthcare). Subsequently, 3D MR angiographic images of the femoro-popliteal and crural locations were acquired sequentially. The contrast agent (gado-pentetate dimeglumine (Magnevist, Schering)) was administered in the antecubital vein using a 20-gauge IV 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/sec for the remaining 35 mL (total injection duration, 52 sec), followed by a saline flush of 15 mL at a rate of 0.8 mL/sec. For this dual-phase injection, an automated injector (Spectris, Medrad) was used to ensure precise contrast agent injections. We used a subtraction technique before maximum-intensity-projection (MIP) reconstructions were performed. The mask images were subtracted from the contrast-enhanced im-

Reproducibility

ages at each station. Twelve rotated volume MIP images ranging from –90° to 90° were reconstructed for each subtracted data set. These volume MIP images were documented on film and sent together with the source data to a remote workstation (Advanced Windows 3.1, GE Healthcare).

Multi-detector row CT angiography
MDCTA was performed on a Sensation 16 scanner (Siemens Medical Solutions). Patients were in the supine position on the CT table with their legs held together.
After an initial scout image (120 kV, 100 mAs) was obtained, 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 the start of contrast material administration and the start of scanning was obtained for each patient individually using a bolus-tracking technique (CARE-Bolus, Siemens Medical Solutions). Subsequently, a nonionic contrast material (iodixanol (320 mg I/mL Visipaque, Amersham Health)) was administered through a 20-gauge cannula that was placed in 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) 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-sec scanning time, 1.25-sec interscan delay) were obtained. After the preset attenuation of 100 H above the baseline attenuation was reached, 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; and 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 using commercially available software on the CT console. All data were then transferred to a dedicated workstation (Easy Vision, Philips Medical Systems) that allowed postprocessing of the images. The reconstructions were performed by one of two technologists experienced in 3D postprocessing 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 data sets, rotating volume MIP images were generated using the commercially available software installed on the workstation. This resulted in 12 angiogramlike images rotating more than 180° for aortoiliac, femoropopliteal, and crural arteries.

Image Analysis
All MR and MDCT angiograms were interpreted independently by two observers. Observer 1 is a vascular radiologist, and observer 2 is a dedicated researcher with 2.5 years of general radiology training and 1 year of experience in vascular radiology. Both observers have extensive experience in interpreting MR angiography and MDCT angiography. The volume MIPs of both MR angiography and MDCT angiog-

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raphy and the curved planar reconstructions of MDCT angiography 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 observers on dedicated workstations. For image interpretation, the observers used both the hard copies and the source data on the workstations. In almost all cases, the observers used the source data. In a few cases—that is, if the volume 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 three anatomic locations to include a total 31 segments—namely, the aortoiliac arteries consisting of the distal aorta, paired common iliac arteries, and external iliac arteries; the femoropopliteal arteries consisting of the paired common femoral arteries, deep femoral arteries, superficial femoral arteries (proximal and distal parts), and popliteal arteries (above and below the knee); the crural arteries consisting of the paired anterior tibial arteries (proximal and distal parts), tibial peroneal trunk, posterior tibial arteries (proximal and distal parts), and peroneal arteries (proximal and distal parts). 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 5-point ordinal scale was used to grade stenotic or occlusive disease: zero 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 observers recorded the presence of vessel wall calcifications on MDCTA and recorded nondiagnostic segments on both CEMRA and MDCTA.

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 kappa statistic indicates the agreement beyond chance. Strength of agreement can be interpreted as poor (K < 0.20), fair (K = 0.21–0.40), moderate (K = 0.41–0.60), good (K = 0.61–0.80), or excellent (K = 0.81–1.0) (21). If a segment was classified as nondiagnostic by at least one of the observers, the segment was omitted from the weighted kappa calculations for reporting the degree of arterial stenosis. In addition, the percentage of 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 kappa 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 three segments per patient (i.e., one aortoiliac segment, one femoropopliteal segment, and one crural segment).

Reproducibility

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 of the trial period). 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 stenoses and for determination of nonoccluded (i.e., stenosis < 99%) versus occluded arteries. Calculations were performed with statistical packages (SPSS (version 11.0), Statistical Package for the Social Sciences; and SAS (version 8.2), SAS Institute) for Windows (Microsoft).
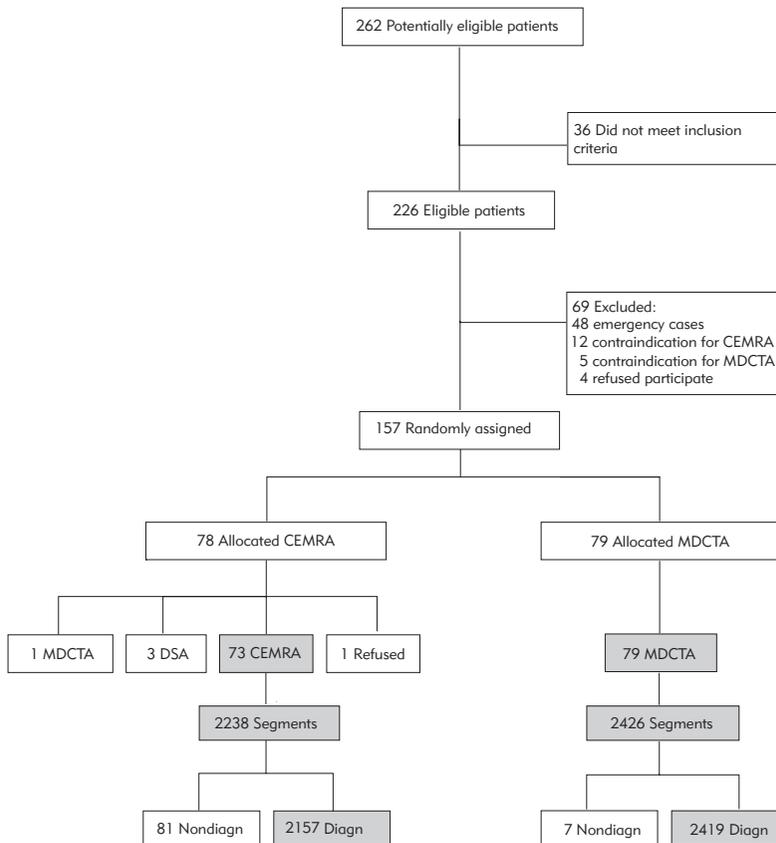

Figure 1 *Flow diagram illustrates reasons for exclusion, random assignment of patients to diagnostic test groups, and diagnostic tests that patients actually underwent. DSA = digital subtraction angiography, CEMRA = contrast-enhanced 3D MR angiography, MDCTA = multi-detector row CT angiography.*

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

Table 1. *Baseline characteristics of patients*

Characteristic	CEMRA Group (n = 78)	MDCTA Group (n = 79)
Age (yr)		
Mean ± SD	63 ± 11	64 ± 12
Range	38–78	20–93
No. (%) of patients		
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 insufficiency[a]	4 (5)	1 (1)

[a] *Mild renal insufficiency or hemodialysis with permission of the nephrologist to undergo MDCT angiography.*

Reproducibility

In the group of patients who underwent CEMRA, 2,238 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 CEMRA, 81 segments were nondiagnostic, which were mainly crural segments and mainly due to venous enhancement. This leaves 2,157 segments in the CEMRA group on which the analyses for reporting the degree of arterial stenosis is based. In the MDCTA group, 2,426 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 MDCTA, only seven segments were nondiagnostic, which were due to a total knee arthroplasty, leaving 2,419 segments on which the analyses for reporting the degree of arterial stenosis is based.

The interobserver agreement for reporting the degree of arterial stenosis or occlusion in all segments was statistically significant lower for MDCTA (K_w = 0.85; 95% confidence interval (CI), 0.83–0.86) than for CEMRA (K_w = 0.90; 95% CI, 0.89–0.92, p < 0.001). Nevertheless, there was excellent interobserver agreement of both CEMRA and MDCTA for reporting the degree of arterial stenosis or occlusion in all segments (Tables 2 and 3). The percentage of overall agreement was 89% (95% CI, 88–90%) for CEMRA and 83% (95% CI, 81–85%) for MDCTA (Tables 2 and 3). The results of the primary and secondary analyses were similar in the different anatomic locations (Tables 4 and 5).

Table 2. *Interobserver agreement of contrast-enhanced MR angiography for grading stenosis in all segments*

Reader 2	Reader 1						
	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. - Data are the number of segments. Weighted kappa (K_w) = 0.90 (95% confidence interval (CI), 0.89–0.92). The percentage of overall agreement is 89% (95% CI, 88–90%).

Table 3. *Interobserver agreement of 16-detector row CT angiography for grading stenosis in all segments*

Reader 2	Reader 1						
	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. - Data are the number of segments. Weighted kappa (K_w) = 0.85 (95% confidence interval (CI), 0.83–0.86). The percentage of overall agreement is 83% (95% CI, 81–85%).

Table 4. *Interobserver agreement of the different anatomic stations including both Legs: primary analysis*

Anatomic station	Interobserver agreement on MR Angiography		Interobserver agreement on 16-detector row CT angiography	
	n	K_w (95%-CI)	n	K_w (95%-CI)
All stations	2157	0.90 (0.89-0.92)	2419	0.85 (0.83-0.86)
Aortoiliac	353	0.91 (0.88–0.94)	395	0.91 (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. - K_w = weighted kappa, CI = confidence interval.

Table 5. *Interobserver agreement of the different anatomic stations including only the symptomatic leg and only one segment per station: secondary analysis*

Anatomic station	Interobserver agreement on MR Angiography		Interobserver agreement on 16-detector row 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	0.92 (0.86–0.98)	78	0.84 (0.74–0.93)
Crural	71	0.88 (0.79–0.97)	78	0.82 (0.71–0.93)

Note. - CI = confidence interval.

Interobserver agreement for classifying nondiagnostic versus diagnostic segments was excellent for MDCTA (K_w = 0.92; 95% CI, 0.77–1.00) and was good for CEMRA (K_w = 0.70; 95% CI, 0.60–0.79). The interobserver agreement of MDCTA for reporting the degree of arterial stenosis or occlusion in all segments was statistically significantly lower for arterial segments with vessel wall calcifications than for segments without vessel wall calcifications (Table 6). 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).

Table 6. *Interobserver agreement of MDCTA in segments with and without vessel wall calcifications*

Anatomic station	Interobserver agreement on MR Angiography		Interobserver agreement on 16-detector row CT angiography	
	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. - K_w = weighted kappa, CI = confidence interval.

Subgroup analyses for disease severity (claudication vs critical ischemia) showed no difference in interobserver agreement of MR angiography (K_w = 0.90 vs 0.92, respectively) and MDCTA (K_w = 0.84 vs 0.86, respectively) (Table 7). Subgroup analyses for trial period (first half vs second half) showed no difference in interobserver agreement of CEMRA (K_w = 0.91 vs 0.89, respectively). Interobserver agreement of MDCTA was

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lower for the second half of the trial period (K_w = 0.88 vs 0.81, respectively) (Table 7). Interobserver agreement for diagnosing hemodynamically insignificant stenosis versus significant arterial stenosis was excellent for both CEMRA (K_w = 0.92; 95% CI, 0.91–0.94) and MDCT angiography (K_w = 0.86; 95% CI, 0.84–0.89). Interobserver agreement for determination of nonoccluded versus occluded arteries was excellent for both CEMRA (K_w = 0.94; 95% CI, 0.92–0.96) and MDCTA (K_w = 0.91; 95% CI, 0.88–0.93).

Table 7. *Interobserver agreement of MR Angiography and MDCT Angiography in different subgroups*

Subgroup	Interobserver Agreement on MR Angiography		Interobserver Agreement on MDCT Angiography	
	n	K_w (95% CI)	n	K_w (95% CI)
Clinical Stage				
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)
Trial Period				
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 - K_w = weighted kappa, CI = confidence interval.

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 interpretations of these new imaging techniques are reproducible. Our results show that interobserver agreement for interpretations of CEMRA and MDCTA for peripheral arterial disease is excellent in both, is significantly higher for MR angiography than MDCTA, and is significantly decreased for calcified segments on MDCTA.

Literature about interobserver agreement of CEMRA and MDCTA in patients with peripheral arterial disease is scarce. Most articles describe agreement only 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 CEMRA, we only found one weighted kappa value of 0.86 representing interobserver agreement in all segments (5). For MDCTA, we did not find any weighted kappa values in the literature. For digital subtraction angiography a weighted kappa value of 0.87 has been reported (22), which is similar

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to our results for CEMRA and MDCTA. Our expectation that kappa 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 kappa values very similar to those of the primary analysis (Tables 4 and 5). Furthermore, in the primary and secondary analyses, we found excellent interobserver agreement for both CEMRA and MDCTA in all locations.
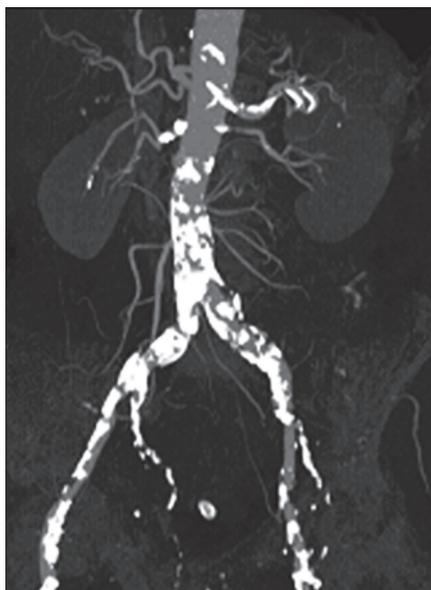

Figure 2a *Images in 68-year-old man with claudication of right leg and critical ischemia of left leg. Volume maximum-intensity-projection image (anteroposterior view) of MDCT angiography performed with only bone segmentation. There are extensive vessel wall calcifications.*

Vessel wall calcifications on MDCT angiograms have been shown to affect image interpretation in several studies (19, 23, 24). 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 (Figures. 2a, 2b, and 2c). The small vessel diameter combined with vessel wall calcifications may have contributed to the lowest agreement, which occurred 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 MDCTA (25).

We expected that data might be affected by 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 half 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 CEMRA, interobserver agreement was similar for both the first half and second half of the trial period. For MDCTA, 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 zero (0–19% stenosis) and 1 (20–49% stenosis) or between grade 2 (50–74% stenosis) and 3 (75–99% stenosis) stenoses due to routine and the realization that these distinctions are less important clinically. This was especially true given that image interpretation is more time-consuming for MDCTA than for CEMRA due

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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 intraobserver agreement, although this information may have been interesting. However, because the interobserver agreement was excellent, it is likely that the intraobserver 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 is not yet used on a routine basis.

An additional limitation is that we had a high number of nondiagnostic segments on CEMRA. Performing an initial high-resolution MR angiography sequence of the tibial vessels

Figure 2b *Images in 68-year-old man with claudication of right leg and critical ischemia of left leg. Volume maximum-intensity-projection image (anteroposterior view) of MDCT angiography with segmentation of both bone and vessel wall calcifications. There seems to be arterial stenosis (arrow) just distal to right iliac bifurcation.*

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 in which the nondiagnostic category can be included in the categoric scale for grading arterial stenosis. Furthermore, our method of analysis is consistent with daily clinical practice in which a nondiagnostic segment will be ignored or reimaged 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 CEMRA and MDCTA and calculated the percentage of 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 CEMRA and MDCTA in our hospital.

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Figure 2c *Images in 68-year-old man with claudication of right leg and critical ischemia of left leg. Even on transverse source images of MDCTA like this one, it was difficult to assess degree of stenosis due to vessel wall calcifications.*

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

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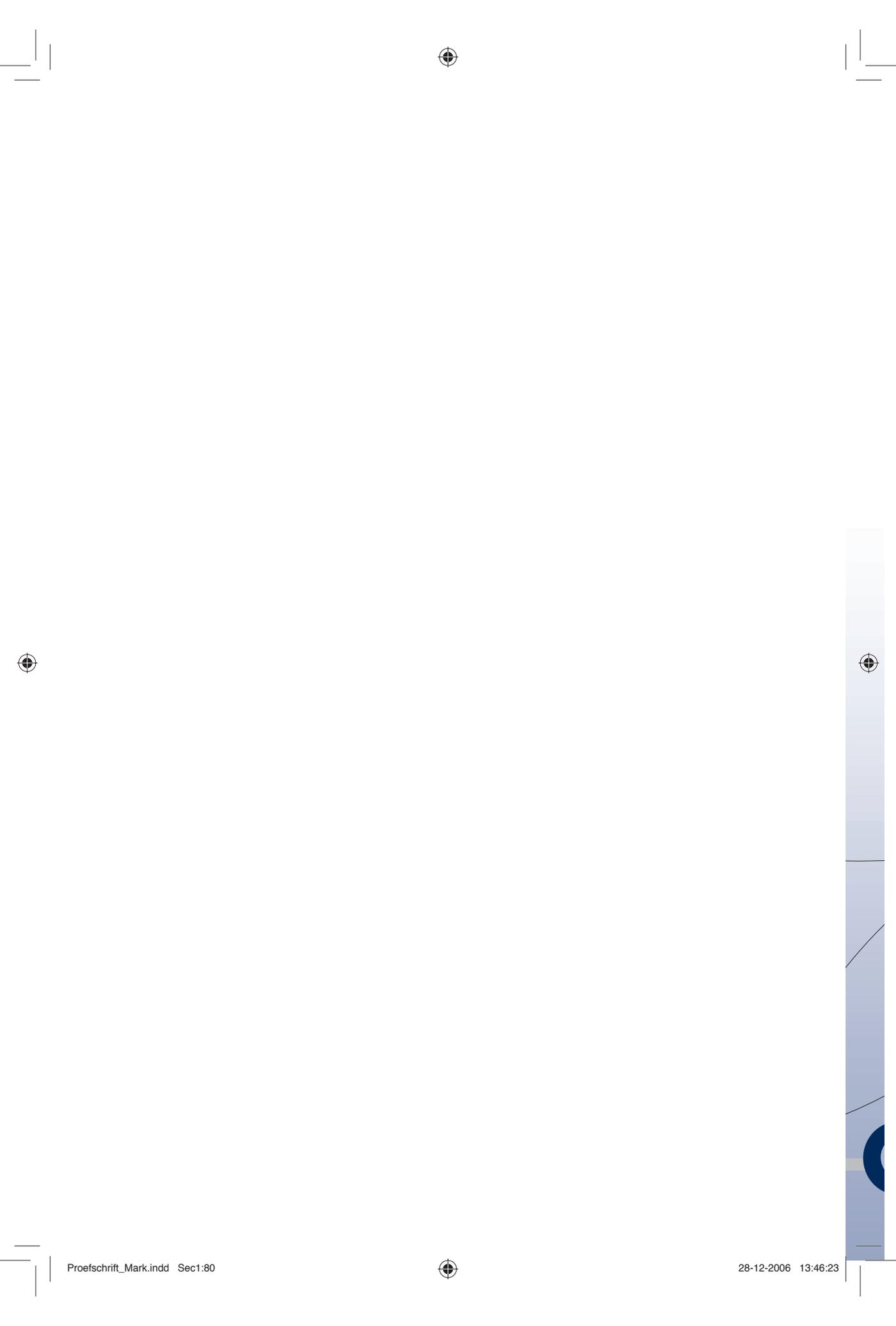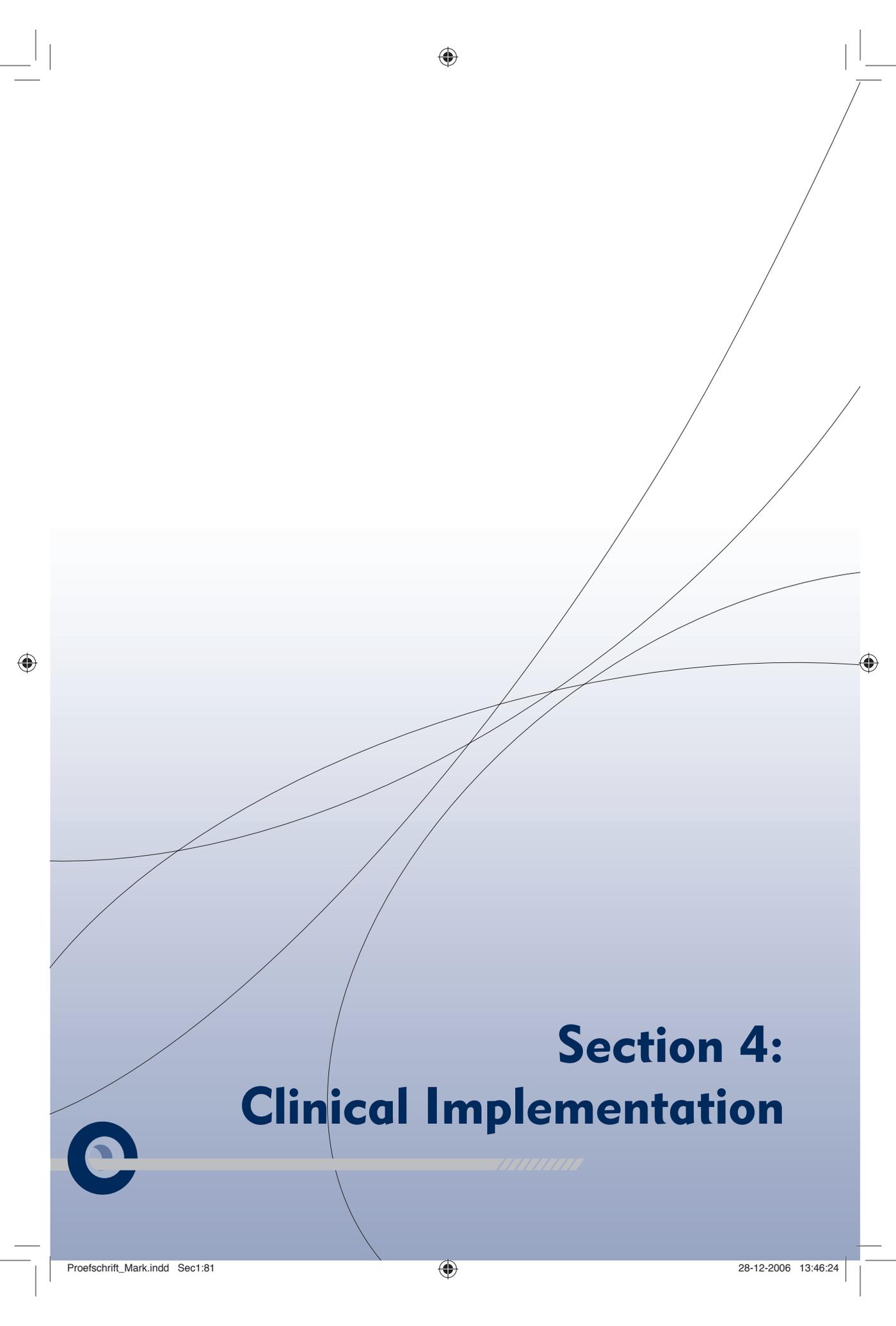
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Clinical Implementation
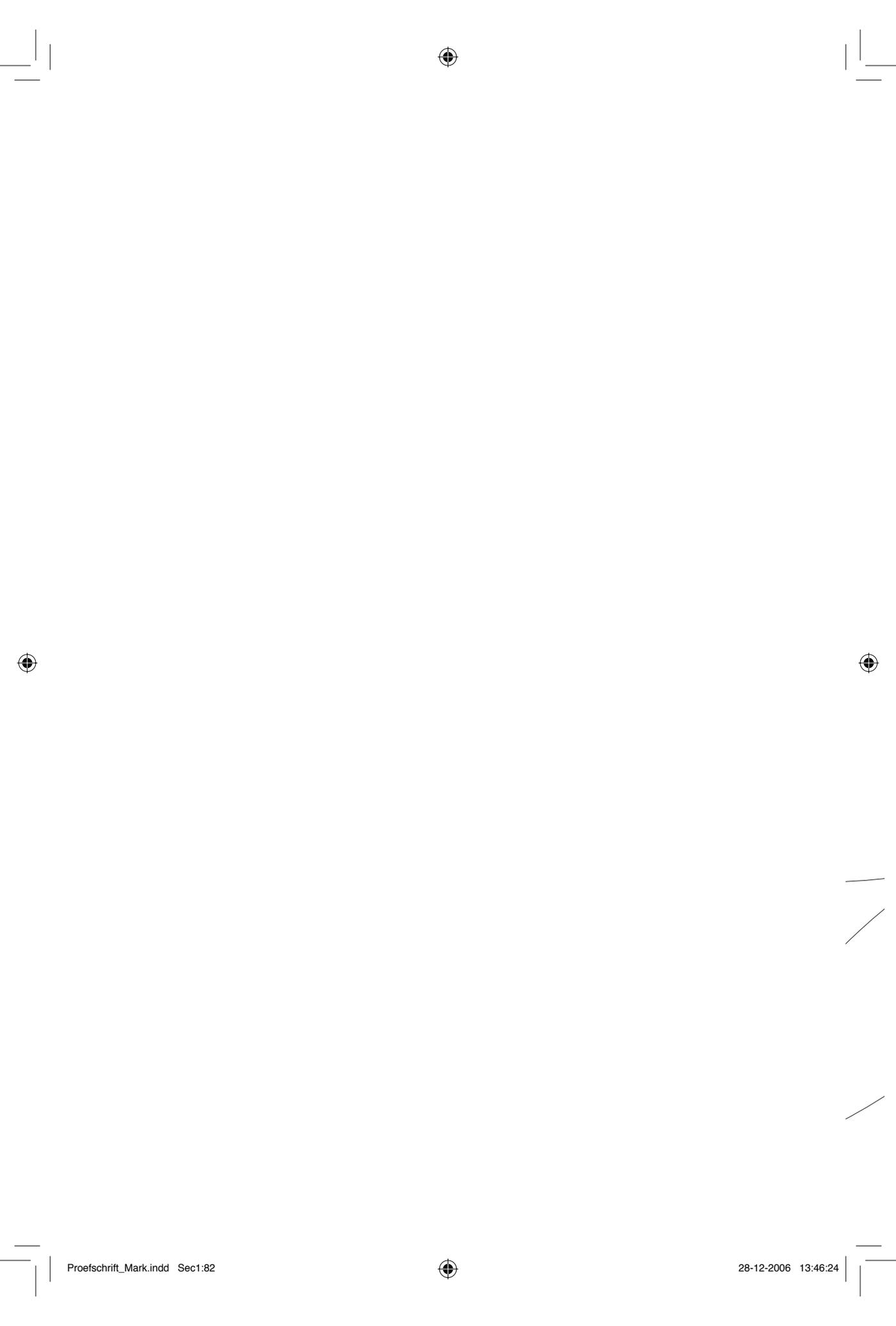
Chapter 5
A Randomized Controlled Trial of Multi-detector Row CT Angiography versus Digital Subtraction Angiography

Kock MCJM, Adriaensen MEAPM, Pattynama PMT,
van Sambeek MRHM, van Urk H, Stijnen T, Hunink MGM.
Radiology 2005; 237:727-737.

Clinical Implementation

4

Abstract

Purpose: To prospectively compare the therapeutic confidence, patient outcomes (quality of life), and costs of digital subtraction angiography (DSA) and multi-detector row computed tomography angiography (MDCTA) for the initial diagnostic imaging test in patients with peripheral arterial disease (PAD).

Materials and methods: Between April 2000 and August 2001 we randomly assigned patients with PAD to undergo either DSA or MDCTA as initial diagnostic imaging test. Outcomes were the therapeutic confidence assessed by physicians (0 to10), the need for additional imaging, the 6 months follow-up health-related quality of life, diagnostic and therapeutic costs, and costs for hospital stay. Costs were computed from the hospital perspective according to the Dutch guidelines for cost calculations in health care. The mean outcomes were compared between the groups with the unpaired t test and adjusted for predictive baseline characteristics with multivariable regression analysis.

Results: From the 145 randomized patients, 72 were allocated to the DSA group and 73 to the MDCTA group. The mean age was 63 and 64 years in the DSA and MDCTA groups respectively. The DSA group was 66% male and the MDCTA group 79%. The confidence of physicians in making a correct therapeutic choice based on DSA (mean 8.2) was significantly higher than that for MDCTA (mean 7.2, p<0.001). During 6 months follow-up, 14% less additional imaging was performed in the DSA group than in the MDCTA group (not a statistically significant difference). No significant differences were found between the groups with respect to quality of life. The diagnostic cost associated with the DSA strategy (564 euros [SD 210]) was significantly higher than the cost for the MDCTA strategy (363 euros [SD 273]), a difference of -201 euros (95% CI -281 to -120, P<0.001). The therapeutic and hospitalisation costs were similar for both strategies.

Conclusion: The results suggest that non-invasive imaging with MDCTA as initial diagnostic imaging test for peripheral arterial disease instead of DSA provides sufficient information for therapeutic decision making and reduces the costs for imaging.

Clinical Implementation

Introduction

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis in the arteries to the lower extremities. Symptomatic PAD often presents with pain during ambulation, which is known as intermittent claudication and is prevalent in 1.6% of the population of 55 years and older (1). In approximately one quarter of the cases, the disease will progress to critical ischemia, i.e. pain at rest, ulceration or gangrene. The diagnosis of PAD is based on patient history and physical examination as well as by treadmill exercise testing at which the ankle-brachial systolic blood pressure index is measured to document the severity of the disease.

Diagnostic imaging of the peripheral arteries is limited to patients for whom a revascularization procedure is contemplated, that is, those with critical ischemia or with severe disabling intermittent claudication unresponsive to exercise therapy. Because the number of revascularization procedures for PAD is increasing (2) (in the Netherlands 8% increase over the last 5 years, adjusted for the aging population), the number of preoperative diagnostic imaging procedures is also increasing (3). Diagnostic imaging tests for arterial disease can broadly be classified into non-invasive (or minimally invasive) and invasive vascular imaging. The reference standard, digital subtraction angiography (DSA), is an invasive imaging technique which requires catheterization of the femoral artery and an intra-arterial injection of iodinated contrast medium. It also requires post-procedural observation and sometimes hospitalization. DSA is associated with a higher complication rate (4) and with higher costs when compared to non-invasive imaging.

Computed tomography (CT) angiography is non-invasive, requires only intravenous injection of iodinated contrast medium, and can be performed as an outpatient procedure. The recently introduced multi-detector-array technology has overcome the limits of single slice CT scanners. Multi–detector row CT angiography (MDCTA) provides a high volumetric resolution and a total longitudinal coverage of the legs (5, 6). A diagnostic work-up with MDCTA as the initial imaging test is potentially less expensive and less of a burden to the patient than a work-up with DSA as initial test.

MDCTA has already been shown to be accurate for imaging peripheral arteries (7-11). Clinical utility, patient outcomes, and the associated costs of performing MDCTA in daily practice instead of DSA have, however, not been evaluated. Therefore, the decision whether MDCTA should replace DSA in the work-up of PAD remains to be clarified (12, 13). Thus, the purpose of our study was to prospectively compare the therapeutic confidence, patient outcomes (quality of life), and costs of DSA and MDCTA for the initial diagnostic imaging test in patients with PAD.

Clinical Implementation

Materials and Methods

Study Population
The institutional medical ethics committee of our tertiary care university hospital (Erasmus MC) approved this study. To be included, eligible patients had to give written informed consent. Eligible patients had symptomatic PAD, an ankle-brachial systolic blood pressure index of less than 0.90, and were referred by the vascular surgeon for a diagnostic imaging work-up to evaluate the feasibility of a revascularization procedure. All patients had severe disabling intermittent claudication unresponsive to exercise therapy or they had critical ischemia. Exclusion criteria were contraindications to angiography, iodinated contrast agents, or revascularization and acute ischemia which required urgent imaging and treatment.

Between April 2000 and August 2001, we approached all eligible patients who were referred from the Department of Vascular Surgery to the Department of Radiology at our university medical centre. Baseline characteristics (ie, age, sex, and risk factors) were collected from each patient during the interview at the time of randomization or from the hospital (electronic) medical records (M.C.J.M.K.). To evaluate the generalizability of our study, we also prospectively collected baseline characteristics of all patients who were eligible but were not randomized, and we documented the reasons for non-participation (M.C.J.M.K.). Data were analyzed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (14).

Study Design
Patients were randomly allocated to either one of the two diagnostic strategies of interest, DSA or MDCTA as initial diagnostic imaging test. An independent employee of our university provided a nonstratified computer-generated randomization sequence with a block size of six. The allocation sequence was concealed by means of sealed opaque envelopes that were numbered consecutively. Eligible patients were enrolled by the trial nurses or the researchers who were unaware of the randomization sequence. Following randomization, patients and clinicians were not blinded for the imaging strategy since this would have been highly impractical and inconsistent with our goal of performing a pragmatic study.

The study was supported by a Health Care Efficiency Grant from the Health Care Insurance Board (00112) and by a Program Grant from the Netherlands Organization for Scientific Research (904-66-091). Since diagnostic imaging and therapy were performed as part of routine clinical practice, equipment, contrast agents and other supplies were not funded. The authors had complete control of the data and the information submitted for publication. No conflicts of interest exist.

Diagnostic Imaging and Evaluation
DSA images were acquired using an image intensifier with a field of view of 38 cm and an acquisition matrix of 512 x 512 pixels on either an Integris V3000 (Philips Medical Systems, Best, the Netherlands) or an Angiostar Plus (Siemens Medical Systems, Forchheim, Germany). Catheterization was performed using a 4-F pigtail cath-

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eter (Pigtail, Cordis Europe, Roden, the Netherlands) inserted through a 5-F intro-ducer sheath (Avantis, Cordis Europe, Roden, the Netherlands) in the asymptomatic common femoral artery.

DSA series were obtained at contiguous anatomic levels from the abdominal aorta (at the level just above the renal arteries) down to the level of the ankles. Images were obtained in the anteroposterior projection and were supplemented with addi-tional oblique views if considered necessary. A total of 150-200 mL nonionic contrast material (iomeprol [300 mg I/mL]; Altana Pharma, Hoofddorp, the Netherlands) was injected at a rate of 10–15 mL/sec and a total of 10–20 mL per series, depending on the position of the catheter tip.

In all patients, the invasive arterial pressure gradients over the left and right iliac arter-ies were measured by comparing pressure measurements obtained in the aorta (at the catheter tip) with simultaneous measurements obtained in the femoral introducer sheath and in an additional 4-F sheath inserted in the contralateral femoral artery. Pressure measurements were obtained at rest and during pharmacologic vasodilation induced with 60 mg of intra-arterial papaverine (Papaverine sulfate CF; Centrafarm, Etten-Leur, the Netherlands). A pressure gradient of more than 10 mm Hg during either rest or vasodilation was considered indicative of a hemodynamically significant stenosis.

All angiographic procedures were performed by radiology residents in training with the supervision of one of three interventional radiologists (including P.M.T.P.), each with at least 3 years of post-residency experience. The DSA studies were recorded on film for presentation at our institution's weekly vascular conference.

CT angiography was performed with a four–row multi–detector CT scanner (Somatom Plus 4 Volume Zoom, Siemens Medical Systems). A 120 mL volume of nonionic contrast material (iodixanol [320 mg I/mL]; Amersham Health, Eindhoven, the Netherlands) was administered through a 20-gauge cannula in an antecubital vein at a rate of 4 mL/sec. Spiral acquisitions were performed in a single scanning pass from the level of the celiac trunk down to the ankles; patients were asked to hold their breath during the first part of the scanning pass.

The scan parameters were a pitch of 1.6, 120 kV, 110 effective mA, and a collimation of 4 x 2.5 mm. Scanning was started at a fixed delay of 25 seconds after the start of contrast material injection with an average acquisition time of 35 seconds. In patients with a history of decreased cardiac output, a longer delay time was used. The images were reconstructed with an effective section width of 3 mm and an increment of 1.5 mm by using the smooth algorithm (B20; Siemens). Three data sets with an overlap of approximately 10 cm were created; each contained approximately 250 images.

The images were transferred to two online workstations (Easy-Vision, Philips; and Volume Wizard, Siemens) for the preparation of reconstructions. Sliding maximum intensity projections were obtained with transverse, coronal, and sagittal projections of each dataset. Whole-volume maximum intensity projection reconstructions with segmentation of bone and vessel wall calcifications were obtained. Finally, central lumen line reconstructions were made through the aortoiliac tract.

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All MDCTA acquisitions were performed by dedicated CT technologists. Postprocessing reconstructions were performed by dedicated CT technologists and a dedicated researcher with one year of general radiology residency training and one year of CTA experience (M.C.J.M.K.). The MDCTA studies were recorded on film for presentation at the vascular conference. All MDCTA and DSA images were prospectively interpreted by experienced vascular or interventional radiologists (including P.M.T.P. and M.G.M.H., both with more than 10 years of experience with vascular radiology) and the dedicated researcher (M.C.J.M.K.). The results were reported at the vascular meeting. Results of the stenosis evaluations of MDCTA and DSA are to be published separately.

Therapeutic Confidence and Additional Imaging
The therapeutic confidence was assessed at the weekly vascular conference where therapeutic decisions were made by consensus between three vascular radiologists and four vascular surgeons. Patient history, physical examination, vascular laboratory results, and the findings from the initial imaging test were discussed. Each clinician was asked to rate his/her individual confidence in making a well-founded therapeutic choice with the available diagnostic information. The therapeutic confidence was measured with a 10-point verbal rating scale: "How sure are you that you can make an accountable therapeutic choice with the diagnostic information available now. Give a number on a scale ranging from 0 (absolutely uncertain) to 10 (absolutely certain)". The 10-point rating scale was similar to the 10-point school grading system in our country. On this scale a 5 or lower implies that there is insufficient information to make a therapeutic choice whereas a 6 or higher implies that there is sufficient information to make a therapeutic choice.

Three radiologists (including P.M.T.P. and M.G.M.H.) and four vascular surgeons (including M.R.H.M.v.S. and H.v.U.) completed the confidence forms during the vascular conferences. Their years of experience with diagnosis and treatment of patients with symptomatic peripheral arterial disease varied from 4 to 30 years. The number of physicians who scored a patient's initial images varied from one to five, with a mean of 2.5.

Furthermore, the physicians at the weekly conference determined whether additional imaging tests (duplex ultrasound, DSA, MDCTA or contrast-enhanced magnetic resonance angiography) were necessary. Any additional vascular imaging test performed within 60 days after the initial test and during the 6 month follow-up period was noted. Consensus was always reached with respect to the therapeutic decision (i.e. exercise therapy, vascular interventions (i.e. percutaneous angioplasty, stent placement, and thrombolysis), vascular surgery (i.e. bypass surgery, endarterectomy, amputation, and aortic bifurcation reconstruction)). The confidence scores and information concerning additional imaging needed, additional clinical information, and procedures performed during follow-up were collected during the vascular conference (M.C.J.M.K.).

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Quality of Life
Patient outcome was assessed using a self-administered health related quality of life questionnaire sent to all patients at the time of randomization and after three and six months of follow-up. The questionnaires contained the generic EuroQol–5D (EQ–5D) and the generic Medical Outcomes Study 36-Item Short Form Health Survey (SF–36) (15).

The EQ–5D covers five different health dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) giving 243 different health states. For each patient a single index score was calculated based on a generalized least-squares regression model (16). A single index score of 0 equals death and a value of 1 equals maximum health. The EQ–5D index for the entire follow-up period was calculated as the mean of the EQ–5D index at 3 months and at 6 months. Quality-adjusted days were calculated as the integral under the EQ–5D index graph as function of time.

The SF–36 is a multi-item scale assessing eight dimensions of the health status of the patient (17). Based on a previous study, we determined that four of the eight health dimensions were relevant to describe the health status of PAD (physical functioning, role functioning limitations due to physical problems, bodily pain, and general health perceptions) (18). We assessed these 4 dimensions and the one-item question: change in health during the past year. Each dimension is valued on a 100 point scale, in which 0 means poor quality of life and 100 indicates maximum health. The score for each of the SF–36 dimensions for the follow-up period was calculated as the mean score of that dimension at 3 months and at 6 months.

For each follow-up period we calculated the response rates for the quality of life questionnaires. If one follow-up quality of life score was missing, it was imputed. Linear interpolation was used when the quality of life score at 3 months was missing, and extrapolation was used when the score at 6 months was missing. The calculations regarding quality of life were done according to standard rules for item recoding and treatment of missing items (M.C.J.M.K.) (16, 17).

Cost Analysis
For the cost analysis, we collected information (from a hospital perspective) regarding all relevant items related to health care (both diagnostic and therapeutic) used by each patient during the entire trial to calculate the average cost per imaging strategy per patient. The cost of diagnostic imaging included the initial imaging test and all additional vascular imaging studies but excluded hospital stay for pre-procedural work-up and post-procedural observation. The cost of imaging and the cost of percutaneous vascular interventions (i.e. percutaneous angioplasty, stent placement, or thrombolysis) were collected prospectively during the performance of these procedures. Surgical costs included costs for vascular surgery (i.e. bypass surgery, endarterectomy, amputation, or aortic bifurcation reconstruction). Hospital stay and outpatient visits during 6 months of follow-up were considered separately. The utilizations of these resources were collected from the patient electronic and hardcopy

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medical record, during the vascular conference, and from the patient questionnaires. Since patients were referred to our hospital for tertiary care, all patients received their therapy in our hospital. All costs were computed from the hospital perspective according to the Dutch guidelines for cost calculations in health care (M.C.J.M.K) — cost of primary care, medication, friction costs, time costs and travel costs were excluded (19).

Diagnostic costs included personnel costs, the costs for supplies such as film, the investment costs for the equipment used, costs for equipment servicing, construction costs, costs of supporting departments, housing, and overhead. Personnel costs were computed using the measured time spent on a diagnostic imaging test or a percutaneous intervention for each involved personnel-category and the mean wage rates from our hospital. Social security taxes including premium for retirement of 37% of the wage was added in accordance with national guidelines. The costs for supplies used in diagnostic procedures were based on the sum of the prices of each item used. The annuitized costs 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) (19). Information on costs of supporting departments was obtained from records of our Financial and Economics Department. The costs for housing (being the rental fees paid by the Department of Radiology to the central administration for the use of floor space) 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 MDCTA and DSA were estimated to be 15% of directly assignable costs (19).

The costs of percutaneous vascular interventions were measured and calculated in a similar fashion. For the costs of surgery, we obtained unit costs from another study with a comparable study domain and setting (20) that allowed us to calculate an overall cost per patient per surgical procedure. The number of days of hospital stay and the number of hospital visits were collected, and the associated costs were calculated using national estimates of hospital stay, intensive care unit stay, and outpatient visits (19). All costs were reported in euros at year 2000 prices (the exchange rate was at 0.84 euro per US dollar, November, 2003). The costs of radiological equipment (CT scanners, equipment servicing, construction, and contrast agents) were validated using a small survey of these costs from five different national hospitals (M.C.J.M.K.). Three tertiary care university centers and two secondary care hospitals were interviewed regarding the investment costs of their imaging equipment regarding CT scanners and interventional angiography system.

Statistical Analysis
The required sample size was estimated based on the mean estimated strategy costs per patient. To demonstrate a significant difference between the strategy costs of DSA (estimated to be 520 euros) and the strategy costs of MDCTA (estimated to be 408 euros) with a SD of 180 euros, a power of 0.90, and an alpha level of 0.05 would require at least 54 patients per strategy. The results were analyzed according to the "intention-to-treat" (here intention-to-diagnose-and-treat) principle.

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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 unit costs for the various procedures performed, the diagnostic costs, the therapeutic costs, the costs of hospital stay and outpatient visits, and the total costs for both groups. 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, the Mann-Whitney test for ordinal outcomes, and the paired t test for equality of mean scores within groups over time. In addition, we analyzed the differences in all outcomes adjusted for predictive baseline characteristics with multivariable linear and logistic regression. Based on previous studies (21) and on clinical experience we assumed that severity of disease (critical ischemia vs claudication), renal insufficiency, cerebrovascular disease, and diabetes mellitus at baseline were potentially predictive for the outcomes. In analyzing the improvement in quality of life during follow-up we also adjusted for the baseline quality of life scores. Furthermore, multivariable linear and logistic regression was used to analyze the trends in therapeutic confidence, additional imaging tests, and costs over time during the trial period. For the therapeutic confidence the trend in the results was illustrated by a comparison of means between the first and last 7 months of the study period. We expressed time by the number of days between the start of the trial and randomization of the patient. The outcome of interest was the dependent variable. The independent variables included time, group allocation, and their interaction term. A one-way sensitivity analysis was performed for the investment of radiology equipment using a range (ie, 33% of the equipment investment) for the life expectancy of radiological equipment and a reduction of 3 years (rather than the 10 years of a base-case scenario) and was performed for the costs of housing by using an increase of 100%.

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.

Results

Patient Enrollment
From the 195 eligible patients, we randomized 145: 72 to the DSA group and 73 to the MDCTA group (Figure 1). One patient in the DSA group did not undergo any diagnostic or therapeutic procedures because he emigrated, and he did not have data of any kind available (did not respond to the questionnaires) and therefore all data from this patient were missing. We were able to document the baseline characteristics of all eligible patients, including the 50 patients who were eligible but not randomized. The reasons for not randomizing eligible patients were: patient refusal to participate in the trial (n = 6), communication barrier with the patient (n = 6), physician refusal to randomize the patient (n = 15: due to clinically absent femoral pulsations or the suspicion of accompanying aneurysmatic disease requiring a MDCTA), emergency admission requiring direct referral to the angiography suite (n = 15), logistical problems (n = 6: due to new residents who were not instructed about this trial), and unknown (n = 2). In 26 of these eligible nonrandomized patients, DSA was

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performed and in 24 of these patients, multi—detector row CT angiography was per-
formed. The baseline characteristics of the excluded nonrandomized patients showed
no significant differences compared to the included randomized patients.
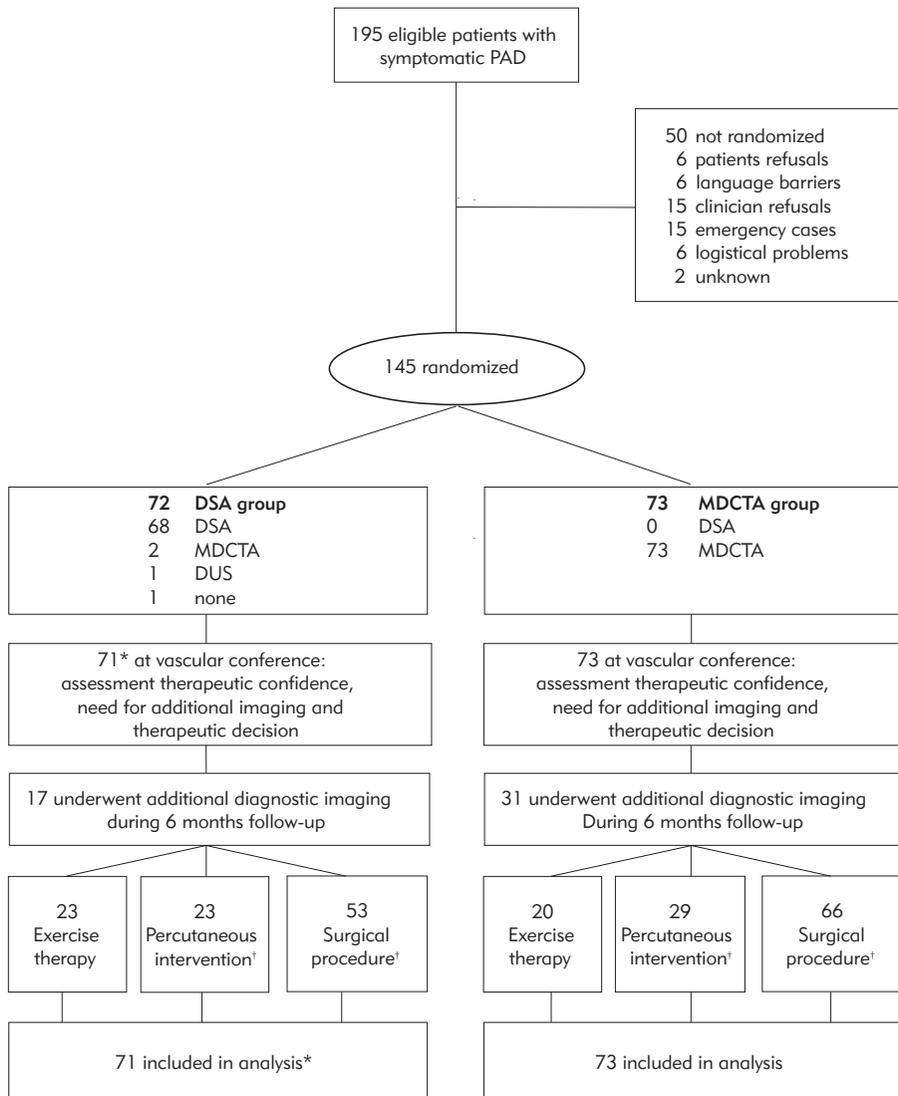


Figure 1. *Flow diagram*

*One patient in the DSA group did not undergo any diagnostic or therapeutic intervention and did not
have data of any kind available (did not respond to the questionnaires) and therefore all data for this
patient were missing.

† Seven patients in the DSA group 7 and eight patients in the MDCTA group underwent a percutaneous
intervention and a surgical procedure.

Baseline characteristics of the participants are given in Table 1. The mean time between randomization and the initial imaging test was 16 days in the DSA group compared to 14 days in the multi—detector row CT angiography group. Three patients in the DSA group did not receive a DSA: in one, the radiologist preferred MDCTA because during preparation for DSA the femoral pulsations could not be located (Figure 2); a second patient changed his mind after randomization and requested MDCTA; and in the third patient, the vascular surgeon preferred duplex ultrasound because the patient was clinically unstable.

Table 1. *Baseline clinical characteristics of the study participants*

Characteristics	DSA (n = 71)[*]	MDCTA (n = 73)[*]
Demographics		
Age, average (SD), y[†]	63 (10)	64 (11)
Male/female (n)	47/24	58/15
General Health History		
Cigarette smoking	49/63 (78%)	59/70 (84%)
Diabetes mellitus	15/59 (25%)	26/68 (38%)
Hypertension	39/69 (57%)	43/68 (63%)
Cerebrovascular disease	10/57 (18%)	18/63 (28%)
Cardiac disease	23/60 (38%)	23/63 (37%)
Renal insufficiency	11/64 (17%)	18/70 (26%)
Hyperlipidemia	40/65 (62%)	33/62 (53%)
Previous revascularization	32/63 (51%)	31/69 (45%)
Amputation	8/63 (13%)	7/69 (10%)
Antithrombotic medication	42/62 (68%)	39/62 (63%)
Ankle/brachial index, symptomatic limb		
At rest[†]	0.68 (0.28)	0.59 (0.26)
After exercise[†]	0.45 (0.30)	0.43 (0.24)
Clinical grade		
Critical ischemia (Fontaine ≥ 4)	24/71 (34%)	28/73 (38%)
Quality of life[†]		
EQ–5D[†‡]	0.40 (0.36)	0.36 (0.36)
SF–36[§]		
Physical functioning	34 (21)	31 (21)
Role functioning (physical)	29 (35)	19 (32)
Bodily pain	38 (19)	34 (20)
Health perceptions	45 (20)	46 (23)
Health change	35 (24)	32 (21)

The denominator has been adjusted for missing data. †Data are given as mean (SD).
‡Index scores = 0–1 (worst–best) scale; responsiveness for the various items ranged from 73 to 75%.
§Dimension scores = 0–100 (worst–best) scale; responsiveness for the various dimensions ranged from 72 to 85%.

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Therapeutic Confidence and Additional Imaging
The mean therapeutic confidence for DSA (8.2) was significantly higher than for MDCTA (7.2, p<0.001). A trend towards increased confidence over time was observed for MDCTA, but for DSA the confidence remained constant over time. The mean confidence was 8.1 and 7.1 in the first half of the study period versus 8.2 and 7.4 in the second half of the study period for DSA and MDCTA, respectively. The difference in confidence between MDCTA and DSA decreased over time, but this decrease did not reach statistical significance. Two DSA examinations could not be performed because the femoral pulsations could not be located. These cases remained in the DSA arm of the study for the analysis in accordance with the intention-to-(diagnose-and-) treat principle. All MDCTA examinations were technically adequate, although in two patients the venous return in the lower extremities made the evaluation more difficult albeit still possible (with confidence scores of 7.2 and 7.8). Four MDCTA examinations were technically adequate but due to heavy general vessel wall calcifications evaluation was hampered and the physicians rated these with a mean confidence lower than 5, despite post-processing with segmentation of the calcifications.

Within 60 days after the initial test, 11 patients in the DSA group compared to 22 patients in the MDCTA group received additional imaging tests (p = 0.04). With adjustment for predictive variables at baseline and trial period, a similar result was found. During the total follow-up of 6 months, 17 patients in the DSA group compared to 31 patients in the MDCTA group received additional imaging tests (p = 0.02). In the DSA group, 7 patients underwent one additional test, compared to 22 patients in the MDCTA group. Eight patients in both groups underwent two tests, one patient in both groups underwent three tests, and one patient in the DSA group underwent four additional imaging tests (p = 0.06). On average less additional imaging tests per patient were performed in the DSA group than in the MDCTA group (0.42 vs 0.56, difference 14% (95% CI -14% to 30%, p = 0.3). We observed a small decrease in the number of additional imaging tests performed during the trial period but this was not significant (p = 0.12) and there was no difference in the trend between the groups (p = 0.3).

Quality of Life
The response rate of the quality of life questionnaires was 91% (131/144) at baseline, 68% (98/144) at 3 months, and 63% (91/144) at 6 months follow-up.

The quality of life assessed with the EQ–5D questionnaire at baseline and follow-up was not significantly different between the two groups. The improvement in the EQ–5D index from baseline to follow-up (Table 2) was slightly larger in the MDCTA group (0.11, 95% CI 0.01 to 0.21) than in the DSA group (0.07, 95% CI -0.02 to 0.16) but there was no statistically significant difference between the groups without and with adjustment for baseline scores and potentially predictive variables.

Figure 2. *Peripheral MSCT angiogram of a 49-year old male patient with absent femoral pulsations due to the Leriche syndrome. A coronal volume maximum intensity projection shows a complete occlusion of the abdominal aorta and both iliac arteries and collateral arterial supply via enlarged epigastric arteries in the abdominal wall (arrowheads), superficial iliac circumflex arteries (arrows), and superficial external pudendal artery (curved arrow).*

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Table 2. *Mean Improvement in the EQ–5D Index and Selected SF–36 Domains during Follow-Up Compared to Baseline and Differences (Unadjusted and Adjusted) between the Two Groups*

Measure of Quality of Life	Mean Score Improvement (95% CI)[*]		Unadjusted Mean Difference (95% CI)[∥]	Adjusted Mean Difference (95% CI)[† ∥]
	DSA (n = 71)	MDCTA (n = 73)		
EQ–5D[‡]				
	0.07 (-0.02 to 0.16)	0.11 (0.01 to 0.21)	0.04 (-0.10 to 0.17)	0.07 (-0.04 to 0.19)
SF–36[§]				
Physical functioning	6 (-1 to 14)	9 (3 to 16)	3 (-7 to 13)	5 (-6 to 16)
Role functioning (physical)	-1 (-13 to 12)	6 (-5 to 16)	6 (-10 to 22)	11 (-4 to 26)
Bodily pain	7 (-1 to 15)	11 (3 to 19)	4 (-7 to 15)	7 (-4 to 19)
Health perceptions	-5 (-10 to 0)	-4 (-9 to 1)	1 (-6 to 8)	4 (-4 to 11)
Health change	8 (-2 to 18)	12 (3 to 21)	4 (-9 to 17)	9 (-4 to 22)

[*] *The response rate of the quality of life questionnaires was 91% (131/144) at baseline, 68% (98/144) at 3 months, and 63% (91/144) at 6 months follow-up. Positive number indicates improvement and negative number indicates worsening during follow-up compared to baseline.*

[†] *Adjusted for baseline quality of life score, and for severity of disease (critical ischemia vs. claudication), renal insufficiency, cerebrovascular disease, and diabetes mellitus at baseline.*

[‡] *Index scores = 0–1 (worst–best) scale.*

[§] *Dimension scores = 0–100 (worst–best) scale.*

[∥] *Positive difference indicates that the MDCTA group has a larger quality of life improvement than the DSA group, and vice versa.*

The mean quality-adjusted days over the course of 183 days of follow-up was 80 (SD 51) for the DSA group, compared to 86 (SD 49) for the MDCTA group—not a statistically significant difference (p = 0.67).

The mean quality of life assessed with the SF–36 at baseline and follow-up was not significantly different between the groups. The improvement in SF–36 dimensions from baseline to follow-up (Table 2) was not statistically significant for the DSA group: the largest improvement occurred in the dimension "health change" (8, 95% CI -2 to 18). In the MDCTA group, however, a significant improvement from baseline to follow-up was demonstrated for three dimensions — physical functioning: 9 (95% CI 3 to 16, p = 0.006); bodily pain: 11 (95% CI 3 to 19, p = 0.006); and health change: 12 (95% CI 3 to 21, p = 0.007). With and without adjustment for baseline scores and predictive variables we found a slightly larger improvement in quality of life for all SF36 dimensions in the MDCTA group (Table 2) but the difference between the groups was not statistically significant.

Cost Analysis
The mean unit cost of the individual imaging tests (excluding hospital stay) was 526 euros for all DSAs (range 493 to 568 euros with sensitivity analysis), and 203 euros for all MDCTAs (range 185 to 233 euros) (Table 3). For the additional imaging tests, the mean unit cost for all contrast-enhanced magnetic resonance angiography tests was 429 euros (range 367 to 509) and 37 euros for all duplex ultrasound tests (range 35 to 40).

The total diagnostic costs over the trial period averaged 564 euros (SD 210) per patient in the DSA group and 363 (SD 273) in the MDCTA group, which represents a significant cost-reduction of 201 euros (95% CI 120 to 281, p < 0.0001; Table 3). This reduction was achieved in spite of the fact that more additional imaging tests were performed following MDCTA. With adjustment for predictive variables, a similar cost-reduction was demonstrated (174, 95% CI 82 to 267, p = 0.0003).

The small survey on costs of equipment investment, service contract, construction, and contrast agents showed that our unit costs were within the range of that in other hospitals. One-way sensitivity analysis for the mean diagnostic costs per image strategy demonstrated a range of 527 to 610 euros in the DSA group and 333 to 402 euros in the MDCTA group.

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Table 3. *Mean unit costs (and range*) of diagnostic and therapeutic procedures and the number of procedures on which the cost estimate is based and mean unit cost for hospital and outpatient visits.*

Procedure	n	Mean cost (Euro)	Range in cost (Euro)
Diagnostic procedures			
DSA (excluding hospital stay[§])	98	526	493 - 568
MDCTA	82	203	185 - 233
CEMRA	3	429	367 - 509
Duplex ultrasound	39	37	35 - 40
Interventional procedures			
Angioplasty	30	662	NA[II]
Stent procedures	19	1983	NA[II]
Fibrinolytic procedures	4	2178	NA[II]
Surgical procedures			
Aorta bifurcation	11	6979	NA[II]
Bypass surgery	41	2000	NA[II]
Local desobstruction	19	1664	NA[II]
Amputation procedure	49	437	NA[II]
Hospital stay and visits			
One day hospital stay	NA[†]	319	NA[II]
One day intensive care	NA[†]	1093	NA[II]
Outpatient visit	NA[†]	69	NA[II]

*A one-way sensitivity analysis of the costs of diagnostic procedures was performed for the investment in radiology equipment using a range (i.e., plus or minus 33% of the equipment investment) for the life expectancy of radiological equipment and a reduction of 3 years (rather than the 10 years of a base-case scenario) and for the costs of housing using an increase of 100%.

[§] Excluding hospital stay for pre-procedural work-up and post-procedural observation.

NA[II] not available, sensitivity analysis was not performed.

NA[†] not available, unit cost for outpatient visits and hospital admissions were obtained from the Dutch guidelines for cost-analysis. Based on reference 19.

The number of treatment procedures performed was similar for both groups for each type of procedure. One third of the patients in each group was assigned walking exercise therapy. The mean cost for all percutaneous vascular interventions for PAD was similar for the groups (difference, 3 euros, 95% CI -354 to 361; Table 3). With adjustment for predictive variables, the average cost for percutaneous interventions was 152 euros (95% CI -196 to 500) higher in the MDCTA group compared to the DSA group. The average cost for surgical procedures was lower in the MDCTA group (-€ 181; 95% CI: -972, 610). With adjustment for predictive variables, this cost difference was -€ 968 (95% CI: -1957, 20).

Table 4. *Mean Costs of the Diagnostic Strategies during 6 Months of Follow-Up and Differences (Unadjusted and Adjusted) between the Two Groups*

Cost component*	Mean Cost (SD)[†]		Unadjusted Mean Difference (95% CI)[‡]	Adjusted Mean Difference (95% CI)[‡§]
	DSA (n = 71)	MDCTA (n = 73)		
Diagnostic procedures (excluding hospital stay)	564 (210)	363 (273)	-201 (-281 to -120)	-174 (-267 to -82)
Percutaneous interventions	516 (1251)	519 (894)	3 (-354 to 361)	152 (-196 to 500)
Surgical procedures	1564 (2722)	1383 (2042)	-181 (-972 to 610)	-968 (-1957 to 20)
Hospital stay and visits	2825 (3358)	5031 (7385)	2206 (214 to 4197)	428 (-1587 to 2443)
Total costs	5468 (5294)	7296 (8951)	1827 (-604 to 4259)	-562 (-3218 to 2094)

* *Only costs related to the diagnosis and treatment of PAD were included.*

[†] *Purchasing power in euros for the year 2000.*

[‡] *Negative cost difference indicates that MDCTA is less costly than DSA.*

[§] *Adjusted for severity of disease (critical ischemia vs claudication), renal insufficiency, cerebrovascular disease, and diabetes mellitus at baseline.*

The hospital admission and outpatient visits for PAD was 2206 euros (95% CI 214 to 4197) more costly in the MDCTA group, which was statistically not a significant difference when considering the multiple comparisons that we performed ($p = 0.03$). In three patients the costs of hospital stay and visits were more than 28000 euros (8 times more than the average costs), and all three were in the MDCTA group. After adjustment for predictive variables at baseline (in this case disease severity (critical ischemia vs claudication), renal insufficiency, cerebrovascular disease, and diabetes mellitus), the cost for hospital admission and outpatient visits was only 428 euros (95% CI −1587 to 2443) more in the MDCTA group.

The total costs were 1827 euros (95% CI −604 to 4259) more in the MDCTA group. With adjustment for predictive variables, the situation reversed and the total costs were higher in the DSA group (562 euros, 95% CI −3218 to 2094) but the differences with and without adjustment were not significant.

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Over time during the trial, the trends in costs for diagnostic tests, percutaneous interventions, surgical procedures, costs of hospital stay, and total costs were not statistically significant and these trends were not statistically different between the groups.

Discussion

To evaluate the clinical implications of a diagnostic strategy we performed a pragmatic randomized controlled trial (13). We assessed the clinical utility, the patient outcomes (quality of life), and the overall costs of the diagnostic work-up, treatment procedures, and hospital stay and visits.

MDCTA provided lower but in most cases sufficient therapeutic confidence than the current reference standard, DSA. Despite there being more additional imaging performed, MDCTA reduced the diagnostic costs for the imaging work-up and did not result in discernible additional therapeutic costs or costs for hospital stay and visits. Furthermore, there was no loss in quality of life compared to DSA – in fact, a slightly larger improvement during follow-up in all quality of life measures was demonstrated in the MDCTA group. Our results suggest that DSA can be replaced by the new MDCTA as initial imaging test for the evaluation of PAD prior to revascularization.

We found that the therapeutic confidence for DSA was higher than that for MDCTA. However, the therapeutic confidence for MDCTA was shown to be sufficient to enable therapeutic decisions in the majority of cases. When the confidence was insufficient after DSA or MDCTA, additional imaging could be performed in order to increase physician confidence to make a well-founded clinical decision. We demonstrated that physicians requested additional imaging tests in the MDCTA group more frequently than in the DSA group, presumably due to the lower confidence in MDCTA.

Low confidence in MDCTA occurred particularly in cases with extensive vessel wall calcifications. A calcified vessel wall indicates severe disease, but this feature can be an impediment to stenosis measurement (22) and, therefore, can result in a lower confidence score. DSA has the advantage that it can provide hemodynamic information for the stenosis; this information is often used as the ultimate standard in clinical practice. When physicians were uncertain about the degree of the stenosis depicted with MDCTA, an additional DSA was performed to verify the stenosis with pressure measurements. Nevertheless, despite the additional testing needed for confident therapeutic decision making in some MDCTA-imaged patients, the additional cost needed to provide sufficient information in those cases where MDCTA did not provide enough information on its own was less than the extra cost needed to perform DSA as standard procedure in everyone. In other words, a diagnostic pathway beginning with MDCTA is overall less costly than one beginning with DSA, despite the higher rate of additional imaging needed. The confidence of therapeutic decisions made on the basis of the imaging tests is considered in more detail in the next chapter (Chapter 6) (23).

The results of the quality of life questionnaires demonstrated no statistically significant differences in patient outcomes between the two groups. This suggests that MDCTA

is likely to have accurately identified the disease, as is to be expected given the studies which have shown MDCTA to be accurate. As a general rule, if the interventional radiologist and vascular surgeon were unable to determine the extent and location of disease correctly using MDCTA plus additional testing as needed, the patient would not have been treated correctly, and his symptoms are likely to have remained or worsened, which would have been reflected by a lower quality of life during follow-up. In fact, patients in the MDCTA group reported a slightly larger gain in quality of life during follow-up. This could imply that patients undergoing MDCTA had a slight advantage, but because the MDCTA group had lower reported quality of life at baseline, they also had more to gain with treatment. We adjusted the improvements in quality of life for the baseline scores and potentially predictive variables and found that the difference in improvement was even larger in favor of the MDCTA group but the difference was still not significant.

The mean diagnostic cost in the MDCTA group was lower than in the DSA group even though additional imaging was performed more frequently during the total follow-up period. This is explained by lower costs of the initial imaging test. MDCTA is less expensive than DSA due to lower investment costs, costs for supplies, and personnel costs.

MDCTA as initial test did not alter clinical decisions with respect to treatment of symptomatic peripheral arterial disease in any major way. This is reflected by the fact that, after adjustment, we demonstrated no difference in the therapeutic costs in the two arms of the study. The data on therapeutic costs, however, should be interpreted with caution since the study lacked the power to make hard conclusions in this area.

The unadjusted mean cost for hospital stay and visits was demonstrated to be 2206 euros lower for the DSA group, but the difference was not statistically significant. Severity of disease (critical ischemia vs claudication), renal insufficiency, cerebrovascular disease, and diabetes mellitus increased the cost of hospital stay and visits substantially and with adjustment for these predictive baseline variables, the large difference between the costs in the DSA and MDCTA groups disappeared. It seems plausible that when wound healing is hampered, e.g. in the case of diabetes mellitus, or when mobilization is difficult, e.g. in the case of cerebrovascular disease, the duration of hospital stay and the necessary care increases and therefore the cost of hospital stay and visits increases. In fact, three patients had extremely high costs related to their hospital admission and outpatient visits. At baseline all three patients suffered from critical ischemia, had a positive history for cerebrovascular disease, cardiac disease, diabetes mellitus, smoking, hyperlipidemia, and hypertension, and one of these patients additionally had severe renal insufficiency. Thus, all three had an extremely poor clinical status prior to randomization and their recovery and rehabilitation was therefore long and costly. Although these three patients were in the MDCTA-arm of the study, it seems highly unlikely that the high costs are the result of the choice of initial imaging modality – these patients would probably have amassed similar hospital costs if they had been randomized to the DSA group.
Because the results of all vascular imaging tests in our hospital are always discussed

prior to revascularization at the weekly (interdisciplinary) vascular conference, we were able to trace all eligible patients (randomized and non-randomized). One reason for non-randomization was clinical absence of femoral pulsations making femoral catheterization impossible. Although brachial catheterization may have been possible, this involves an increased risk (4). In such cases MDCTA is a safe and robust alternative to DSA and was used to evaluate the patients. The baseline characteristics of the randomized patients and the non-randomized patients were comparable, indicating that bias in the selection of the patients was unlikely. This indicates that our results can be generalized to the entire population of patients presenting with intermittent claudication or critical limb ischemia without contraindications for MDCTA.

Comparative studies of MDCTA for the complete peripheral arterial system have reported a sensitivity between 91-92%, a specificity between 92-97%, and an agreement with DSA ranging from 78% to 92% (7, 9, 10). These results are, however, difficult to translate into patient outcomes and patient-management decisions which requires either a decision analysis or a randomized controlled trial (12). Randomized controlled trials are not frequently used to compare diagnostic tests (24-29, 30). Contrary to what opponents of randomized controlled trials argue, we found this pragmatic randomized trial to be both feasible and inexpensive (13, 31).

Limitations of our study included the lack of all data for one patient who could therefore not be analysed (32). Although patients were randomized, baseline characteristics could have biased the outcomes both in the case where there was a large imbalance in baseline characteristics, each with a small effect on outcome, and in the case where there was a minor imbalance in baseline characteristics, each with a strong effect on outcome. Therefore, multivariable linear and logistic regression was used to adjust for potentially predictive variables (33-35).

Furthermore, the clinicians could not be blinded for group allocation, since the images produced by MDCTA and DSA are clearly different. Subjective attitudes may have influenced the assessment of scoring the therapeutic confidence, but we attempted to adjust for this by normalizing the scores across physicians. A possible shortcoming is that we focused on quality of life as measure of effectiveness and did not assess functional outcomes such as the ankle-brachial systolic blood pressure index and walking distance. Although quality of life outcomes are sometimes perceived to be soft data due their subjectivity, as opposed to outcomes that provide quantitative hard data, they do reflect the outcome most important to the patient. In this we are consistent with the recommendations given by the recent Transatlantic Inter-Society Consensus on peripheral arterial disease which states that quality of life is the most important primary endpoint (21).

Although the therapeutic and hospital costs varied considerably between individual patients in our study population–some patients underwent exercise therapy, while others underwent expensive interventional or surgical revascularizations, or had a delayed recovery or prolongued rehabilitation–no significant differences between the

groups could be demonstrated. A study with a larger sample size, however, would be necessary to demonstrate differences in therapeutic costs or make equivalence plausible. Another important limitation of our findings is that the costs reported may be unique to our institution and thus not applicable to other settings. Since they could be subject to the setting, we compared our cost estimates with two other national university hospitals and two national private hospitals. We found our costs to be within the range of costs in other settings. Furthermore, we analyzed the effect of uncertainty in the cost estimates by performing a one-way sensitivity analysis. Varying the costs of equipment (the life years of equipment, the costs of construction, and the costs of housing) did not affect our conclusions. In addition, in our clinic all patients first undergo diagnostic imaging whereas in other settings percutaneous intervention may immediately follow DSA in the same session when warranted.

We make exceptions only in emergency situations, when a patient may be treated directly following diagnostic DSA but this was an exclusion criteria for our study. Our vascular surgeons and interventional radiologists prefer to discuss each case at the weekly conference with the entire team and carefully choose and plan treatment. The cost of the DSA arm would be reduced if diagnosis and therapy are combined in a single session where possible. It is impossible to predict whether this would be enough of a reduction to reverse the conclusions of this study. The amount of any such reduction will depend strongly on the percentage of patients who would have a combined diagnostic-treatment session and the average reduction in cost per patient, which will vary per hospital.

Furthermore, in calculating the diagnostic imaging costs, we excluded the costs for hospital stay for the preprocedural work-up and postprocedural observation because we chose to focus on the costs incurred by the radiology department for this cost outcome; this exclusion resulted in a underestimation the actual cost difference between DSA and MDCTA. In spite of this underestimate, we still found the difference to be statistically significant. Finally, since costs were analyzed from the hospital perspective, cost of primary care, patient costs, friction costs, time costs, travel costs, and cost of medication supplied outside the hospital were excluded. We did not expect that these costs would differ between the two groups eg. almost every patient used thrombocyte aggregation inhibitors and many were on lipid lowering medication and these did not differ between the groups.

In comparison to other non-invasive techniques, MDCTA can depict the entire arterial system of the legs, is inexpensive, and is a fast and robust scanning technique. Furthermore, MDCTA is rapidly becoming widely available. Other non-invasive techniques, i.e. duplex ultrasound and contrast-enhanced magnetic resonance angiography, have the advantage of not using radiation but this should be assessed in relation to the age of the patient population with peripheral arterial disease. Although duplex ultrasound has been useful in evaluating selected arterial segments, the assessment of the entire lower extremity arterial tree remains an arduous task, is associated with a lower sensitivity and specificity, and does not provide a roadmap (20). Contrast-enhanced magnetic resonance angiography is increasingly being used in patients

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with PAD, especially in patients with chronic renal insufficiency. Magnetic resonance angiography is, however, not widely available and requires expensive equipment investments, skilled personnel, and more time for imaging.

Our randomized trial suggests that it is feasible to replace DSA with MDCTA as initial imaging test for the evaluation of peripheral arterial disease. MDCTA as initial imaging test for the evaluation of peripheral arterial disease provides sufficient information for decision making, reduces imaging costs, leads to similar costs for therapy, hospital stay, and outpatient visits, and leads to similar quality of life improvement compared to DSA.

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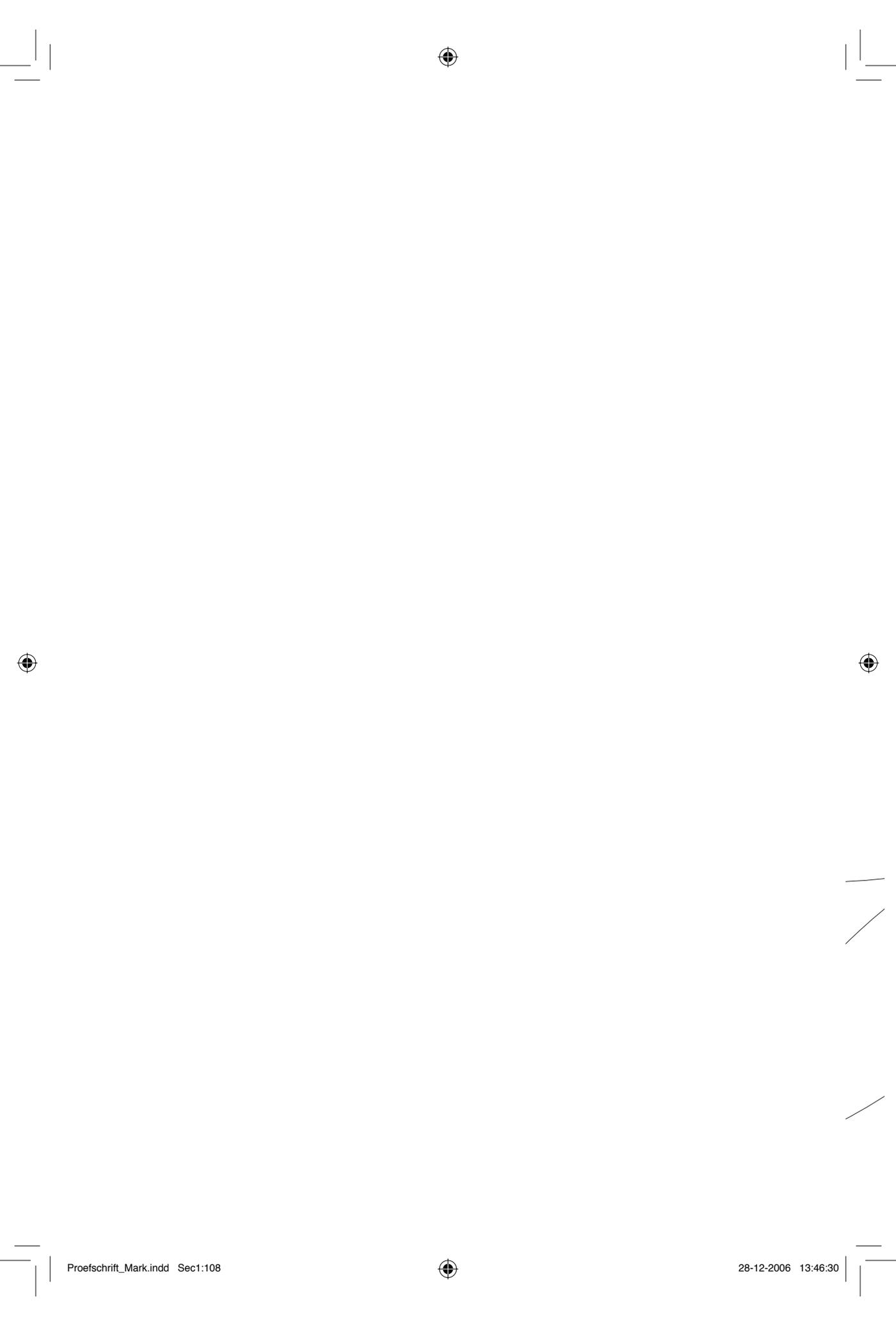
Chapter 6
Therapeutic Impact of Multi-detector Row CT Angiography and Digital Subtraction Angiography

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Abstract

Purpose: To compare multi–detector row CT angiography (MDCTA) and digital subtraction angiography (DSA) prior to revascularization in patients with symptomatic peripheral arterial disease for the purpose of assessing recommendations for additional imaging and physician confidence ratings for chosen therapy.

Materials and methods: In a randomized controlled trial, 73 patients were assigned to MDCTA, and 72 were assigned to DSA. Physician confidence in the treatment decision was measured as a continuous outcome on a scale of 0–10 (uncertain to certain) and as a dichotomous outcome (further imaging recommended, yes or no). Mean confidence scores and additional imaging recommendations were compared between MDCTA and DSA groups in an intention-to-diagnose-and-treat analysis. To detect trends in confidence, confidence scores were plotted over time, and multiple linear regression analysis was performed. To detect trends in additional imaging recommendations, logistic regression analysis was used. Data from eligible nonrandomized patients were analyzed separately.

Results: No statistically significant difference in baseline characteristics between randomized groups was found. MDCTA had a lower confidence score than did DSA (7.2 vs 8.2, p < 0.001). Further imaging was recommended more often after MDCTA (25 of 71 patients, 35%) than after DSA (nine of 66 patients, 14%; p = 0.003). Analysis of trends demonstrated increasing (but not statistically significant) confidence in MDCTA and stable confidence in DSA. No significant difference was found in baseline characteristics between randomized and nonrandomized patients. Among nonrandomized patients, no significant difference in mean confidence score (8.2 vs 8.3, p = 0.26) was found between MDCTA (n = 24) and DSA (n = 26).

Conclusion: With MDCTA, physician confidence decreases with an associated increase in additional imaging prior to revascularization in patients with symptomatic peripheral arterial disease. Given that MDCTA is less invasive than DSA; results suggest that MDCTA may replace DSA in selected cases.

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Introduction

Prior to revascularization, intra-arterial digital subtraction angiography (DSA) is standard practice in the diagnostic work-up of patients with symptomatic peripheral arterial disease (1,2). Approximately 12500 patients in the Netherlands undergo this work-up annually (3). DSA has several serious drawbacks, however. It requires catheterization with intra-arterial injection of contrast medium, which may cause patient morbidity, and it is time consuming for the patient because it requires postprocedural monitoring.

Multi–detector row computed tomographic (CT) technology has made a number of new CT applications possible (4). One of these, multi–detector row (MDCTA), is a minimally invasive method of visualizing the vascular system as an alternative to DSA. MDCTA does not require catheterization and intra-arterial injection of contrast medium and therefore causes less patient morbidity than DSA. It is also quicker because it requires no postprocedural monitoring. If MDCTA can provide all the information necessary to determine which revascularization procedure to perform in a patient with symptomatic peripheral arterial disease, CT could replace DSA in the diagnostic work-up of these patients. MDCTA is a relatively new procedure and physicians may thus be less experienced with it, have less confidence in it, and recommend additional imaging more frequently than they would with DSA.

The hierarchical approach to assessment of new diagnostic imaging technology entails assessment of technical performance, diagnostic accuracy, effect on clinical decision making, and effectiveness and cost-effectiveness of the new technology (5,6). Technical performance and diagnostic accuracy of MDCTA for peripheral arterial disease have been reported (7–13). Prior to implementation of MDCTA for assessment of peripheral arterial disease on a wide scale, knowledge is also required about its effect on clinical decision making—that is, confidence in diagnosis and therapeutic decision making (5,14–19)—and the effect on patient outcomes and costs (5,6).

We performed a randomized controlled trial to evaluate how MDCTA used in the assessment of peripheral arterial disease affects clinical decision making, quality of life, and cost. In this study, our purpose was to compare MDCTA and DSA with regard to recommendations for additional imaging and physician confidence ratings for the chosen therapy. To report our findings, we applied the Standards for Reporting of Diagnostic Accuracy (STARD) and the revised Consolidated Standards Of Reporting Trials (CONSORT) recommendations, as appropriate (20,21).

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Materials and methods

Study Design, Patient Population, and Randomization

We performed a pragmatic randomized controlled trial (6,22). The institutional review board of Erasmus MC approved the study protocol, and all randomized patients gave informed consent. Those eligible for the trial were adult patients with symptomatic peripheral arterial disease who presented to the Department of Vascular Surgery of our medical center from April 2000 until August 2001. The patients were candidates for percutaneous or surgical intervention and normally would have undergone DSA. Our medical center is an academic hospital and a secondary and tertiary referral center. After patients gave informed consent, they were randomly allocated to one of two diagnostic strategies. The diagnostic strategies were defined by the initial imaging modality, either MDCTA or DSA. After the initial imaging examination, any additional imaging methods desired could be used with both strategies. Patients were block randomized with a block size of six. An independent statistician prepared the randomization list. The allocation sequence was concealed by means of sealed and numbered opaque envelopes. Research nurses who were not involved in patient care and who were unaware of the allocation sequence enrolled the patients.

Imaging Modalities

Intra-arterial DSA

DSA was performed by using a standardized protocol with equipment from two manufacturers (Integris V3000, Philips Medical Systems, Best, the Netherlands; or Angiostar Plus, Siemens Medical Systems, Forchheim, Germany). The procedures were performed by radiology residents in training with the supervision of one of three interventional radiologists (including P.M.T.P.) with at least 3 years of postresidency experience.

Aortic flush series were obtained by using a 4-F pigtail catheter inserted through a 5-F introducer sheath in the left or right femoral artery. DSA series were obtained at contiguous anatomic levels from the abdominal aorta (at the level of the renal arteries) down to the level of the ankles. Images were obtained in the anteroposterior projection and were supplemented with additional oblique views if considered necessary.

Injection rates for nonionic contrast material (Iomeron 300; Altana Pharma, Hoofddorp, the Netherlands) (iodine concentration of 300 g/L) were 10–15 mL/sec for a total of 10–20 mL per series, depending on cardiac output and the position of the catheter tip. Typically, 150–200 mL was used per patient. DSA images were obtained by using an image intensifier 38 cm in diameter with a 512 x 512 acquisition matrix. In all patients, the invasive arterial pressure gradients over the left and right iliac arteries were measured by comparing pressure measurements obtained in the aorta (at the catheter tip) with simultaneous measurements obtained in the femoral introducer sheath and in an additional 4-F sheath inserted in the contralateral femoral artery. Pressure measurements were obtained at rest and during pharmacologic vasodilation induced with 60 mg of intra-arterial papaverine (Papaverinesulphate CF [50 mg/mL]; Centrafarm, Etten-Leur, the Netherlands). A pressure gradient of more than

10 mm Hg during either rest or vasodilation was considered indicative of a hemodynamically significant stenosis.

Multi–detector row CT angiography
MDCTA was performed with a multi– detector row CT scanner (Somatom Plus4 Volume Zoom; Siemens). The procedures were performed by dedicated CT technologists. A total volume of 120 mL of nonionic contrast material (Visipaque [320 mg/mL]; Amersham Health, Eindhoven, the Netherlands) with an iodine concentration of 320 g/L was injected in an antecubital vein by using a power injector at a monophasic flow rate of 3 mL/sec. Spiral acquisitions in a single examination began at the level of the celiac trunk and ended at the ankles. The scan parameters were pitch of 7, tube current of 110 mAs (120 kV), and 3-mm sections acquired with 4 x 2.5-mm collimation.

Scanning was started 25 seconds after the start of contrast material injection (fixed delay time). The acquisition time was 35 seconds, on average. In patients known to have impaired cardiac output, a longer delay time was used. The images were reconstructed with an increment of 1.5 mm and an effective section width of 3 mm by using the smooth algorithm (B20; Siemens), which resulted in three overlapping data sets of approximately 250 images each. The images were transferred to an online workstation (Easy-Vision, Philips; or Volume Wizard, Siemens) for the preparation of reconstructions.

Sliding maximum intensity projections were obtained with transverse, coronal, and sagittal projections. Whole-volume maximum intensity projection reconstructions with segmentation of bone were obtained. If the aortoiliac arteries were highly calcified, we made additional volume maximum intensity projection reconstructions of these arteries with segmentation of both bone and calcified plaque. Finally, central lumen line reconstructions were obtained in the aortoiliac arteries.

Data Collection and Analysis
We analyzed the data according to the intention-to-diagnose-and-treat principle, which implies that patients belong to the group to which they were assigned by means of randomization, regardless of the actual (sequence of) events surrounding diagnosis and treatment.

Baseline patient characteristics and statistical analysis
At the time of patient inclusion, research nurses obtained baseline characteristics (ie, age, sex, and risk factors) of each patient from the patients themselves, from medical records, and from the hospital information system. To verify that randomization resulted in comparable groups, we compared baseline characteristics of the MDCTA group with those of the DSA group. For dichotomous variables we used the chi-square test, and for continuous variables we used the two-sample t test.

For regression analyses, we calculated one comprehensive variable for the risk factor profile of a patient by counting his or her total number of risk factors. Risk factors

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were male sex, current smoking status, diabetes mellitus (i.e., non–insulin dependent diabetes mellitus or insulin-dependent diabetes mellitus), hypertension (i.e., diastolic blood pressure > 90 mm Hg and/or use of antihypertensive medication), use of anticoagulants (i.e., coumadin or aspirin), coexisting cardiac disease (i.e., myocardial infarction, angina pectoris, chronic heart failure and/or decompensatio cordis, percutaneous transluminal coronary angioplasty, coronary artery bypass graft), coexisting cerebrovascular disease (i.e., transient ischemic attack, reversible ischemic neurologic deficit or cerebral infarction), hyperlipidemia (i.e., cholesterol level > 5.0 mmol/L and/or use of lipid-lowering agents), renal insufficiency (serum creatine level > 130 μmol/L and/or dialysis), and previous surgical and/or radiologic intervention for peripheral arterial disease.

Therapeutic confidence and statistical analysis
We measured the therapeutic confidence of staff physicians during a weekly meeting of vascular surgeons and radiologists (hereby referred to as "the vascular conference"). All DSA and CT angiographic images were interpreted by experienced vascular or interventional radiologists (usually P.M.T.P. and M.G.M.H., each with more than 10 years of experience). At the vascular conference, physicians were shown volume maximum intensity projections with bone segmentation and, if necessary, with segmentation of calcified plaque, sliding of maximum intensity projections in several projections, and central lumen line reconstructions. Presentation of DSA images at the vascular conference included hemodynamic information. After reviewing the information and images, each physician was asked to complete a confidence form independently. The therapeutic confidence was measured with the following verbal rating scale (translated from Dutch): "How sure are you that you can make an accountable therapeutic choice with the diagnostic information available now? Give a number on a scale from 0 (absolutely uncertain) to 10 (absolutely certain)."

Three radiologists (including P.M.T.P. and M.G.M.H.) and four vascular surgeons (including M.R.H.M.v.S. and H.v.U.) completed the confidence forms during the vascular conferences. Their years of experience with diagnosis and treatment of patients with symptomatic peripheral arterial disease varied from 4 to 30 years. The number of physicians who scored a patient's initial images varied from one to five, with a mean of 2.5. Each score given by a physician with regard to a single patient was considered a separate data point. Raters tend to use scales differently as a result of different attitudes toward numeric data. Furthermore, not all raters evaluated all cases.

To adjust for variability in interpretation, we therefore normalized scores for each physician by subtracting that physician's mean score from the individual score and then dividing by that physician's standard deviation. To make it conceptually easier, we transformed the normalized scores back to the 0–10 scale. Through visual inspection of the scatter plot, we detected outliers in the confidence score that were all more than 3 standard deviations away from the mean and were excluded from the main analysis. We compared physician confidence in MDCTA and DSA at several levels: the mean scores of all physicians per patient, the mean scores per patient per specialty (radiologists vs vascular surgeons), and the individual physician scores. We

compared the mean score in the MDCTA group with that in the DSA group by using the two-sample t test.

To detect trends in confidence, we plotted the confidence physicians had in CT and DSA over time, and we made separate graphs for the radiologists, the vascular surgeons, and each physician who scored more than one-third of all diagnostic tests. We expressed time by ranking the dates of the vascular conferences at which a confidence form was completed. To detect trends in confidence over time, we also used multiple linear regression analysis. The outcome of interest (ie, the dependent variable) was the confidence score. Two different models were fitted. In the first model, the independent variables were the diagnostic test, time (ranking), and the interaction term between them. In the second model, we included patient characteristics (ie, age, risk factor profile, and symptoms at presentation [critical ischemia vs claudication]) with the variables in the first model.

Recommendations for additional imaging and statistical analysis
Recommendations for additional imaging were measured with the second part of the confidence form, on which we listed possibilities for further diagnostic testing or treatment and requested that the physician indicate the best next step for the patient. We analyzed the recommendations for additional imaging as a dichotomous outcome—namely, additional diagnostic imaging recommended, yes or no. Because each physician completed the confidence form independently and individual physicians did not always agree on the best next step for a particular patient, all physicians had to recommend additional imaging (strict criterion) before we counted this as a recommendation for additional imaging in the analysis. We used this strict criterion before including a recommendation for additional imaging in the analysis because if all physicians wanted more diagnostic imaging to be performed, then the patient would surely undergo another imaging test.

To compare recommendations for additional imaging between the MDCTA group and the DSA group, we used the chi-square test. To detect trends in recommendations for additional imaging, we used logistic regression analysis. The outcome of interest (the dependent variable) was additional imaging recommended versus not recommended. As with the analysis of the confidence scores, we fitted two different hierarchical models with the same independent variables.

Sensitivity analyses
To check the internal consistency of our results, we analyzed the association of the dichotomous outcome (additional imaging recommended, yes or no) with the continuous outcome (confidence score). We calculated the mean confidence scores for all cases in which additional imaging was recommended and for all cases in which additional imaging was not recommended. To compare the mean confidence scores (ie, additional imaging recommended vs not recommended), we used the two-sample t test. To investigate how robust our results were, we performed a per-protocol analysis. In this analysis, the MDCTA group and the DSA group were defined by the initial diagnostic test the patients actually underwent. We also repeated the intention-

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to-diagnose-and-treat analysis, including the outliers. Furthermore, we documented how many patients actually underwent additional imaging within 60 days after initial imaging. To detect selection bias, we collected data from all eligible patients—that is, randomized and nonrandomized patients. We performed similar analyses on the group of nonrandomized patients, and we documented why they were not randomized. Analyses were performed with statistical software (SPSS for Windows, version 10.0; SPSS, Chicago, Ill). Two-sided P values of 0.05 or less were considered to indicate a statistically significant difference.

Results

Patient Population and Randomization
One hundred forty-five patients were randomized (Figure 1). Seventy-two patients were assigned to DSA, of which 68 actually underwent DSA: Two patients crossed over and underwent MDCTA because of absent femoral pulsations, one underwent duplex ultrasonography (US), and one moved out of the country before imaging took place. Seventy-three patients were assigned to MDCTA, and all underwent the CT examination. Images from six examinations (four with DSA, two with MDCTA) were not scored at the vascular conference because of logistics. No significant difference was found in the baseline characteristics of patients randomized to the CT or DSA groups (Table 1).

During the same period, 50 eligible patients were not entered into the trial but did undergo initial diagnostic imaging, either MDCTA (n = 24) or DSA (n = 26), for symptomatic peripheral arterial disease. The reasons that eligible patients were not entered into the trial were patient refusal (n = 6), physician refusal (combined pathologic findings and no femoral pulsations, n = 15), logistics (physician did not know about the trial, n = 6), emergency admission (n = 15), and language barriers (dementia, illiteracy, patient did not understand Dutch; n = 6). For two patients, the reason for nonparticipation was unknown.

Therapeutic Confidence
Seven physicians (three radiologists [P.M.T.P., M.G.M.H.] and four vascular surgeons [M.R.H.M.v.S., H.v.U.]) completed confidence forms during the vascular conferences. Each individual physician scored a similar number of CT angiographic images and DSA images. The median physician confidence score ranged from 6 to 8, and the mean score ranged from 6.2 to 8.3. Three outliers were detected: two in the DSA group in the beginning of the trial (confidence scores of 3.3 and 3.2 compared with a mean of 8.1 ± 1.4 [standard deviation]) and one in the CT angiography group when more than half of the patients were already included (confidence score of 2.3 compared with a mean of 7.2 ± 1.6). These outliers were excluded from the main analysis. *

Analysis of the mean physician confidence scores showed that there was less confidence in CT than in DSA (7.2 vs 8.2, p < 0.001; Table 2). When analyzed according to specialty or individual physician, CT also resulted in a lower confidence score than

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Diagnostic test Performed:

Confidence score Obtained:

Abroad: 1

DUS: 1

DSA: 68 — Yes: 64 / No 4

DSA: 72

MDCTA: 2 — Yes: 2 / No: 0

Randomized: 145

DSA: 0 — Yes: 0 / No: 0

MDCTA: 73

MDCTA: 32 — Yes: 71 / No: 2
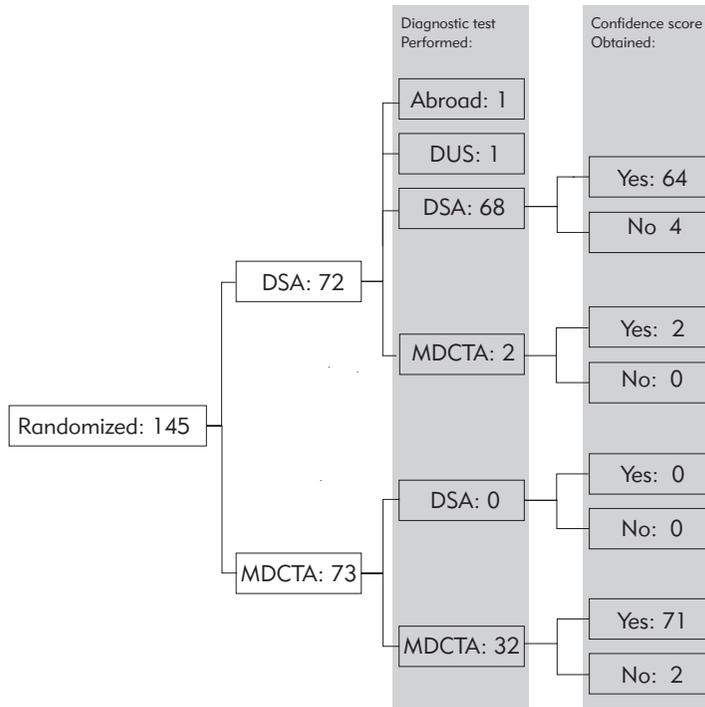
Figure 1. Flow chart shows patient progress through the study from left to right. Patients who gave informed consent were randomized to one of two intention-to-diagnose-and-treat protocols (DSA or CT angiography [CTA], second column). Initial imaging technique actually performed is shown in the third column. Two patients randomized to the DSA protocol crossed over because of absent femoral pulsations and underwent CT instead. Fourth column indicates the number of patients for whom confidence forms (minimum of one) were completed. Abroad = patient moved to a different country before imaging took place, duplex = duplex US, No = no confidence form was completed, Yes = at least one confidence form was completed.

that of DSA. This difference was statistically significant in four of the seven physicians.

Over time, confidence in CT increased, and confidence in DSA remained stable (Figure 2). Thus, the difference in confidence between CT and DSA decreased over time. However, this trend did not reach statistical significance either before or after adjusting for patient characteristics. Separate plots for the radiologists and for the vascular surgeons (not shown) demonstrated increasing confidence in CT and a slight increase in confidence in DSA over time, whereas the difference in confidence between CT and DSA decreased over time. At the individual level, more variation was seen, but the increasing confidence in CT over time was always present, and none of the physicians rated one diagnostic imaging test consistently higher or lower than the other.

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Table 1. *Baseline characteristics of patients with symptomatic peripheral arterial disease undergoing a diagnostic imaging work-up*

Characteristic	Randomized MDCTA (*n* = 73)	Randomized DSA (*n* = 72)	*p* value
Mean age (y)	64 (43-90)*	63 (41-90)*	0.77
Sex			0.08
Male	79 (58/73)	67 (48/72)	
Female	20 (15/73)	33 (24/92)	
Current smoker	84 (59/70)	78 (49/63)	0.34
Diabetes	38 (26/68)	25 (15/59)	0.12
Hypertension	63 (43/68)	56 (39/69)	0.42
Use of coumadin or aspirin	63 (39/62)	68 (42/62)	0.57
Cardiac commorbidity	36 (23/63)	38 (23/60)	0.83
Hyperlipedemia	80 (33/41)	89 (41/46)	0.26
Renal insufficiency	26 (18/70)	17 (11/65)	0.21
Previous intervention	51 (35/69)	57 (36/63)	0.46
Risk factor profile	4	4	0.43
Fontaine stage 1-2 ‡	62 (45/73)	66 (47/71)	0.57
Fontaine stage 3-4 ‡	38 (28/73)	34 (24/71)	0.57

Note. - Data are percentages, unless otherwise indicated. Numbers in parentheses are raw data.
* Numbers in parentheses are the age range in years.
† Average number of known risk factors (male sex, current smoking, diabetes mellitus, hypertension, use of anticoagulants, coexisting cardiac disease, coexisting cerebrovascular disease, hyperlipemia, renal insufficiency, and previous surgical and/or radiologic intervention for peripheral arterial disease) per patient.
‡ Fontaine's stages of the classification of peripheral arterial disease: 1 = asymptomatic, IIa = mild claudication, IIb = moderate to severe claudication, III = ischemic rest pain, IV = tissue loss (Table 1, page 4).

Table 2. *Comparison of outcomes (therapeutic confidence and recommendations for additional imaging) between MDCTA and DSA*

Outcome	MDCTA	DSA	*p* value
Mean therapeutic confidence score	7.2	8.2	< 0.001
Additional imaging recommendations (%)	35 (25/71)*	14 (9/66)*	0.003

* *Numbers in parentheses are raw data*

Recommendations for Additional Imaging
Physicians recommended additional diagnostic tests more frequently after MDCTA than they did after DSA (Table 2). Additional tests were recommended for 25 of 71 patients who had undergone MDCTA (35%) and for nine of 66 patients who had undergone DSA (14%) (p = 0.003). Multiple logistic regression analysis did not show a statistically significant trend in recommendations for additional imaging over time either before or after adjusting for patient characteristics. Diagnostic imaging tests recommended after initial MDCTA were duplex US, selective DSA, and DSA. Diagnostic imaging tests recommended after initial DSA were duplex US, MDCTA, contrast-enhanced magnetic resonance angiography (CEMRA), and selective DSA.

Sensitivity Analyses
We analyzed the association between the continuous outcome (confidence score) and the dichotomous outcome (additional imaging recommended, yes or no). When further diagnostic imaging was recommended, the mean confidence score was lower than it was when no further diagnostic imaging was recommended (6.1 and 8.2, respectively; p < 0.001), which indicated internal consistency of our results. This difference was statistically significant in all groups (all randomized patients together, the MDCTA group, and the DSA group).

The per-protocol analysis in which groups were compared according to whether patients actually underwent MDCTA or DSA produced results similar to those of the intention-to-diagnose-and-treat analysis. Similarly, inclusion of the outliers in the intention-to-diagnose-and-treat analysis did not significantly change the results (mean confidence score, 7.2 for MDCTA and 8.1 for DSA; p < 0.05). Within 60 days after initial imaging, 22 patients in the CT group and 11 patients in the DSA group actually underwent additional imaging (30% [22 of 73] and 15% [11 of 72], respectively; p = 0.03).
For the 50 patients who were not randomized, patients who underwent MDCTA had significantly higher baseline cardiac morbidity (53% [10 of 19]) than that in patients who underwent DSA (20% [five of 25]; p = 0.02). No statistically significant difference in the other characteristics between patients undergoing MDCTA versus DSA was found. Furthermore, no statistically significant difference was found in baseline characteristics of patients who were randomized and patients who were not randomized.

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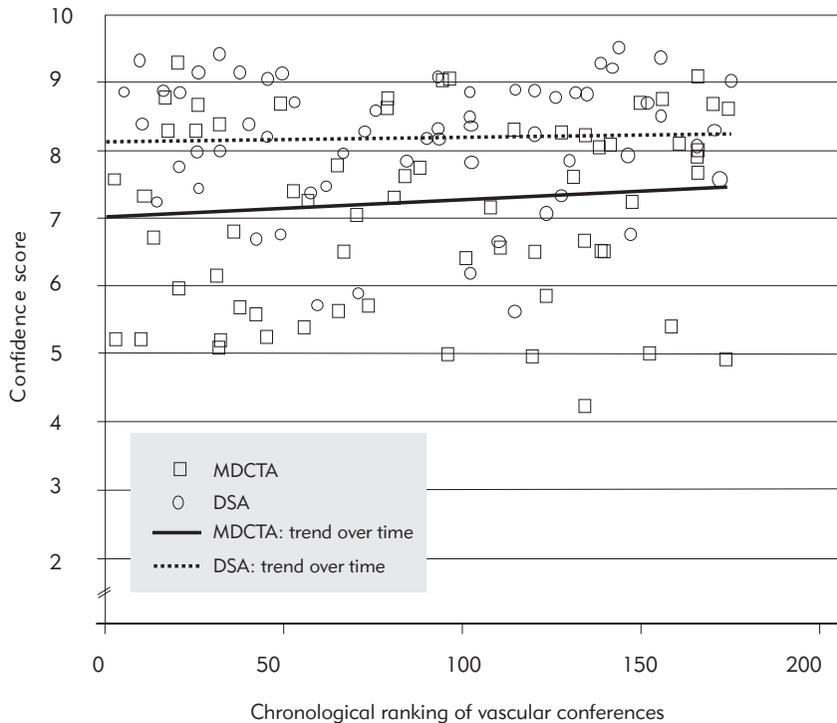
Figure 2. *Mean physician confidence scores over time. Scatter plot of mean physician confidence scores versus time (date of scoring ranked chronologically) shows therapeutic confidence in MDCTA and DSA over time. Individual symbols indicate mean score of all physicians for one patient. Lines show linear regression. Over time, confidence in MDCTA increased, and confidence in DSA remained stable. The difference in confidence between MDCTA and DSA decreased over time.*

Within the nonrandomized patient group, no statistically significant difference in mean confidence scores was found between MDCTA and DSA (8.2 vs 8.3, p = 0.73). Analysis of trend showed increasing confidence in both MDCTA and DSA. The difference in confidence between MDCTA and DSA for the nonrandomized patients was small at the beginning of the study and absent at the end.

Discussion

The ultimate goal of technologic advancements in medicine is to improve patient safety and care (16). The present study was performed to determine the effect of MDCTA on clinical decision making in patients with symptomatic peripheral arterial disease, since MDCTA is less invasive than DSA. If MDCTA provides sufficient information to make treatment decisions, it could replace DSA in the diagnostic imaging work-up prior to revascularization. Within the context of a randomized controlled trial, we compared intermediate outcomes, namely confidence ratings and recommendations for additional imaging, between patient groups for which MDCTA or DSA was

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the initial diagnostic test. MDCTA resulted in a lower confidence score (7.2 vs 8.2) and consequently more recommendations for additional imaging (35% vs 14%) than did DSA.

In the Dutch grading system, a score of 5.5 or higher on a 10-point scale is a passing score. A 7.2 and an 8.2 on a 10-point scale are considered good scores. Although MDCTA resulted in a significantly lower confidence score than that of DSA, the confidence scores of both imaging tests are far above the threshold of a 5.5. Given the less invasive nature of MDCTA when compared with DSA, we feel that the slight decrease in physician confidence and the associated increase in additional imaging after initial MDCTA would probably be acceptable in selected cases.

Furthermore, if DSA is still required after MDCTA, it can often be combined with percutaneous intervention. Thus, MDCTA will generally provide enough information to guide planning of the procedure in the sense of reserving room time and choosing the means of arterial access. As such, we believe that MDCTA can replace DSA as the initial imaging test in selected patients with symptomatic peripheral arterial disease prior to revascularization. To justify this approach, analysis of patient outcomes and costs are still required. Furthermore, delineation of patient selection for which this approach is appropriate would also be required.

So far, to our knowledge, investigators who have reported intermediate outcomes for MDCTA and DSA have measured only diagnostic accuracy (7–13). With DSA as the reference standard, the values of sensitivity and specificity for CT angiography varied from 80% to 100% and from 94% to 100%, respectively (7–12). To our knowledge, studies have not yet been reported with the regard to (a) the effect of each on diagnosis and therapy choice and (b) cost-effectiveness analyses of MDCTA compared with DSA for peripheral arterial disease.

Previous studies outside the field of peripheral arterial disease have involved measurement of diagnostic and therapeutic effects in a before-after setting—that is, one measurement was performed before the diagnostic test and one after (5,14,15,17,18,23–28). In our study, however, the diagnosis was already known to be symptomatic peripheral arterial disease, and patients were undergoing diagnostic imaging work-up prior to revascularization. Thus, the question was not whether the diagnosis or the decision to perform revascularization would change but whether MDCTA provided sufficient information in daily practice to determine which revascularization procedure should be used.

MDCTA is not the only less invasive imaging modality that could possibly replace DSA in the assessment of peripheral arterial disease—others include CEMRA and duplex US. Results of a meta-analysis (29) showed that CEMRA had better discriminatory power than that of US and that CEMRA was a highly sensitive and specific test when compared with DSA. The recent development of multi–detector row CT angiography for the evaluation of peripheral arterial disease has shown promising results, which is why we chose to use MDCTA as the less invasive imaging modality.

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We performed our measurements in the setting of a randomized controlled trial. A randomized controlled trial is the most reliable setting because, in theory, known and unknown confounders are distributed equally between the two groups (30–32). To minimize selection bias, we included patients consecutively and kept records of all eligible patients. Indeed, no statistically significant difference in baseline characteristics between the MDCTA group and the DSA group was present. However, a slight imbalance was present in the number of male patients, patients with diabetes, and patients with cerebrovascular comorbidity—more were present in the MDCTA group. Within the nonrandomized patients, there was a tendency to perform MDCTA, which is less invasive, in case of cardiac morbidity. No statistically significant difference in baseline characteristics was found between randomized and nonrandomized patients. This implies that no obvious selection bias was present and suggests that our results are generalizable to all patients with symptomatic peripheral arterial disease.

The principal limitation of our study design was that physicians were not blinded to the diagnostic test performed. At the same time, however, this was one of its strengths, since we wanted to determine whether MDCTA could provide physicians with sufficient diagnostic information to replace DSA in daily clinical practice. Blinding by means of transferring the information to a schematic drawing, for example, would have introduced an extra step that could have hampered interpretation and confidence and would probably never be used in daily clinical practice. As a result of our pragmatic study design, however, a physician's enthusiasm for MDCTA or DSA could have influenced his or her rating (26).

Furthermore, physicians could have distorted their ratings deliberately. Because they knew the purpose of the study and may have preferred one test to the other, it is possible that they tried to manipulate the direction of the study results. Inspection of the graphs of the physician confidence scores at the individual level, however, suggested that this did not occur. None of the physicians rated one diagnostic imaging test consistently higher or lower than the other.

Another limitation of our study design is that although a physician can be confident about the interpretation of the images, he or she can still be wrong. Technical performance and diagnostic accuracy of MDCTA for peripheral arterial disease have already been reported and were found to be excellent (7–12). The purpose of the present study was, therefore, not that of a standard diagnostic study. Instead, we set out to evaluate the effect on clinical decision making.

All physicians did not attend all vascular conferences. Therefore, the number of physicians who scored a patient's imaging test varied. Furthermore, the scoring behavior between physicians varied. Some scored consistently higher than others for both tests, and some used a broad range, while others used a narrow range. To make the scores of different physicians comparable and to adjust for differing attitudes toward uncertainty, we normalized the scores by assuming that every physician saw a mix of high- and low-quality images. Inspection of the minimum, maximum, median, and mean confidence scores per physician suggested that every physician

did indeed see a representative mix of images.

This trial started immediately after the introduction of MDCTA for peripheral arterial disease at our hospital. Therefore, we expected to find a learning curve for CT angiography (ie, the confidence physicians had in MDCTA would increase over time) (33). To detect such a trend, we plotted the confidence physicians had in MDCTA and DSA over time and analyzed this with multiple linear regression (33). We expected to find stable confidence in DSA over time, since this diagnostic imaging test has already been used for many years—and indeed, this was the case. We also expected to find a decreasing difference in confidence between MDCTA and DSA over time, as the physicians became more comfortable with MDCTA. In our multiple linear regression model, the difference in confidence between MDCTA and DSA decreased over time, but this never reached the point of statistical significance.

Fifty eligible patients were not randomized but did undergo initial diagnostic imaging (MDCTA or DSA). In at least 42 of these 50 patients, the physician decided which test was most suitable on the basis of clinical characteristics and practical considerations. The mean confidence scores were 8.2 in patients who were not randomized and underwent MDCTA, 8.3 in patients who were not randomized and underwent DSA, and 8.2 in patients randomized to DSA. This suggests that in daily practice, physicians learned very quickly how to select patients with symptomatic peripheral arterial disease for whom MDCTA would provide sufficient diagnostic information and thus for whom MDCTA is a feasible alternative to DSA in the diagnostic imaging work-up prior to revascularization.

Additional imaging was recommended after both MDCTA and DSA. Diagnostic imaging tests recommended after initial MDCTA were duplex US, selective DSA, and DSA. Imaging tests recommended after initial DSA were duplex US, MDCTA CEMRA, and selective DSA. This demonstrates that both DSA and MDCTA have a place in the diagnostic imaging work-up of patients prior to revascularization. Identification of patients in whom MDCTA can be expected to provide sufficient information should help with patient selection in the future.

In conclusion, initial MDCTA results in a decrease in physician confidence and an associated increase in additional imaging in the diagnostic work-up prior to revascularization in patients with symptomatic peripheral arterial disease. Given the less invasive nature of MDCTA than that of DSA, our results suggest that initial MDCTA may replace initial DSA in selected cases.

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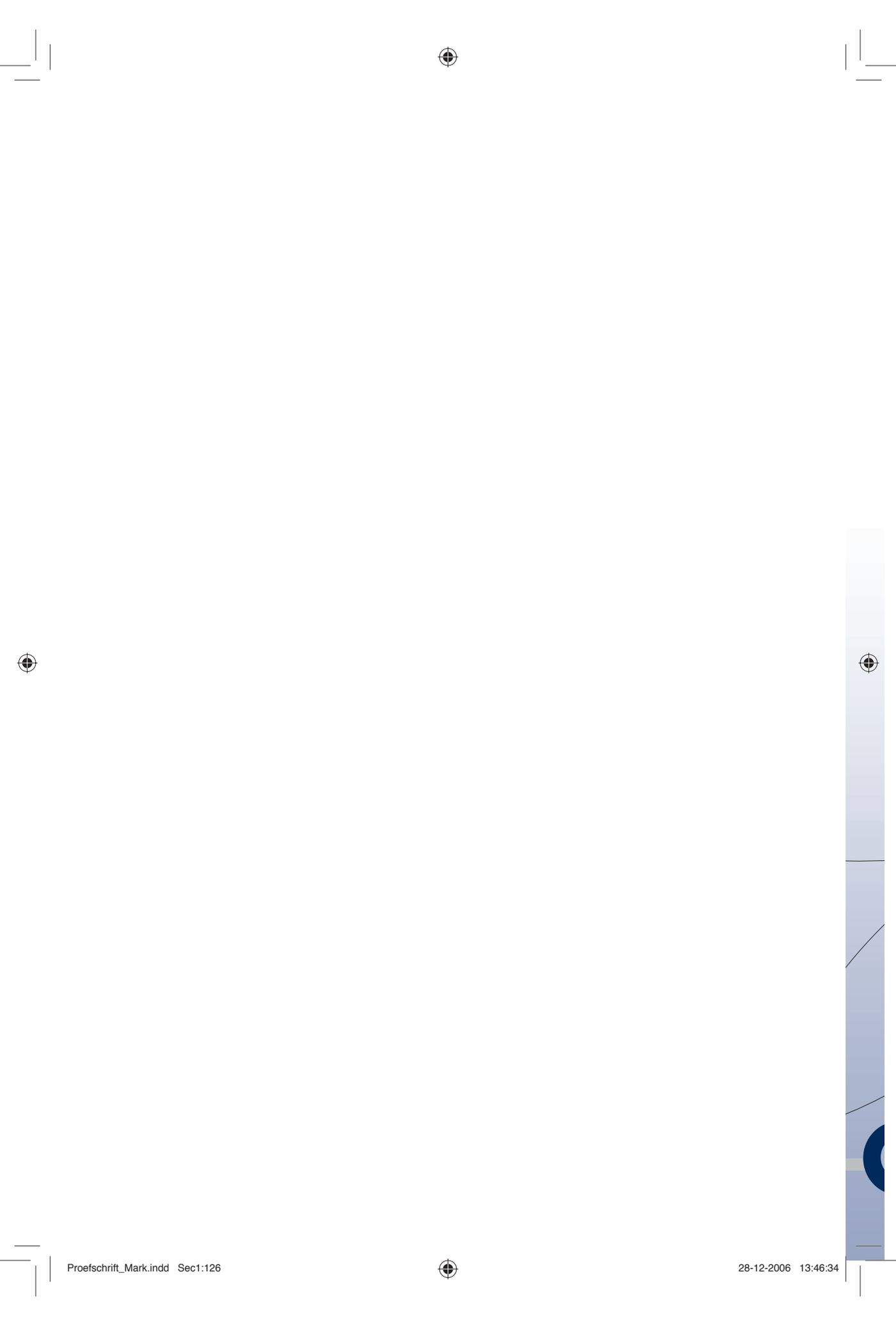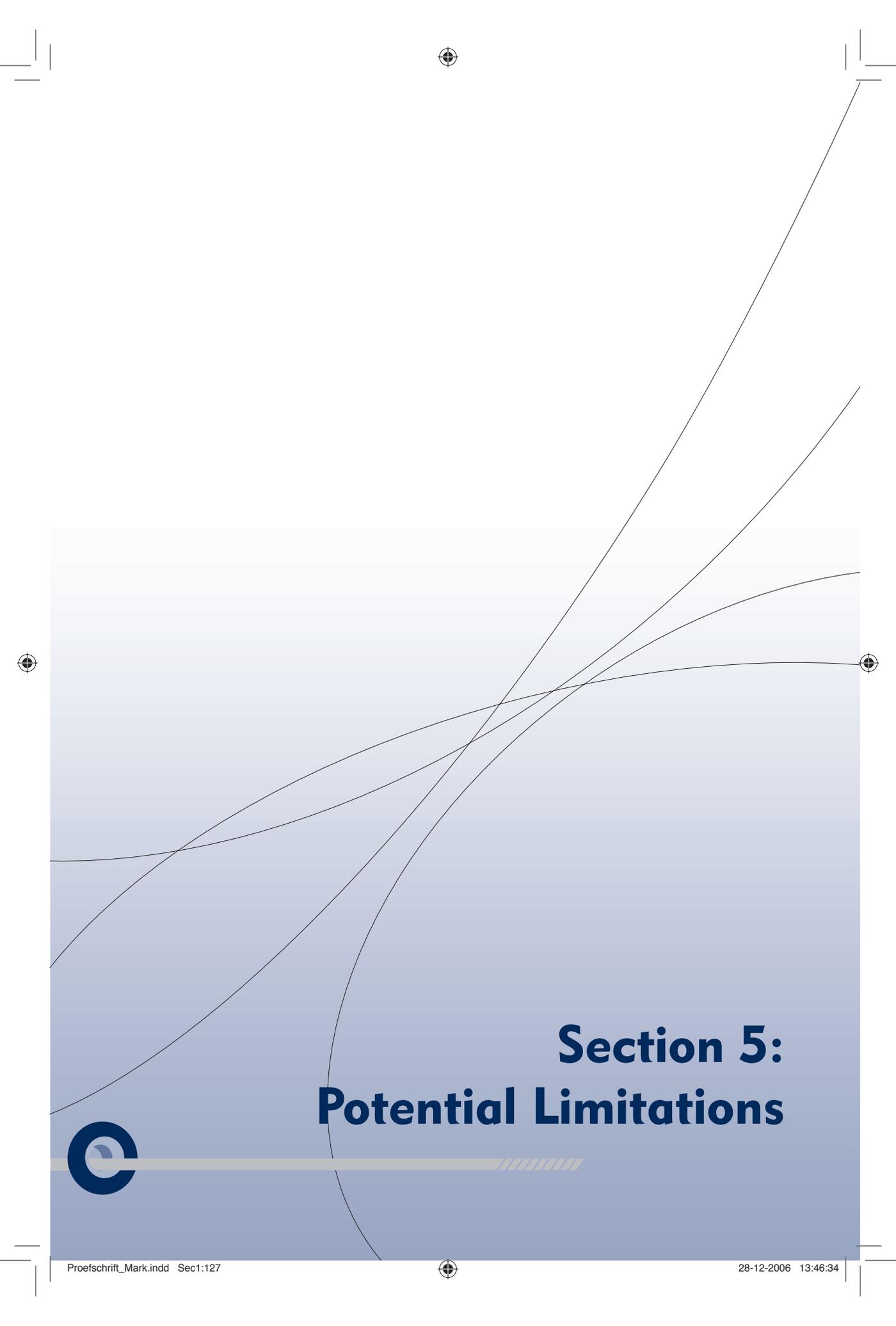
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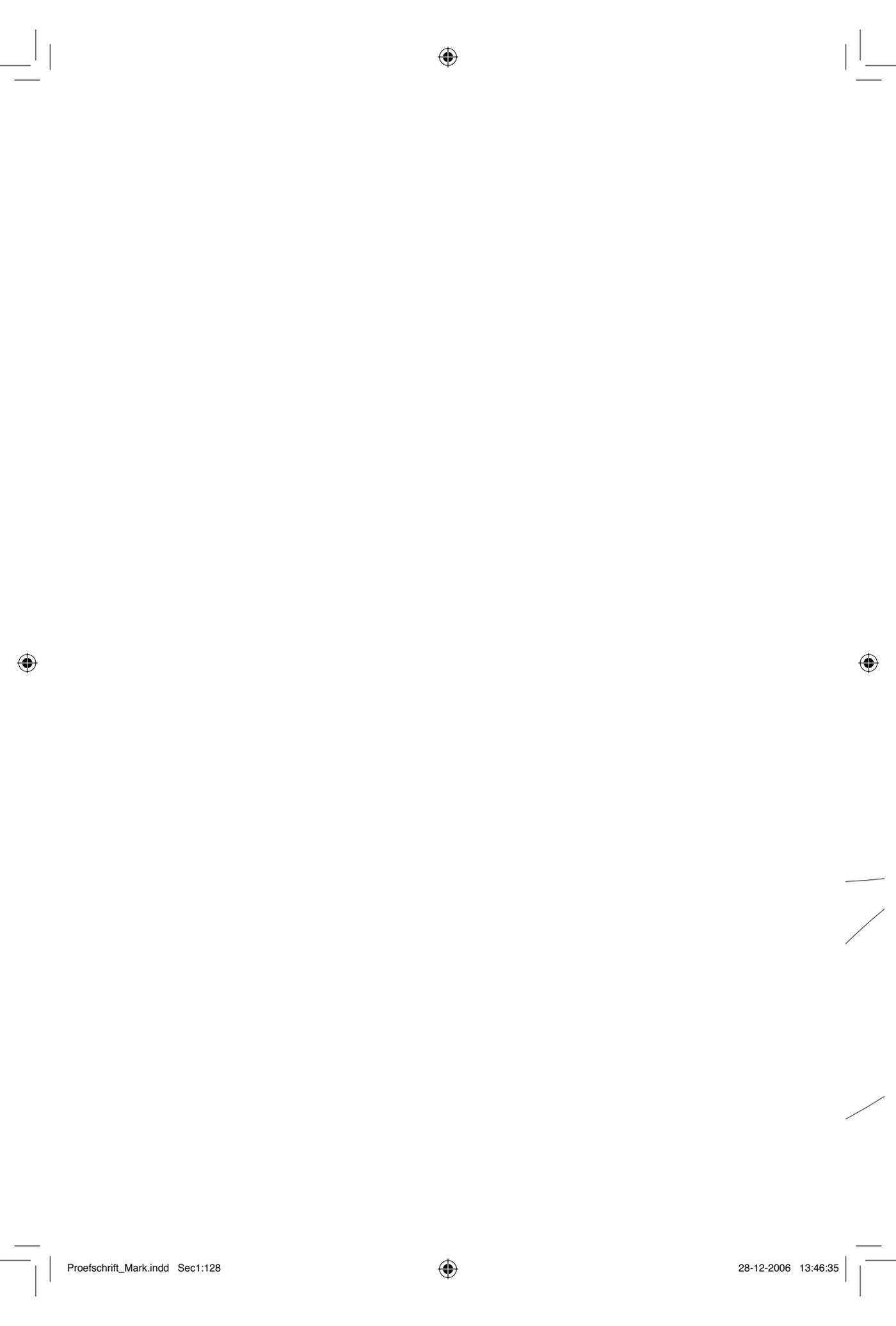
Chapter 7
Vessel Wall Calcifications on
Multi-Detector Row CT Angiography

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Abstract

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

Materials and methods: The study was approved by the hospital institutional review board, and informed consent was obtained from all patients. For this study we included 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 MDCTA and were followed for 6 months. Clinical utility was measured with therapeutic confidence (0-10) in the initial MDCTA 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 effect of vessel wall calcifications on clinical utility and patient characteristics for their ability to predict the number of calcified segments on MDCTA.

Results: A total of 145 patients were included (mean age, 64 years; 70% men). We found that the number of calcified segments was a significant predictor of the need for additional imaging (p = 0.001) and of the confidence scores (p<0.0001). Furthermore, the number of calcified segments discriminated between patients requiring additional imaging following MDCTA 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).

Conclusions: Vessel wall calcifications decrease the clinical utility of MDCTA in patients with peripheral arterial disease. Diabetes mellitus, cardiac disease, and elderly age (above 84 years) are independently predictive for the presence of vessel wall calcifications.

Potential Limitations

Introduction

Multi-detector row computed tomographic angiography (MDCTA) is increasingly used for diagnostic imaging in patients with peripheral arterial disease (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 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 MDCTA were comparable with both digital subtraction angiography (DSA) and CEMRA, but MDCTA incurred lower diagnostic costs compared to both DSA and MRA in patients with PAD (11, 12). These results suggest that MDCTA is the optimal strategy for the initial diagnostic work-up of PAD.

A major drawback of MDCTA 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 MDCTA (3, 5, 10). In the presence of extensive vessel wall calcifications, especially in small arteries, it is difficult to produce interpretable MIP images. Continuous calcification of the vessel wall may cause false-negative findings of patency, whereas high-attenuation artifacts, known as "blooming" of calcification on axial images may result in a false-positive diagnosis of a substantial 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 endproduct of MDCTA is of no, or questionable, diagnostic value and that these cases could not be managed without digital subtraction angiography for accurate evaluation (5, 6).

The effect of vessel wall calcifications on the clinical utility of MDCTA 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 MDCTA is less clinically useful. The purpose of our study, therefore, was to retrospectively evaluate the effect of vessel wall calcifications on the clinical utility of MDCTA in patients with PAD and to identify clinical predictors for the presence 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 MDCTA or DSA as the initial imaging test. In a second study (11) between December 2001 and September 2003 patients with PAD were randomized between MDCTA and CEMRA.

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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 CEMRA (eg, pacemaker or claustrophobia) or MDCTA 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 was obtained for both studies. The approval and consent applied as well for all manuscripts deriving from the studies.

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 for the first and second study, respectively: collimation, 2.5, 0.75 mm; number of detector rows, 4,16; pitch, 1.6, 1.5; X-ray tube voltage setting, 120, 120kV; current, 110, 140 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 MDCTA, 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, independently 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

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vessel segment, the most severe lesion was used for grading. Furthermore, the readers recorded the presence of vessel wall calcifications. The presence of calcifications (ranging from a single spot to extensive calcifications) in each segment was counted as 1 and the absence of calcifications was counted as 0. The final calcification score was the sum of the individual scores from all the segments ranging from 0 to 31, so that per patient one sum score was determined. After the first independent evaluation, the readers evaluated the images by a consensus reading. These consensus readings were used for the data analysis. All images were evaluated without knowledge of further work-up.

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

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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. To investigate if the effect of predictor variables on the number of calcified segments differed between three regions (aortoiliac region, femoropopliteal region, crural region), we calculated the percentage calcified segments per region. Subsequently a multivariable linear regression following the generalized estimating equations (GEE) approach was performed with the regional scores as the dependent variable and the same predictor variables as in the final model, with addition of the interaction terms with the regions. All calculations were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, Il), except for the GEE analysis which was carried out with Proc Genmod from the SASpackage (SAS version 8.2; SAS Institute Inc., NC).

Results

In both studies a total of 152 patients were randomized to MDCTA (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.
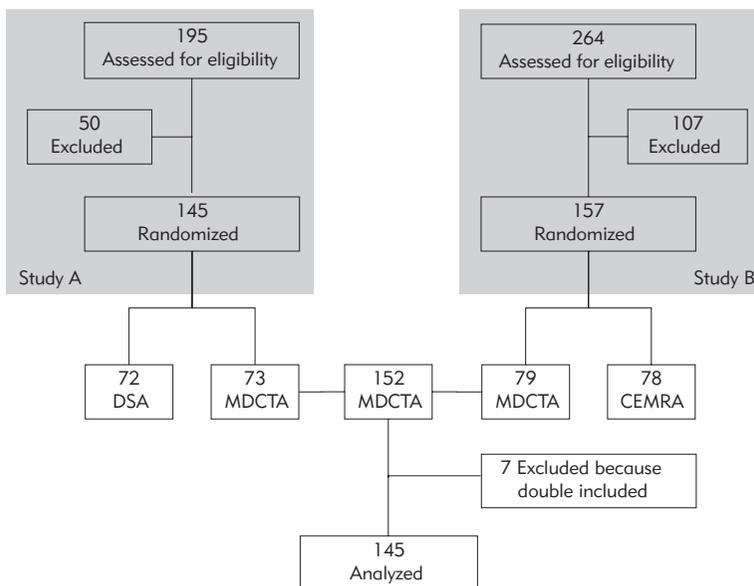

Figure 1. *Flow diagram of patients passing through both randomized controlled trials (RCTs) and those included in the current study.*

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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).

Table 1. *Baseline characteristics of study population*

Characteristics	Study population (n = 145)
Age, mean (SD)*	64 (17)
Male sex, (%)	101 (70)
Diabetes mellitus, (%)	43 (30)
Hyperlipidemia, (%)	72 (50)
Smoking†, (%)	111 (77)
Arterial hypertension, (%)	72 (50
Cardiac disease, (%)	42 (29)
Cerebrovascular disease, (%)	32 (22)
Renal Disease‡, (%)	17 (12)
Previous revascularization, (%)	60 (41)
Critical Ischemia, (%)	42 (29)

Note. - Data are numbers of patients and percentages in parentheses.
* Values of continuous variables are expressed as mean, SD in parentheses.
† Includes current and former smokers.
‡ Mild renal insufficiency or hemodialysis with permission of the nephrologist to undergo MDCTA.

The regression coefficients and 95% CIs of all clinical variables that were 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). The GEE analysis on the regional calcification scores showed that only the effect of age was significantly (p = 0.02) different for the three regions, the effect on the

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femoropopliteal region being about two times as strong as for the crural region, with the aortoiliac region in between.

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

Note. - Variables with p-value <0.10 were included in the multivariable analysis.
[†] *Per 20-year increase.*
[‡] *Includes current and former smokers.*
[§] *Mild renal insufficiency or hemodialysis with permission of the nephrologist to undergo MDCTA.*

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)[†]	3.30 (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

[*] *Final multivariable model was obtained using a stepwise backward selection with a p-value < 0.05.*
[†] *Per 20-year increase. R-square = 0.17.*

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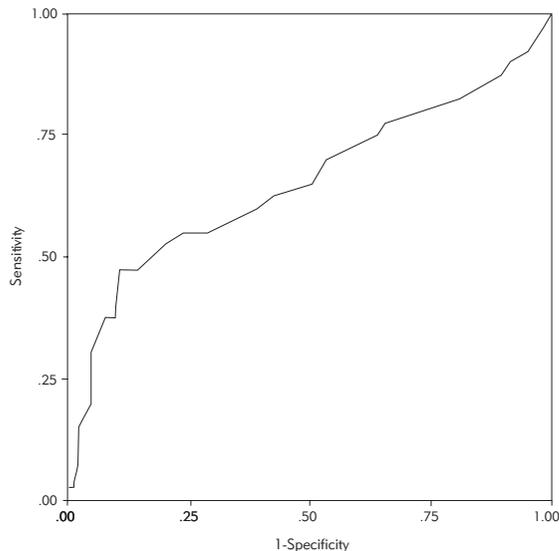
Figure 2. *Receiver operating characteristic curve for the number of calcified segments for prediction of the need for additional vascular imaging.*

Discussion

Multi-detector row CTA is increasingly used for clinical decision-making in patients with suspected arterial occlusive disease. Because interpretation of MDCTA images is difficult in extensively calcified vessels, it is important to evaluate the effect of vessel wall calcifications on the clinical utility of MDCTA. Subsequently, if vessel wall calcifications decrease clinical utility of MDCTA, it would be useful to identify clinical predictors of calcifications in peripheral arteries to select patients for whom MDCTA 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 MDCTA is less clinically useful due to decreased clinical utility. In these patients CEMRA 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 CEMRA instead of MDCTA 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,

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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 our 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. In particular, the number of patients with renal disease was very limited implying that our study could probably not demonstrate renal disease as an independent predictor for calcified segments in the multivariable analysis even if it is predictive, which is likely. 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 ours is the first study evaluating the effect of vessel wall calcifications on the clinical usefulness of MDCTA in patients with peripheral arterial disease. We showed that vessel wall calcifications on MDCTA 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 MDCTA 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 MDCTA. 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 MDCTA in patients with peripheral arterial disease and that diabetes mellitus, cardiac disease, and elderly age (above 84 years) are independently predictive for the presence of vessel wall calcifications.

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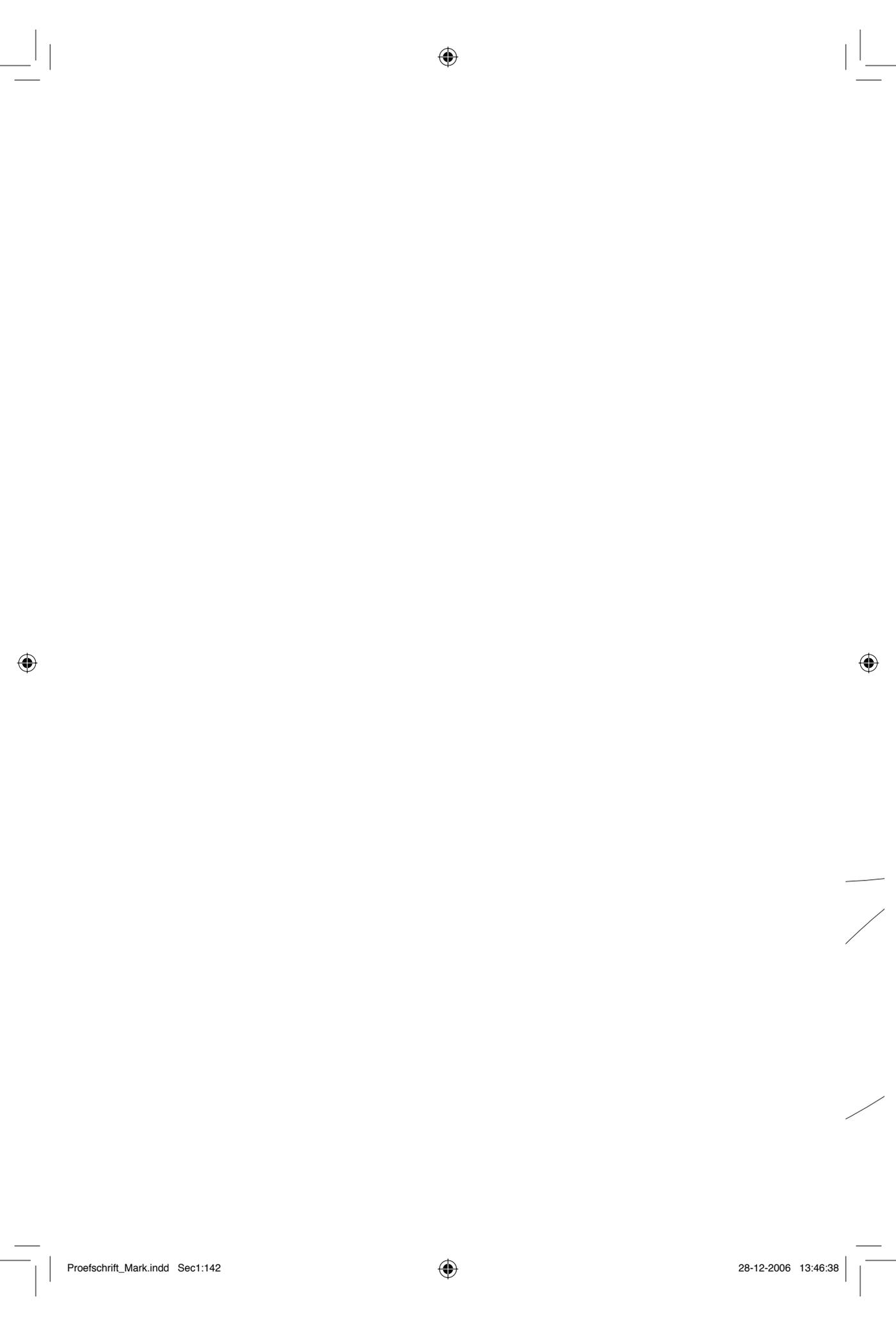
Chapter 8
Patient Radiation Dose of Multi-Detector CT Angiography: A Negligible Risk?

Kock MCJM, Geleijns J, Kuiper JW, Pattynama PMT, Hunink MGM.

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Abstract

Purpose: To estimate the excess radiation risk corrected for the mortality of peripheral arterial disease (PAD) from the effective dose from multi-detector row CT angiography (MDCTA) and digital subtraction angiography (DSA) in patients with PAD.

Material and methods: Consecutive patients with peripheral arterial disease were prospectively included in our study to undergo either MDCTA (n = 152) or DSA (n = 54) which was performed according to standard clinical protocols. Effective dose was derived from the radiation exposure which was measured as computed tomography dose index or as dose-area product. The excess risk of radiation induced fatal cancer was estimated using the multiplicative model of the ICRP 60 which was modified in order to account for the reduced life expectancy of patients suffering from PAD.

Results: The mean age of the patients was 64.3 years (MDCTA) and 63.8 years (DSA). The mean effective dose at MDCTA and DSA was 8.3 mSv (SD 1.3) and 9.9 (SD 4.9) mSv, respectively. The estimated excess lifetime radiation-associated risk of fatal cancer for a patient with moderate PAD, associated with a mortality ratio of 2.5, and a mean age and doses as observed in our study, is 0.007% for MDCTA and 0.008% for DSA, respectively.

Conclusion: Patients are exposed to similar radiation doses with MDCTA compared to DSA performed for the evaluation of PAD. The excess mortality risk associated with these radiation doses can be qualified as negligible compared to the mortality rate from their underlying disease of PAD.

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Introduction

Multi-detector technology continues to drive practice patterns by combining fast scanning with high quality data sets. This has resulted in new applications as well as improved use in traditional applications. CT scanning accounts for more than 10% of diagnostic radiology examinations in Western countries. Consequently, CT examinations have more than doubled their contribution to radiation exposure and are now responsible for 40-75% of medical exposure (1, 2). Currently, issues related to radiation exposure from multi-detector row CT scanners are receiving increasing attention (3-6) (1, 7-10). It has been reported that the dose from a multi-detector CT can be higher than that from a single-detector row CT scanner, depending on the selected acquisition parameters (11, 12). Familiarity with CT dosimetry and the actual effective doses delivered by CT are important issues as they provide a basis for understanding the potential cancer risks from radiation exposure incurred by CT. Moreover, this justifies developing strategies to minimize radiation dose. Strategies include obtaining only necessary CT examinations; adjusting the examinations based on scan indication, region examined, and patient size; and technology aimed at radiation dose reduction.

Peripheral arterial disease (PAD) is a symptom of atherosclerosis in the arteries to the lower extremities. Patients suffering from PAD have a poor prognosis because they have an increased risk of fatal cerebrovascular and cardiovascular events (13-21). Although MDCTA and MRA are increasingly performed to evaluate PAD, DSA is still regarded as the reference standard. Purpose of this study was to assess the effective dose and excess radiation induced mortality risk from MDCTA and DSA in patients with PAD.

Materials and methods

Patients

The patient population included in this study are patients recruited in two tertiary care university hospitals. Inclusion criteria were written informed consent, symptomatic PAD, an ankle-brachial systolic blood pressure index of less than 0.90, and referred for imaging prior to a revascularization procedure. Exclusion criteria were contraindications to angiography, iodinated contrast agents, or revascularization and acute ischemia which required urgent imaging and treatment. Patients who underwent MDCTA (n = 152) were recruited from two randomized controlled trials in one hospital that evaluated the clinical impact of MDCTA as the initial imaging test in the diagnostic work-up of PAD and one pilot study. In the first study between April 2000 and August 2001 patients with PAD were randomly assigned to undergo MDCTA or DSA as the initial imaging test. In the second study between December 2001 and September 2003 patients with PAD were randomized between MDCTA and MR angiography. In a pilot study, to evaluate the feasibility of 64-detector CT angiography in the work-up of PAD, consecutive patients were included to undergo MDCTA. Patients who underwent DSA (n = 54) were recruited in the other hospital. During one year starting in June 2000, patients with PAD were included consecutively, to undergo

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DSA prior to a revascularization procedure. The institutional medical ethics committee of the tertiary care university hospitals approved these studies and informed consent was obtained.

Multi-detector CT angiography of the peripheral arteries

MDCTA examinations were performed using a multi-detector row CT scanner (Somatom Plus 4 Zoom, Sensation 16, or Sensation 64; Siemens Medical Systems, Forchheim, Germany). Ninety-five patients underwent 4-detector row CT angiography, fifty-two underwent 16-detector row CT angiography, and five underwent 64-detector row CT angiography. Patients were in the supine position on the CT table. 120 ml of non-ionic contrast material (Visipaque 320 mg iodine/ml, Amersham Health, Buckinghamshire, UK) was injected via an antecubital vein at a rate of 4 ml/sec. MDCTA acquisitions were performed using an effective tube charge of 110-130 mAs, a tube voltage of 120 kV, and a table speed of approximately 35 mm/s (Table 1). The acquisition time in all examinations was approximately 32 seconds.

Table 1. *MDCTA protocol*

Multi-Detector Row CT Scanner	Section Collimation width (mm)	Gantry rotation period (s)	Table feed (mm per rotation)	Pitch
4-Detector CT	2.5	0.5	17	1.7
16-Detector CT	0.75	0.5	18	1.5
64-Detector CT	0.6	0.5	12	1

Note. - Tube potential was 120 kVp for all CT scanners and tube current-time varied per patient. Scan time in all patients was approximately 33 seconds.

Peripheral Digital Subtraction Angiography

DSA was performed using an Integris V3000 X-ray unit (Philips Medical Systems, Best, the Netherlands) with an image intensifier diameter of 38 cm. All patients were catheterized from a femoral artery and a 5-French sheath was placed. Using a 4-French pigtail catheter multiple boluses of iomeprol (Altana Pharma, Hoofddorp, the Netherlands [non-ionic, 300 mg iodine/ml]) were injected at a rate of 10–15 ml/sec and a total of 10–20 ml per series, depending on the artery where the tip of the catheter was located. Acquisition series were contingently obtained in the anteroposterior projection from the abdominal aorta down to the ankles. The radiologist supplemented the images with oblique projections when necessary. All studies were performed by a radiologist who was experienced in angiography. The angiography unit provides a read-out of the cumulative dose-area product (DAP) values for fluoroscopy and radiography after each procedure.

Effective Dose

For MDCTA examinations volume CT dose index (CTDI) and dose length product (DLP), and the effective dose for each patient were determined by the ImPACT CT

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Patient Dosimetry Calculator (version 0.99w, ImPACT, London, UK) (22). This calculator is a software application that provides an automatic calculation of volume CTDI and DLP values by specifying scanner manufacturer, scanner model, and our scanning parameters as input. The effective dose values are provided by the application using the incorporated organ dose conversion coefficients established by National Radiological Protection Board (NRPB) (23) and are based on the recommendations of the International Commission on Radiological Protection (ICRP) (24). The software application is limited to estimate the dose of the scanned region of abdomen and pelvis to the lowest level of 10 cm below the level of the symphysis.

Dose area product (DAP) was recorded after each DSA examination. DAP for fluoroscopy was recorded separately and was added to the DAP reading from the radiography series. The dose-area product read out was calibrated. Conversion coefficients for the calculation of effective dose (E) from DAP were reported by Struelens et al. for seven different hospitals (25). Clinical practices at one of these seven hospitals closely matched with the technique and protocol for peripheral digital subtraction angiography as described in our study (filtration, projections, and tube voltage). The authors found an effective dose conversion factor of that particular practice of 0.15 mSv/Gy.cm2, which was applied for assessment of effective dose in our study.

Risk Estimation
A risk estimation model was developed to estimate the specific excess risk of fatal cancer associated with radiation exposure from MDCTA or DSA for evaluation of the peripheral arteries. The calculation was performed specifically for patients presenting with symptoms of PAD and for their mean age, sex, and mortality risk. We adjusted the excess risk of fatal cancer for the higher mortality rate associated with PAD by modifying the multiplicative model of publication 60, Annex C of 1990 from the International Commission on Radiological Protection (ICRP) (24). Baseline assumptions were a latent period of leukemia of 2 years, a latent period of other cancers of 10 years, a plateau length of leukemia of 40 years, an infinite plateau length of other cancers, and a dose-and-dose-rate effectiveness factor (DDREF) of 1.5.

The first modification of the model was by using the age dependent annual background mortality for the Dutch population (Figure 1). From the official death certification data managed by the national Central Bureau of Statistics, recent mortality data (1999) were used on annual total background mortality, mortality of leukemia, and mortality of fatal solid cancers as coded according to the International Classification of Diseases (26).

The second modification was the inclusion of the reduction of life expectancy of patients suffering from PAD in the ICRP multiplicative model. This enabled us to study the interaction between mortality from PAD and mortality from radiation exposure during a diagnostic X-ray examination. The PAD specific mortality was expressed as the mortality ratio. From epidemiologic reports various mortality risks of patients suffering from PAD were collected and used in our risk calculations. In the model, the annual mortality associated with having PAD was used in the calculations in the age

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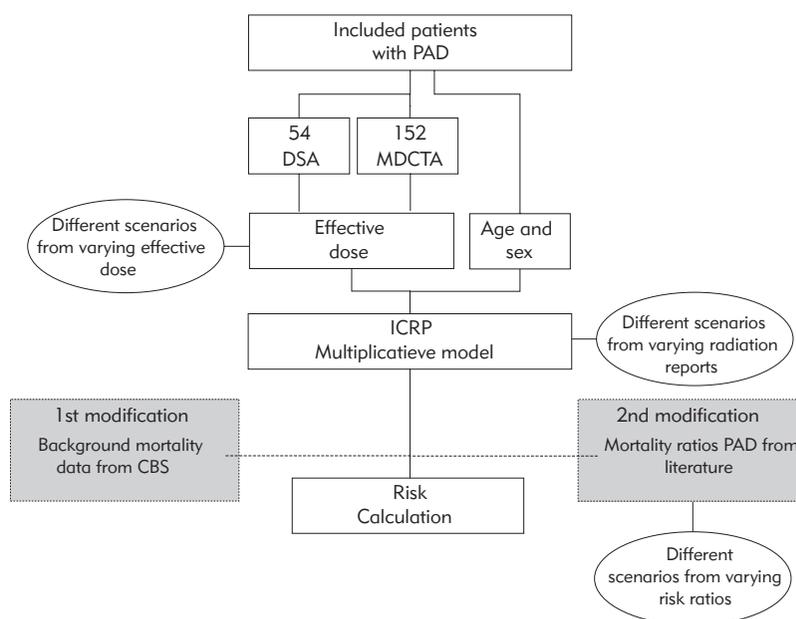
Figure 1. Flow chart of the model

periods after the age of exposure to the X-ray radiation. Before the age of exposure they were assumed to be healthy without the increased mortality associated with PAD. From the perspective of radiation risk in non-diseased patients the background mortality for the Dutch population was used in the calculations to reflect the excess risk in the average Dutch population without PAD. The excess risks were plotted for a given age from 40 to 100 years. For the calculations of the risk of a base case we used a 64-year old patient suffering from moderate PAD with an average reported mortality ratio of 2.5 (13-18, 20, 21, 27) and the average effective dose at a single examination. This reflects our average patient population and average effective dose and the average published mortality rate.

Sensitivity analysis was performed by varying the annual mortality rate from PAD and the effective dose. For the calculations we used the minimum and maximum reported mortality ratio from PAD of 1.3 (19) and 4.5 (17) and the minimum and maximum published effective dose from MDCTA of 2.7 and 14.3 mSv (28, 29) and from DSA of 3 and 36 mSv (28, 30).

To verify the estimates from the multiplicative model of ICRP 60 (24) we compared the sex-averaged lifetime cancer mortality risk of exposure to 1 Sv using a DDREF of 1.5 with that of other reports on excess radiation induced cancer mortality risk. We used the BEIR V report published in 1990 and, more recently the prepublication of part VII from the Committee of the Biological Effects of Ionizing Radiations (BEIR) Committee of the National Academy of Sciences (31) (32), the report R260 of 1994 from the National Radiological Protection Board (NRPB) (33), the report of 2000 volume II Annex 1 from the United Nations Scientific Committee on the Effects of

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Atomic Radiation (UNSCEAR) (34), and the report of 1994 with the addendum of 1999 from the Environmental Protection Agency (EPA) (35).

The estimates of all these reports are based on relative risk models that are dependent on patient sex and age at exposure and assume a linear extrapolation without threshold (LNT) of risks to low doses (less than 100 mSv) of ionizing radiation. At dose levels of about 0.1 to 4 Sv excess cancers have been observed in the Japanese atomic-bomb survivors. These excess cancers are numbers of cancers above the expected level of cancer in the population. Solid cancers show a linear increased rate without threshold at an increased dose. For leukemia, the reports found a linear-quadratic dose-effect relation. The risk estimations use the DDREF as a multiplicative downward adjustment of the rate. We used a value of 1.5 to compare the reports which is currently regarded as a realistic value (32). This value is derived from combining analyses of dose response curvature for cancer risk using animal radiobiology data and medical data from the Japanese atomic bomb survivors. However, there is still statistical uncertainty in the DDREF selection. The estimates of cancer mortality from the utilized reports used the data from the Life span Study cohort of the atomic bomb survivors of Japan as a major source of information. The reports calculated mortality rates for the population of the USA (BEIR), the UK (NRPB), or other countries (UNSCEAR).

Results

Patient Study

Mean age of the patients of the MDCTA and the DSA group was 64.3 years (SD 11) and 63.8 years (SD 14), respectively. The proportion of males in the MDCTA group and the DSA group was 70% and 69%, respectively. No significant difference was found in age and sex between the groups undergoing MDCTA vs DSA.

Effective Dose

The mean effective tube current for MDCTA was 117.3 mAs (SD 25.8). For the different multi-detector CT scanners the mean effective tube current was 111.4 mAs (SD 25.1), 123.4 mAs (SD 21.4), and 167.9 mAs (SD 6.7) for the 4-, 16-, and 64-detector CT scanners, respectively. The mean volume CT dose index and the mean dose length product (DLP) for MDCTA were 9.5 mGy (SD 1.4) and 509.2 mGy.cm (SD 76.8), respectively. The mean estimated effective dose for patients undergoing 4-, 16-, and 64-detector CT angiography was 8.0 mSv (SD 1.0), 8.5 mSv (SD1.4) and 12.0 mSv (SD 0.7), respectively. Mean estimated effective dose for patients for MDCTA was 8.3 mSv (SD 1.3).

For DSA the mean fluoroscopy time was 4.1 minutes (SD 3.5) with acquisition of on average 96.4 frames (SD 31.0). This resulted in a mean fluoroscopic dose of 11.1 (SD 11.8) Gy.cmK and a mean acquisition dose of 55.5 Gy.cmK (SD 27.4). We calculated a mean estimated effective dose of 9.9 mSv (SD 4.9) for DSA of the peripheral arteries.

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Risk Estimation

Figure 2 shows the excess attributable lifetime risk of induction of a fatal cancer per examination using MDCTA or DSA in a patient suffering from PAD, from a given age. For the 64-year old base case patient who undergoes a MDCTA or DSA of the peripheral arteries, with moderate PAD which corresponds to an average mortality ratio of 2.5, the excess lifetime risk of radiation induced fatal cancer would be 0.007% or 0.008%, respectively. When the arterial disease is more severe the mortality ratio due to PAD will increase from 2.5 to maximally 4.5. The excess lifetime cancer mortality risk due to radiation would be 0.003% and 0.004%, respectively, for MDCTA and DSA (Table 2). In comparison, the lifetime risk from radiation attributable to a MDCTA or a DSA examination in a 64-year old person of the Dutch population without PAD would accrue an estimated lifetime attributable risk of cancer mortality of 0.018% and 0.022%, respectively.
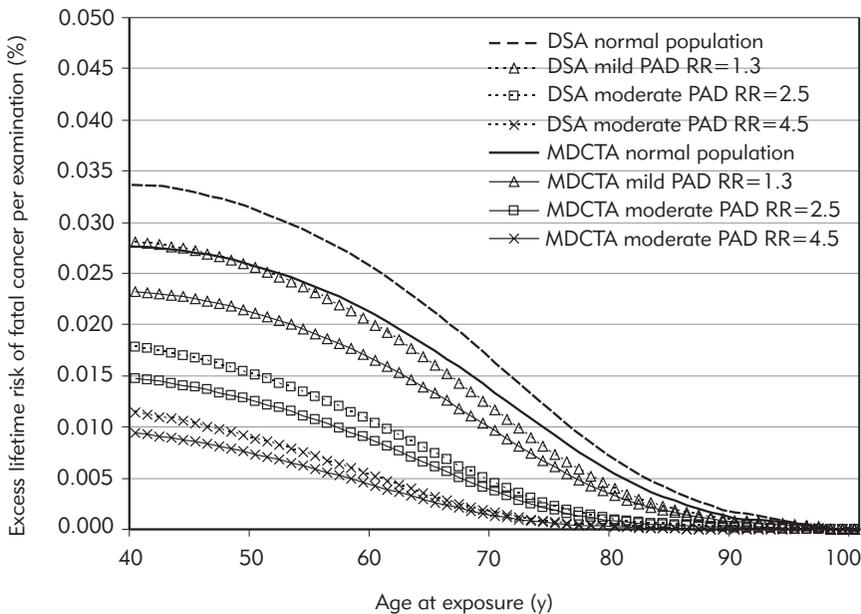

Figure 2. *Excess lifetime risk of fatal cancer per examination using multi-detector row CT angiography or digital subtraction angiography.*

Graph shows estimated age-dependent excess lifetime risks of fatal cancer associated with the radiation from a single multi-detector row CT angiography or digital subtraction angiography. The excess lifetime risk decreases with age at exposure because of the decreasing overall risk of fatal cancer during the remaining lifetime. Excess risk was estimated by using a radiation dose of 8.3 mSv for multi-detector row CT angiography and 9.9 mSv for digital subtraction angiography with the modified multiplicative model of ICRP 60 with a DDREF of 1.5. Different scenarios were calculated for varying hazard rates of annual PAD mortality. A higher annual mortality rate in a patient suffering from PAD leads to a relative decrease of radiation induced fatal cancer risk. The excess cancer risk in patients with PAD was calculated using the background national age-specific annual mortality rates multiplied with the mortality ratio from PAD.

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Table 2. *Estimated excess lifetime risk of fatal cancer mortality associated with radiation from a single examination at various DDREFs and annual mortality rates from peripheral arterial disease in a 64 year-old patient with peripheral arterial disease compared to a 64 year-old member of the Dutch population without peripheral arterial disease.*

	Excess lifetime risk of fatal cancer mortality (%)					
	DDREF 1.5				DDREF 1	DDREF 2
	No PAD	Mild PAD	Moderate PAD	Severe PAD	Moderate PAD	Moderate PAD
Hazard ratio*	1	1.3	2.5	4.5	2.5	2.5
MDCTA	0.018	0.014	0.007	0.003	0.009	0.005
DSA	0.022	0.017	0.008	0.004	0.012	0.006

Note. - MDCTA = multi-detector CT row angiography, DSA = digital subtraction angiography, DDREF = dose-and-dose-rate effectiveness factor.

A 64 year-old person without PAD has an annual mortality of the Dutch population. The calculations of these excess risks are based on mortality data of the Dutch population. Mortality ratios from PAD reflect the severity of disease and are multiplied with the background mortality rate from the Dutch population.

Different scenarios were calculated from varying the effective dose in a 64-year old patient with moderate PAD. When the highest published dose was used for MDCTA of 14.3 mSv (28) and for DSA of 36 mSv (36) the excess radiation risk will increase to a maximum of 0.03% and 0.01%, respectively. When the lowest published effective dose was used for MDCTA of 2.7 mSv (29) and DSA of 3.1 mSv (30), the excess radiation risk estimation can further decrease to 0.002% and 0.003%, respectively.

The reviewed reports on health risks of medical radiation all show that radiation-attributable lifetime risk of fatal cancer, both of solid cancers and leukemia, varies with gender and predominantly with age at time of exposure (Figure 3). With increasing age at exposure the lifetime mortality risk decreases. The figure also shows that the risk estimation based on the multiplicative model of IRCP 60 is comparable to risk estimations of other reports after an acute exposure normalized to 1 Sv and using a DDREF of 1.5.

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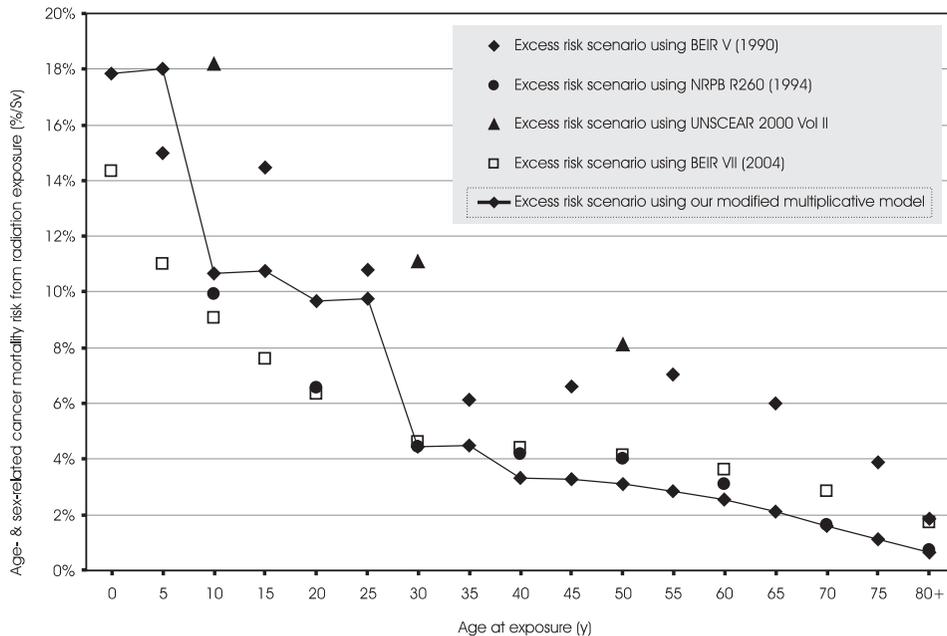
Figure 3 *Excess cancer mortality risk according to age at time of exposure in a stationary population that is exposed to an acute radiation dose of 1 Sv.*
Graph shows estimated excess cancer mortality risk according to age at time of exposure in a stationary population that is exposed to an acute radiation dose of 1 Sv. Data from different reports evaluates the differences between the estimated risks.

Discussion

Multi-detector CT technology combines fast scanning with high quality data sets which has resulted in new applications as well as improved use in traditional applications. A fairly new application of multi-detector row CT is angiography of the entire peripheral arterial tree in patients with peripheral arterial disease and its practice is increasing rapidly. The technique is performed to characterize the level, multiplicity, and severity of stenoses prior to a revascularization procedure. The evaluation of potential risks is an important issue in the assessment of a new radiological technology. The individual radiation risk for the patient in the context of other individual risks is an integral part of the risk-benefit evaluation of every diagnostic imaging procedure. The assessment of radiation risk is only valuable if the risk from the disease is taken into account. In this study, we compared the patient radiation dose at multi-detector row CT angiography with the reference standard, digital subtraction angiography, and estimated the patient specific excess lifetime cancer mortality risk associated with a single multi-detector row CT angiography or digital subtraction angiography examination.

We found a similar effective dose at MDCTA compared to DSA in PAD. For performing MDCTA we used a 4-, 16-, or 64-detector row CT scanner to visualize the peripheral vessels. Since we started performing these examinations within the context of a

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randomized controlled trial before dose reduction applications were installed, we did not use a protocol with dose reduction. Also, the acquisition duration was maintained when increasing the number of detector rows allowing an improvement of image quality. Since the radiation dose of the legs contributes minimally to the total effective dose to the patient, we did not include this in our calculations. Our estimation of patient radiation dose at MDCTA in PAD was comparable to the average reported dose of 7.4 mSv (28, 29, 36-38). Moreover, our estimation of patient radiation dose at DSA was comparable to the average reported dose of 9.4 mSv (28-30, 37-46). This dose must be seen against the context of the average annual background radiation (2-5 mSv in the United States of America). More important is to place the risk of inducing a fatal cancer due to medical radiation exposure in the perspective of a specific patient population which undergoes this examination. Therefore, we estimated the excess lifetime mortality risk of radiation induced fatal cancer in patients with symptomatic peripheral arterial disease. Patients suffering from PAD have a limited survival, which has been published by several authors. We found some variation in the survival of these patients and we used all studies which reported mortality ratios to evaluate the effect of the minimum and maximum mortality from PAD (13-21).

Recently, articles have focused on the estimation of the risk of developing fatal cancer due to X-rays (47-50). Concordant with their findings we found that a single MDCTA or DSA can add a small risk to the lifetime mortality risk. However, to justify the indication for a diagnostic imaging examination in a specific clinical problem, the benefits need to outweigh the risks. To our knowledge, no study has been performed to estimate the excess risk of radiation induced fatal cancers in a specific patient population. Our model, which is based on the multiplicative model of ICRP 60, incorporates two modifications to address the effect of mortality of an underlying disease of a specific patient population. The fist modification of the model was by using the age dependent annual background mortality for the Dutch population. The validity of the death registry is generally considered sufficiently good for epidemiological use (51, 52). The second modification was the inclusion of the high mortality rate of patients suffering from PAD. This enabled us to study the interaction between mortality from PAD and mortality from medical radiation exposure. Our results showed that the excess mortality risk associated with radiation doses from a single MDCTA or DSA in patients with PAD can be qualified as insignificant compared to the mortality rate from their underlying disease.

There are some assumptions in this model which deserve consideration. We assumed that the data on atomic bomb survivors provide accurate risk estimations of low linear energy transfer radiation. Also our model assumes a linear no-threshold function (LNT) for predicting health effects from radiation, which means that every exposure causes some risk and that risks are generally proportional to dose. Some authors claim that when dose-response data in atomic bomb survivors is extrapolated this may lead to a slight underestimation of actual risks in the relevant dose range (47). In contrast, the French Academy of Sciences and Medicine published that this LNT will lead to an overestimation (53). Considering these controversies, we assume that our approach is the best that we can currently achieve for risk estimations. Another as-

Potential Limitations

sumption is the use of a DDREF of 1.5 (instead of 2) which means that the projected number of health effects at low doses is larger than previously assumed.

Automatic exposure control systems are currently installed in new CT systems that are based on angular and longitudinal online current modulation which could significantly reduce radiation dose with approximately 30% (29, 54, 55). Besides the awareness to further reduce patient dose, the cooperative labor of radiologists, physicists, technologists, and manufacturer is necessary to implement this technique in clinical practice (56).

Given the high average age of patients with symptomatic peripheral arterial disease, we found it more valuable to estimate the risk of inducing a fatal cancer than including a small contribution to the risk of genetic defects due to gonadal radiation. In fact, we assumed that the hereditary effects could be largely disregarded.

A limitation of our study is that our data applies to the Dutch situation and for generalizability to other countries, the demographic data of those particular countries would need to be used. However, we do not expect large differences in the outcomes between Western countries since the demographic data, annual mortality rates, and prognosis with PAD are comparable across countries.

A possible limitation of this study is that dose estimations at DSA were made indirectly by using the DAP readout. In contrast with TLD measurements, DAP monitoring is easily performed and includes field size. In the literature, authors report an excellent correlation between the DAP measurement and thermoluminescent dosimeter for the dose estimates to calculate reliably effective patient doses in general as well as for imaging the lower extremities (44, 45, 57). This indicates that using simple conversion coefficients to estimate the effective dose is an acceptable method to calculate effective doses (49, 58). The average conversion coefficient we used was close to the findings in a recent study of conversion coefficients of angiography of the lower limbs (25). A number of authors have reported dose measurements for DSA. Our DAP values in PAD were comparable with those given by Vano et al. (59), Ruiz-Cruces et al. (60), and Hoskins et al. (42). Some authors have reported somewhat lower DAP values than our estimations (39, 44, 46, 61, 62) (63). A much lower DAP value is reported by others, probably due to the use of other techniques than digital subtraction angiography, such as conventional angiography (30, 40, 41, 43, 45, 63, 64). One author reported a higher DAP value (65). The effective dose conversion factor used in this study was within the range of published conversion coefficients for the calculation of effective dose from DAP in angiography of the lower extremities varying from 0.08 to 0.24 (25, 29, 30, 37-46, 58).

In conclusion, we found that the patient effective dose from MDCTA is comparable to the dose from DSA in patients with peripheral arterial disease. Furthermore, we found that the excess risk of radiation from MDCTA or DSA to induce fatal cancer is very small in this patient population. It is clear that this risk is insignificant due to the high age and high total mortality risk in these patients. We conclude that the radiation risks

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from pre-operative evaluation of peripheral arterial disease using MDCTA or DSA is of no major concern. However, according to the principle to maintain radiation exposure as low as reasonably achievable, efforts should still be made to optimize acquisition protocols, such as using automatic exposure control systems, to further decrease the radiation dose.

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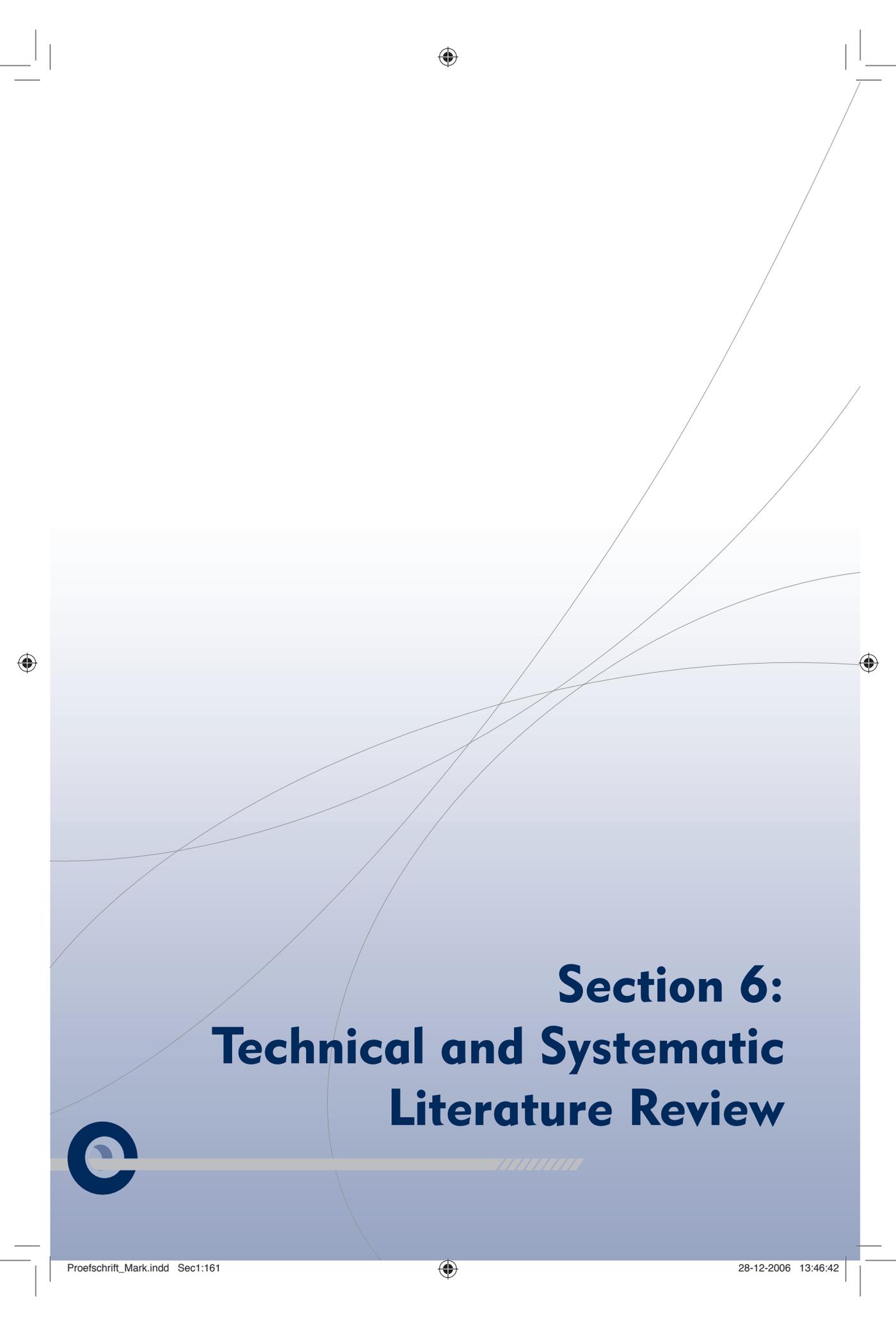
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Technical and Systematic Literature Review
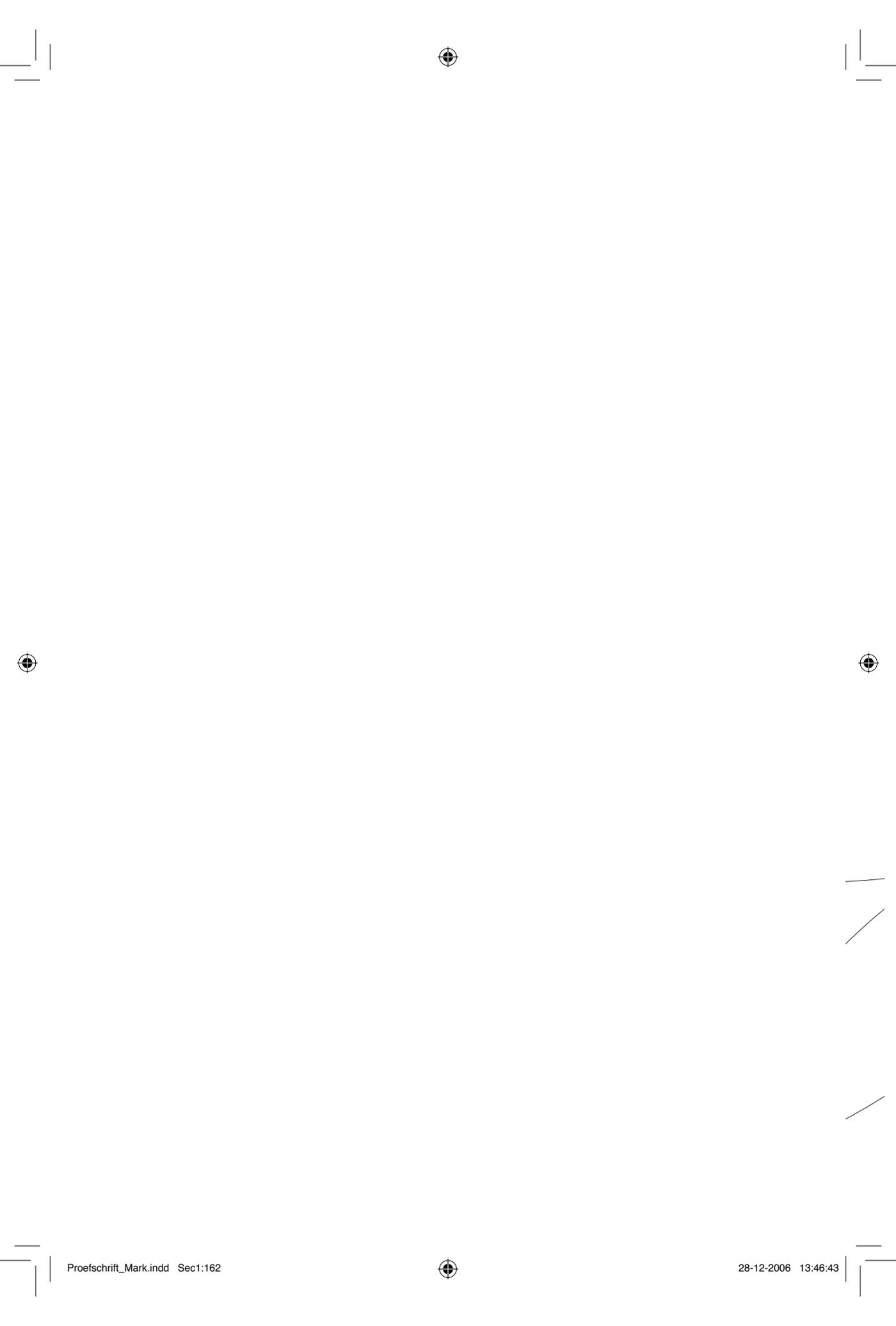
Chapter 9
Technical Review

Kock MCJM, Dijkshoorn M, Pattynama PMT, Hunink MGM.

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Technical and Systematic Literature Review

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Abstract

With the introduction of multi-detector row CT, scan speed and image quality has improved considerably. Since the longitudinal coverage is no longer a limitation, multi-detector row CT angiography is increasingly used to depict the peripheral arterial runoff. Hence, it is important to know the advantages and limitations of this new non-invasive alternative for the reference test, digital subtraction angiography. Optimization of the acquisition parameters and the contrast delivery is important to achieve a reliable enhancement of the entire arterial runoff in patients with peripheral arterial disease using fast CT scanners. The purpose of this review is to discuss the different scanning and injection protocols using 4-, 16-, and 64-detector row CT scanners, to propose effective methods for evaluation and presentation of large datasets, to discuss its clinical value and major limitations, and to review the literature on validity, reliability, cost-effectiveness, of multi-detector row CT in the evaluation of the peripheral arterial disease.

Technical and Systematic Literature Review

Introduction

Before multi-detector technology was available, the evaluation of peripheral arterial disease using CT was restricted to imaging only a portion of the peripheral arterial tree (1-8). With the introduction of four-detector row CT (4D-CT) in 1998, this major limitation was overcome. A complete coverage of the lower extremity inflow and run-off arteries was possible with one acquisition using a single contrast bolus. With the launch of the 16-detector row CT (16D-CT) in 2002 the spatial resolution increased to a near isotropic voxels and the contrast medium efficiency improved (9-11). In 2004, a true isotropic high spatial resolution of the entire volume was possible using the 64-detector row CT (64D-CT) scanner. In addition, improved X-ray tube capacity and scan speed allow submillimeter acquisition of a large coverage without limitations. These developments made multi-detector row CT angiography (MDCTA) an accurate alternative to the reference test, digital subtraction angiography (DSA), for the assessment of the peripheral arteries (12-25). CT angiography of the peripheral arteries can be performed on any multi-detector row CT scanner without any special hardware. With standardized scanning and reviewing protocols, peripheral CT angiography is a robust technique for chronic and acute problems of the peripheral arteries. The non-invasive examination can be performed in an outpatient setting and will take approximately 10 minutes of room time. We present a review concerning our experience with 4-, 16-, and 64-detector row CT scanners in patients with chronic obstructive peripheral arterial disease.

Technique

Preparation

There are no specific prescanning preparations necessary for multi-detector row CT angiography of the peripheral arteries. The patient is placed comfortably to avoid movement, in supine position with raised arms on the CT table. The legs are stabilized with cushions around the legs and slightly strapped with adhesive tape distally. It is important that the patient does not wear metal zippers or buttons on their clothing since this can have a negative influence on the image quality especially when using postprocessed images. Oral contrast should not be used as this complicates postprocessing display (Table 1). Contrast material needs to be administered at body temperature to decrease the viscosity. The protocol can be completely programmed into the scanner.

Data acquisition

Using the scanogram, the coverage of the acquisition is planned from the celiac trunk to the ankle joint at the level of the talus (Figure 1). We measured an average length of 118 cm (range 88-166 cm) from the diaphragm (to include the renal arteries) down to the ankles. When using the 4D-CT or the 16D-CT scanner, the optimal image quality of the entire arterial tree is a trade-off between scan speed and resolution. The choice of collimation varies with type of machine and protocol; 4-detector row CTs are limited to a collimation of 2.5 mm, whereas the 16- and 64-detector row CTs allow a submillimeter collimation of 0.75 and 0.6, respectively. As a rule of thumb,

the collimation should be as narrow as possible for the optimal scan duration. The speed of a contrast bolus to travel from the aorta to the popliteal arteries varies from 29 to 177 mm/sec in these patients (26). When the table speed is approximately 30-35 mm/s, which is obtained by adjusting the pitch factor and rotation time, there is little chance that the scan is faster than the intravascular contrast medium bolus. However, when using the increased acquisition speeds of 16D-CT and 64D-CT, the scanner may outrun the bolus. On the other hand, longer scan duration will increase the risk of venous contamination. Therefore, the optimal scan duration is approximately 35 seconds for a scan length of 1200 mm to have little risk of outrunning the bolus or venous contamination. It is not impossible to find, unexpectedly, an even more delayed arterial opacification in the distal arteries. To anticipate for this a second acquisition protocol should be programmed into the scanner to start immediately if poor enhancement is detected (Figure 2).

Table 1. *Prescanning preparation*

Parameter	Description
Clothing	No metal parts on clothing
Oral contrast	None
I.V. canula antecubital	Minimally 22 G (0.6 mm inner diameter, blue valve)
Positioning	Supine, stabilized and lightly strapped feet, feet-first, arms elevated
Scanned range	Diaphragm to ankles in 4D-CT Diaphragm including feet in 16D-CT, or 64D-CT*
Average range length (mm)	1200
Respiratory phase	Inspiration during abdominal-pelvic range
Window setting	Variable, set contrast as gray; set calcifications as white

To include feet using 16-detector row CT is possible at nominal slice width of 1 mm. To include feet using 64-detector row CT is possible at nominal slice width of 0.6 mm.
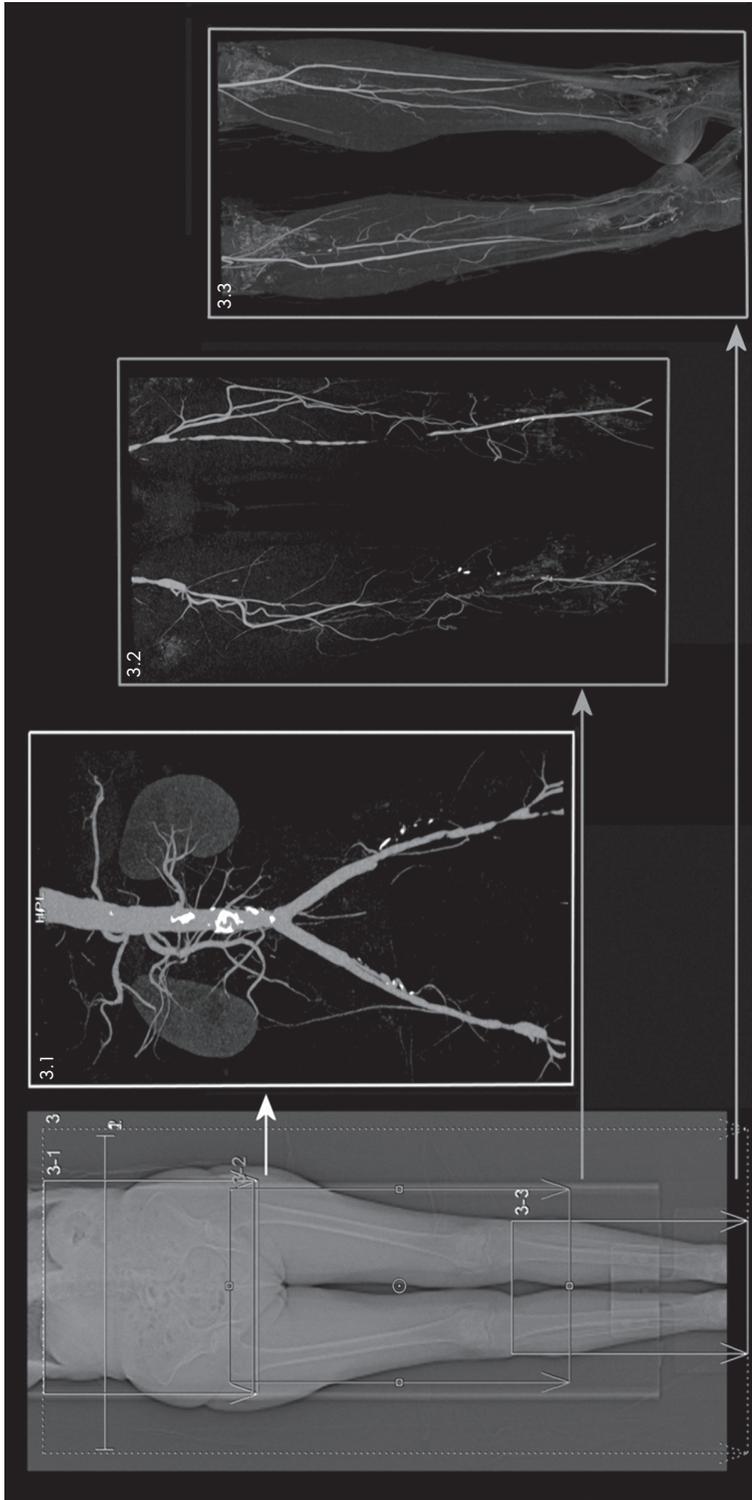
Figure 1. Scout image (left) with three planned reconstruction batches of the abdomen, the upper legs, and the lower legs to preserve postprocessed image resolution. The frames 3-1, 3-2, and 3-3 depict the field of view of the three batches, which needs to be as narrow as possible to optimize pixel size of the whole-body volume MIP images after semiautomated bone removal (right).
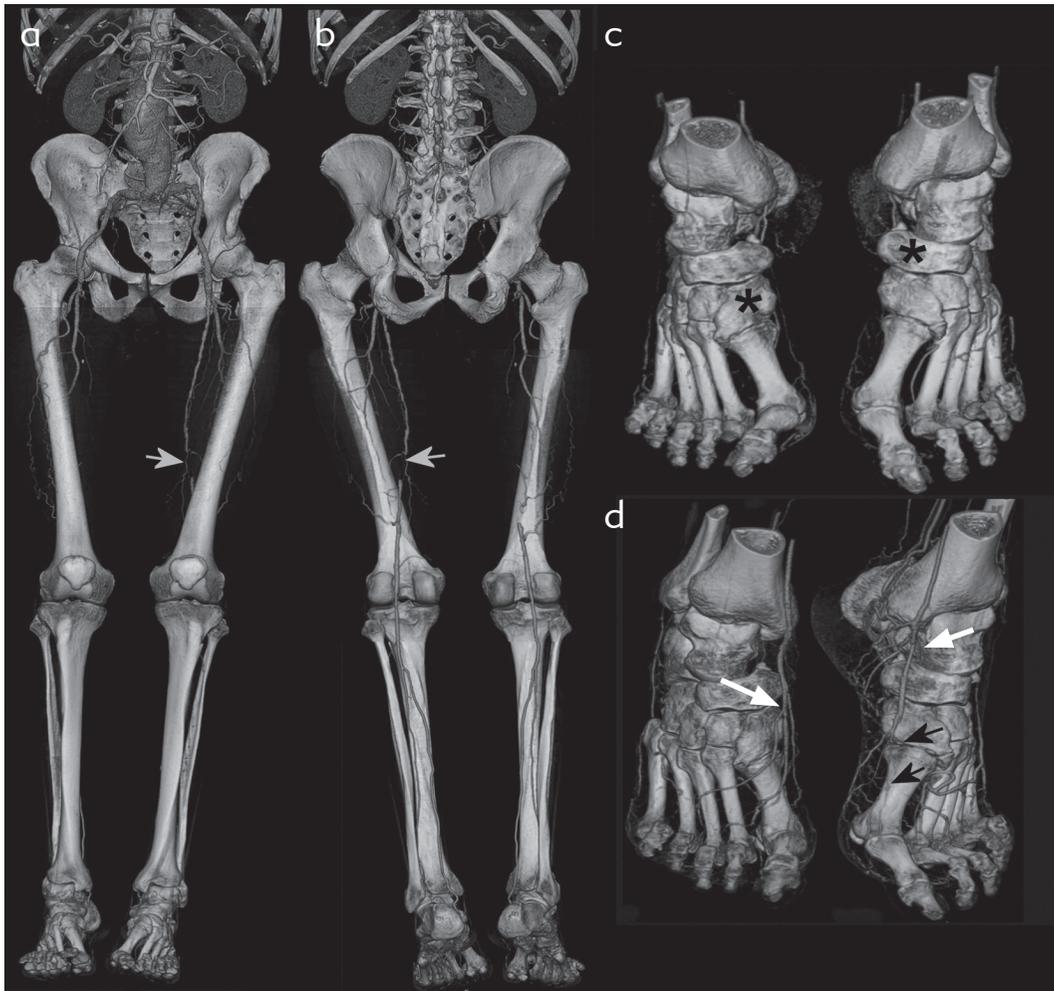
Figure 2. Images from the first and second, delayed, acquisition, of a 37-year old male with blue toe syndrome of the left hallux. (a and b) VRT images of the first acquisition show an aneurysmatic abdominal aorta with a short occlusion of the left femoral artery (arrow) due to thrombo-embolism and an occlusion of the entire right superficial femoral artery. The anterior tibial arteries seem occluded in both legs. (c and d) VRT image of the feet with the first and the delayed, second, acquisition. The first acquisition (c) shows that the arteries of the feet are not enhanced yet due to slow flow (black asterisk). The delayed acquisition (d) shows that both dorsal pedal arteries are patent (white arrow) and that the proximal arcuate artery and the first dorsal metatarsal artery (black arrow) of the left foot are occluded due to thrombo-embolism. (A full color version of this illustration can be found in the color section).
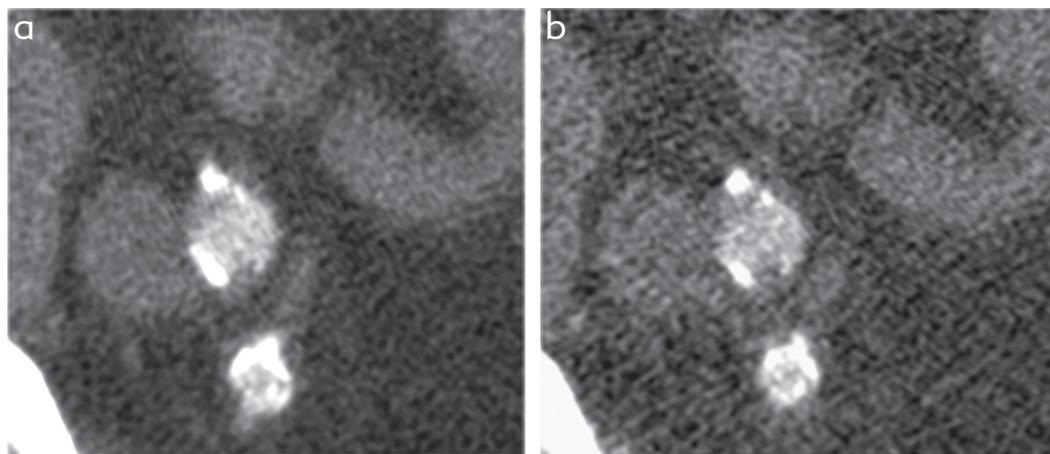
Figure 3. Images of 16D-CTA acquired with a collimation of 0.75 mm showing the effect of slice width (SW) on the blooming of the arterial wall calcifications. (a) Reconstructed axial image of the right external and internal iliac artery with SW of 3.0 mm using a B46 reconstruction kernel shows more blooming of the calcifications than (b). (b) Reconstructed axial image of the right external and internal iliac artery with SW of 0.75 mm using a B46 reconstruction kernel with less blooming of calcifications.

Using a 4D-CT (Volume Zoom Plus, Siemens) , the collimation must be wide enough (4 x 2.5 mm) and the pitch sufficiently high as needed to obtain the necessary table speed of 30 to 40 mm/s. As a result, the thinnest effective slice width achievable is 3 millimeter. Using a reconstruction increment of 1.5 mm the dataset is adequate for the assessment of the entire peripheral arterial tree. A 4 x 1 mm collimation of the entire longitudinal coverage will result in unacceptable long acquisition times (>50 s) or unacceptable image quality when increasing the pitch.

Sixteen-detector row CT (Sensation 16, Siemens) has overcome the limited resolution in the z-axis by allowing a detector configuration of 16 x 0.75 mm and shorter scan durations (Table 2). A slice width reconstruction of 1 mm is suitable at an interval of 0.5 mm. A minimization of the collimation allows a narrow effective slice width and a higher spatial resolution. Therefore, the partial volume effect and blooming effect of calcium will be reduced (Figure 3) (10). The downside is that image noise will increase and contrast to noise ratio will decrease but image quality remains acceptable in most patients. However, in obese patients, this protocol leads to unacceptable noise levels in the abdomen and pelvis. One of the reasons is that the tube is unable to deliver the necessary dose in this submillimeter configuration. In order to enable the tube to deliver a higher dose, a wider collimation must be used (16 x 1.5 mm) with a reduced pitch factor of 0.75 (Table 2) to improve the image quality in obese patients.

The 64D-CT scanner (Sensation 64, Siemens) we used has a 32-row detector, but due to double sampling in the z-direction, it acquires 64 overlapping slices per rotation.

Table 2. *Acquisition parameters for various multi-detector row CT configurations for angiography of peripheral arteries*

	Section Collimation Width (mm)†	Rotation Time (sec)	Pitch‡	Table Feed (mm/rotation)	Table Speed (mm/s)	Scan Duration (sec)§	Characteristics
4-DCT*	4 x 2.5	0.5	1.5	15	30	40	Slow scan protocol, thick minimal slice width
16-DCT*	16 x 0.75	0.5	1.3	16	32	38	Slow scan protocol, high resolution
	16 x 1.5	0.5	0.75	17	33	36	Slow scan protocol, less resolution, better in obese patients
	16 x 1.5	0.5	1.25	24	48	25	Fast scan protocol, less resolution, reduction contrast media
64-DCT*	2 x 32 x 0.6	0.5	0.9	17.1	34	35	Slow scan protocol, high resolution, isotropic voxel, double z-sampling, scanning of obese patients possible
	2 x 32 x 0.6	0.33	0.8	15.4	46	26	Fast scan protocol, reduction contrast media, high resolution, isotropic voxel, double z-sampling, scanning of obese patients possible
	2 x 32 x 0.6	0.33	1	19.8	60	20	Fast scan protocol, reduction contrast media, high resolution, isotropic voxel, double z-sampling, scanning of obese patients possible, risk of outrunning the bolus

Note. - *Protocols designed for Siemens CT scanners (Siemens Medical Systems, Erlangen, Germany) and should be modified appropriately for other models and manufacturers.*

†Values are number of sections times section width.

‡Pitch as the ratio of the table feed per rotation over the total width of the collimated beam.

§Scan times representing a scanned range of 120 cm.

There is a further improvement of the submillimeter collimation (2 x 32 x 0.6 mm) to increase the spatial resolution in the scan axis direction, allowing a high spatial resolution in all planes. The X-ray tube has a higher heat capacity and the X-ray beam widths are larger and allow scanning the crucial long lengths, with narrow slices, at high tube current–time product (mAs) levels. There is no longer a trade off between resolution and scan speed. Submillimeter scanning is not limited in obese patients. The high resolution and the double z-sampling decrease the blooming of vessel wall calcifications that can improve the assessment of the lumen of smaller arteries. Furthermore, it allows reconstructing 0.6 mm slices without reduction of image quality. The key issue is to refrain from using the maximum scan speed to avoid outrunning the bolus. This can be obtained for example by limiting the gantry rotation speed from 0.33 to 0.5 rotations per second or reducing the pitch (Table 2).

Fast scanning is possible using the 16D-CT and 64D-CT. Faster scanning leads to a reduction the scan duration and the amount of contrast media. Furthermore, a fast scan with an increased pitch could lead to a reduction of radiation dose. However, this doss not apply for the MDCT scanners of Siemens or Philips, where an effective mAs (which is mAs divided by the pitch) is used that automatically decreases or increases mAs with a decrease or increase in pitch to keep image noise constant. For the 16D-CT with a collimation width set at 1.5 mm and a pitch factor of 1.25, the scan duration is only 25 seconds (Table 2). Evidently, this leads to a decrease of longitudinal spatial resolution. Contrary, the 64D-CT is able to perform a fast scan at very high table speeds of 60 mm/s or more without decreasing the resolution.

Contrast Injection
The major challenges in CTA of the peripheral arteries are to obtain a high and homogenous enhancement of the arterial tree and to synchronize the acquisition with the enhancement. The optimization of acquisition timing and contrast medium delivery is essential in order to improve vascular assessment and quality of post-processed images. Normally, attenuation values higher than 200 HU in the arteries is considered suitable for MDCTA purposes (12, 13). For intravenous injection of contrast medium in the antecubital vein, at least a 22-gauge intravenous cannula is needed (0.6 mm inner diameter with a blue valve). The maximal flow rate for 22 and 20-gauge cannula is 3.5 and 5.0 mL/sec, respectively.

Acquisition timing
The time of intravenously injected contrast medium to arrive in the aorta varies from 12 to 40 seconds (on average 20 seconds). The time to enhance all arteries including the pedal arteries is on average 15 seconds (range 7 to 40 seconds) (26, 27). This large unpredictable variability does not necessarily correspond to a patient's severity of peripheral arterial disease. Thus, an accurate timing of the acquisition for each individual examination ensures that the scan is performed during the arterial enhancement and prior to venous enhancement. In the past, the delay was often fixed (approximately 30 seconds) and based on previous experience of the maximum aorta arrival time. Timing techniques that are more reliable are currently available and preferred when using modern scanners and power injectors. The test-bolus technique

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relies on the dynamic monitoring of a small contrast bolus in the arteries of interest, while the bolus-triggering technique is based on a repetitive sequential scanning at the level of the abdominal aorta to monitor the arrival time of the contrast material. About 10 seconds after the start of the contrast material injection, low-dose sequential scans are performed with a short interscan delay of e.g. 1.25-second to monitor the enhancement. Using automated bolus-triggering, the acquisition starts automatically when the preferred threshold is reached, approximately 100-to150 HU above the baseline value. During the transition delay, which is the time needed to move the table and start the scan, breathing instructions can be given to the patient and is approximately 4 seconds. During this delay, the enhancement of the aorta will further increase to an absolute value of more than 200 HU.

Using a fast scan protocol on a 16- or 64D-CT scanner with acquisition duration of 25 seconds or less, it is important to add an extra delay to the contrast arrival time. This extra delay can be calculated as 35 seconds minus the scanning time. This will ensure that all peripheral arteries, including the smaller distal arteries, are enhanced (28). Thus, for a scan time of 25 seconds an extra delay of 10 seconds is necessary that is added to the transition delay. Another option is to start the scan manually when enhancement is visualized at the level of the distal superficial femoral artery. Consequently, the time of contrast arrival increases with approximately 8 seconds (26, 27) and the transition delay of the scanner increases to 11 seconds.

A difficulty of performing a fast scan is that there is a greater risk of asymmetric enhancement in patients with severe unilateral stenotic or occlusive disease. It is safer to increase the injection duration of the contrast media and choose a slower scan speed. Especially in slow scanning protocols, enhancement of superficial and deep veins of the lower legs can occur, especially, when there is critical ischemia and inflammation. When venous contamination is nevertheless present, the discrimination of the arteries from the veins is often possible due to the stronger arterial enhancement and the anatomic 3D information (12).

Contrast delivery
A power injector is necessary to produce infusion rates of 3 to 4 ml/s, which is necessary for adequate arterial enhancement (12). These rates are equivalent to an iodine administration rate of 1.0 to 1.4 g/s when injecting a standard contrast media concentration of approximately 320 to 350 mg I/mL. By increasing the iodine concentration to a concentration of 400 mg I /mL, the iodine administration rate can be increased to 1.6 g/s leading to a higher maximum enhancement (29). The volume of contrast medium depends on the injection rate and on the acquisition duration. Using a slower scan protocol with a regular table speed of 30 mm/s or less, the volume of contrast material will range from 120 to 160 ml. In literature a volume of on average 134 ml at a mean injection rate of 3.5 ml/s, a mean concentration of 341 mg I/mL, and a mean iodine administration rate of 1.2 g/s is reported for imaging the peripheral arteries (9, 11-25, 30-37). Because the last volume of the bolus will not contribute to the enhancement when scanning below the knees, the injection duration can be shortened with 5 seconds, e.g. a 30 seconds injection time is used

for an acquisition of 35 seconds. However, to ensure enhancement of all arteries, the injection duration should not be shorter than 30 seconds and the delay time needs to be chosen appropriately to prevent outrunning the contrast bolus.

Using a monophasic injection rate the arterial enhancement increases over time to decrease at the end of the bolus. Consequently, the Hounsfield values of the enhanced arteries start lower at the level of the aorta and increase at the level of the popliteal artery to the highest attenuation value, and subsequently decrease distally in the run-off arteries. This is more important when longer scan durations are used (26). A more homogenous enhancement can be achieved using a biphasic injection rate using a higher rate (5-6 ml/s) at the beginning (during 5 seconds) of the injection and a lower rate (3 ml/s) for the remaining volume. In clinical practice a monophasic injection rate is often preferred because it is a simple method and has resulted in adequate image quality (29).

To optimize the enhancement in the area of interest during the acquisition, 20 to 60 mL saline can be used as a bolus chaser preferably using a parallel injector device. With a saline flusher a tighter bolus is created leading to an increase of the attenuation or allowing the use of less contrast medium volume (20-40% less) without affecting the enhancement (38). Finally, the body weight can influence flow rate and contrast volume. Good results are achieved with 1.8 to 2.0 ml/kg body weight for obtaining optimal enhancement (32, 37).

Patient Dose in MDCT
A particular concern with MDCT scanners is delivering potentially higher radiation dose. Current MDCT scanners are no longer restricted due to improved tube design with high heat capacity and wide beam widths that make it possible to scan long lengths with thinner slices. To prevent that the advantage of higher resolution is not to be lost due to increased image noise the radiation dose needs to increase proportionally to maintain the noise level. Conversely, through simultaneous acquisition of narrow slices with a wider beam width, improved active detector area, and reduced beam width that is not used for imaging the dose efficiency, is improved of these systems.

Radiation reduction for patients is based on justification and optimization. Justification implies that the benefit for the patient outweighs the risk of radiation exposure, i.e. the avoidance of unnecessary examinations. Current MDCT scanners can present on the scanner console an indication of patient dose to increase dose awareness and help to optimize the scan protocol. Effective dose can be derived from these dose quantities. The average patient dose reported in the literature in the assessment of PAD with CT angiography is 7.47 mSv (range 2.7 to 14.3) (9, 12, 24, 32, 39) and with conventional angiography this is 9.79 mSv (range 3.1 to 36.2) (9, 12, 24, 32, 39-56). The literature shows that patients with PAD have an average age of 64 years and, additionally, a poor prognosis due to their systemic atherosclerosis (57-59). Although often radiation risk to develop a fatal malignancy during their remaining lifetime is reported as a limitation of MDCT, we have calculated that this risk is legible in

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this population after correction for the mortality of peripheral arterial disease.
Optimization of the scan protocol can lead to dose reduction. Selecting 100 kVp in
CT angiography can lead to a dose saving of approximately 40% (60-62). Another
method for dose reduction is to adjust X-ray output automatically by varying the tube
current between rotations to account for changing attenuation along the patient's
length, which is known longitudinal tube current modulation and by varying the tube
current during the course of a rotation to compensate for the changing attenuation
through different projections around the patient, which is called angular tube current
modulation (9, 63, 64).

Display and Evaluation

Image Reconstruction

Because of the large volumes that need to be covered, it is easy to create 2500 axial
images depending on slice width and reconstruction increment. Saving all images in
the Picture Archiving and Communication System (PACS), can lead to storage capac-
ity problems. In addition, working with these large data sets can result in performance
problems due to limited memory, which can lead to laborious and time-consuming
postprocessing and image reviewing. A solution is to reconstruct separate data sets,
which will have more benefits.
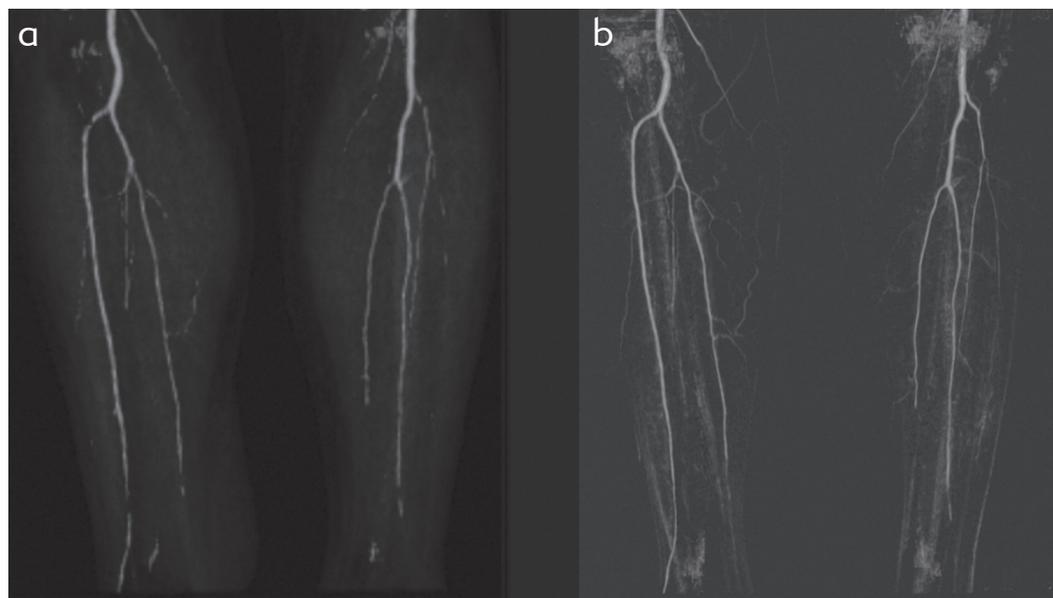
*Figure 4. Reconstruction method and image quality of MDCT in a 71-year-old female with symptoms of
acute thrombo-embolisms. (a) Section of VRT of the distal run off arteries, reconstructed from the entire
data set has a reduced diagnostic image quality compared with (b). (b) VRT image reconstructed using
only the section data of the distal part of the extremities that depicts more detail of infrapopliteal arteries.
(A full color version of this illustration can be found in the color section).*

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Routinely, we create three separate axial datasets of the peripheral runoff with an overlap of 5 to 10 cm to ensure complete demarcation of the disease (Figure 1). The first advantage is that it allows to reconstruct thicker slices, e.g. of 1.5 mm for the abdominal and femoral data set, and when clinically relevant additionally the thinner slices can be calculated, to minimize the load of data. Especially for the infrapopliteal arteries the lumen assessment can be more problematic and for the crural dataset the thinnest slices can reconstructed to obtain the necessary resolution (9, 10, 16, 20, 23).

Secondly, postprocessed images that are calculated from the entire data set can have a decreased resolution, due to the limited display matrix (512 x 512) used (33). To take full advantage of the longitudinal resolution, reconstructed images of separate batches will preserve the initial longitudinal resolution, which is especially important the smaller vessels of the calf and foot (Figure 4). The field of view (FOV) can be selected as small as possible to optimize pixel size. For the abdominal data set, the FOV is approximately 380 mm, for the upper legs, the FOV is 350 mm, and for the lower legs, it is 300 mm. This results in a pixel size of approximately 0.74, 0.68 and 0.58 mm, respectively. For evaluating infrapopliteal arteries, especially when severely diseased, it can be rewarding to reconstruct two separate datasets of the lower legs. The FOV can be further decreased to 200 mm leading to a resolution in the xy-plane of 0.4 mm.

A smooth to medium convolution kernel (B20 to B31 for Siemens CT scanners), is generally used in CT angiography and leads to an accurate depiction of the diameter of the vessels and is very appropriate for post-processing. A sharp kernel (B46) is used, when stents or severe vessel wall calcifications are present. It improves lumen delineation by minimizing the effect of blooming, at the cost of some increase of the noise level (65). However, this kernel is not suitable for all postprocessing techniques. Additionally, the abdominal-pelvic region can be reconstructed with 5 mm consecutive slices using the window settings for a standard abdominal review to screen for incidental non-vascular pathology. There is a need to standardize the tasks related to image reconstruction and archiving when performing MDCTA of the peripheral arteries on a routine basis.

Advanced Postprocessing and Image Evaluation
Additional two-dimensional (2D) and three-dimensional (3D) postprocessing techniques are required to facilitate interpretation and presentation. Reviewing exclusively the transverse images is inefficient and less accurate than reviewing a combination of reformatted images. The decision which postprocessing techniques are necessary depends on the disease and the purpose of the images (analysis or presentation). When extensive calcifications or stents are present, the vessel lumen visibility and the clinicians' confidence in the CT images will decrease (25), and adequate postprocessed imaging is required for optimal lumen depiction (Figure 5).
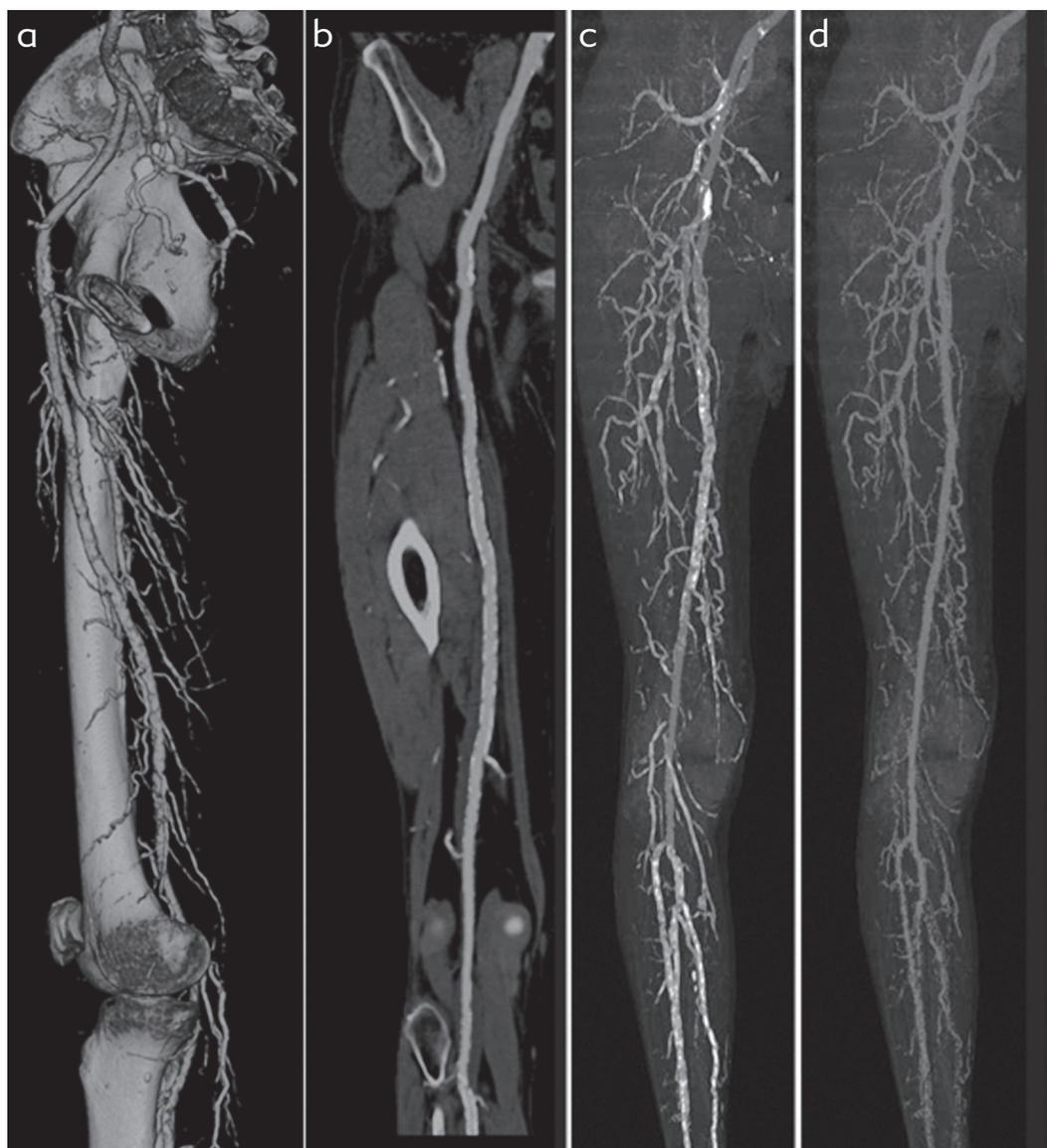
Figure 5. Influence of vessel wall calcifications on postprocessed images and the ability of lumen assessment. (a) VRT image (medial view) of right femoropopliteal segment showing arterial wall calcification and does not allow luminal assessment. (b) CPR image (anteroposterior view) shows the interior of blood vessels as a longitudinal cross-section even in the presence of the arterial wall calcifications. Volume-MIP (anteroposterior view) after bone removal (c) does not allow lumen evaluation and Volume-MIP after additional calcification removal (d) again shows the patency of the arteries. (A full color version of this illustration can be found in the color section).
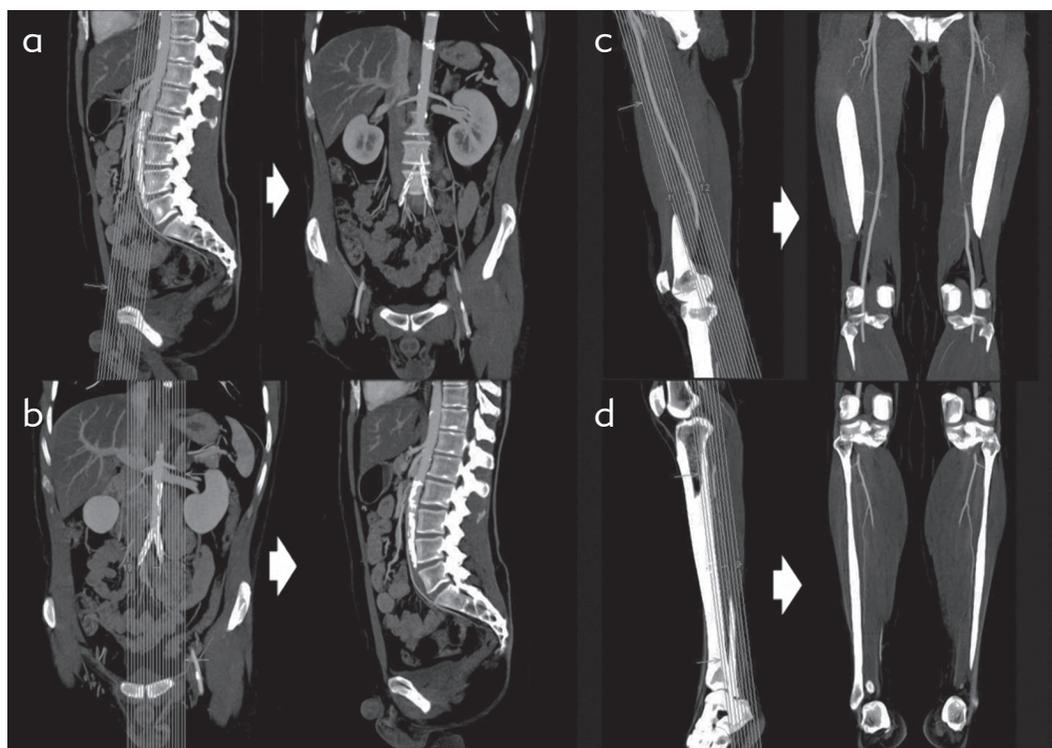
Figure 6. Standard slab-MIP images in the postprocessing protocol make MDCTA of peripheral arteries on a routine basis feasible. Slab-MIPs are easy and fast to create and to evaluate. The images depict the vasculature without superimposing bones (a and b). From the abdominal data set MIP images are created in coronal projection, to depict the renal arteries (b) and in sagital projection to depict the celiac trunk and mesenteric arteries (d). The aorta is also depicted for evaluation. (c) Standard coronal slab-MIPs from the data set of the upper legs are created which are parallel to the superficial femoral and popliteal artery. (d) Standard coronal slab-MIPS from the data set of the lower legs display the crural arteries.

To preserve image quality for vessel assessment and clinical decision-making, a standard set of postprocessed images needs to be included in the protocol. Preferably, dedicated 3D laboratory technologists create the standard set of images. These include thin-slab maximum-intensity projections (MIPs) through visceral and renal arteries and the abdominal aorta, through femoropopliteal arteries and through crural arteries (Figure 6); whole-volume MIPs of the separate data sets after bone removal (Figure 1) and when necessary, after removal of vessel wall calcifications (Figure 7); curved planar reformations (CPRs) through both iliac arteries projected in at least two orthogonal projections (Figure 7) or with true cross-sectional images; and volume renderings (VRs) of the entire volumes or focused on the sites of disease in more detail (Figure 2). The data sets are reviewed effectively by evaluating the standard set of postprocessed images and, interactively, exploring the axial images or multiplanar reformations (MPRs) in any direction through the dataset. The transverse images (or the true cross-sectional images in iliac arteries) always need to be considered during interpretation for stenosis verification (Figure 8) (4, 6, 19). To communicate effec-

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tively with the clinicians, it is important to focus on images that produce a roadmap of the vasculature, to facilitate the subsequent decision processes for planning a revascularization procedure.
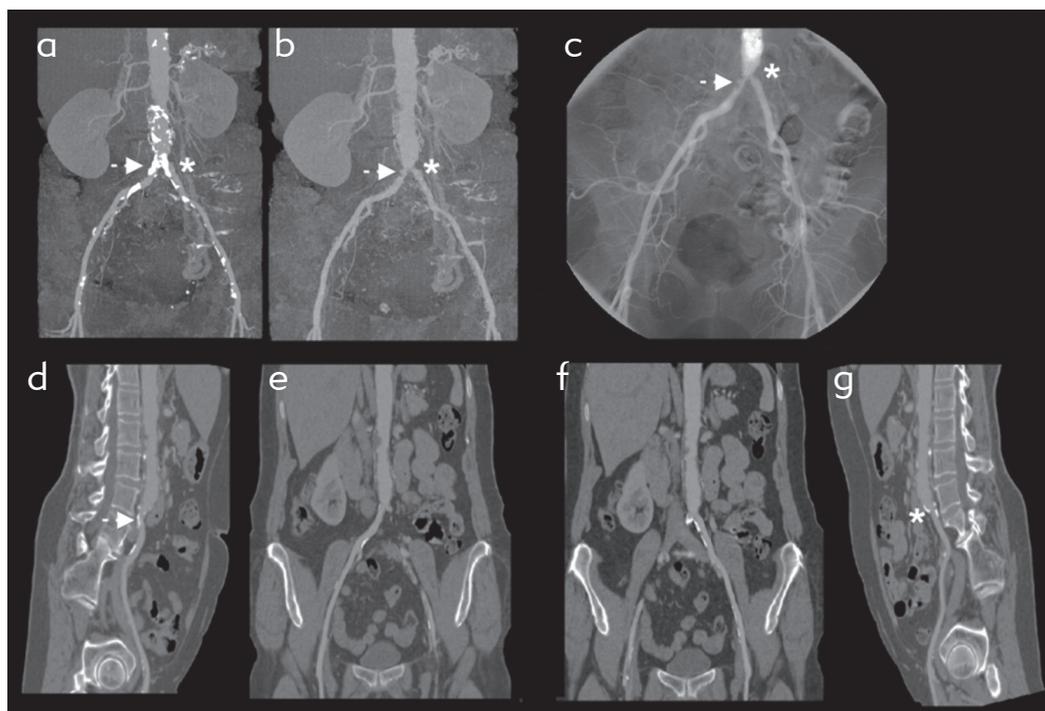

Figure 7. *Curved aortoiliac arteries need additional postprocessing for lumen assessment in a 57-year-old female with intermittent claudication of both legs. (a) Lumen is not visible in the volume MIP after bone removal showing vessel wall calcifications. (b) Volume MIP after removal of bones and vessel wall calcifications shows moderate stenosis (arrow) of the right common iliac artery and severe stenosis (asterisk) of the origin of the right common iliac artery. (c) Digital subtraction angiogram confirmed the stenoses. (d-g) CPR images in two orthogonal directions unfold the iliac arteries allow lumen assessment and show asymmetrical stenoses on lateral projections on right (arrow) and left side (asterisk).*

MPR is a simple technique for the interactive evaluation of the data by flying through the dataset in every orientation. A derivative of this is CPR, which displays the lumen as a longitudinal cross-section, which is very practical in the assessment of curved arteries, in particular when arterial wall calcifications or stents are present. The central lumen line can be (semi-)automatically detected after the manual definition of start- and endpoint of the vessel. The projection can be rotated around the longitudinal axis or should include at least two perpendicular longitudinal projections (Figure 7). The true cross-sectional images need to be viewed for lumen assessment (Figure 9) (19). Additionally, software tools are available for automatic quantitative evaluation of the lumen by creating a graph that depicts the diameters of the lumen along its longitudinal axis (Figure 9). A pitfall of CPR is that misinterpretation can occur when an inaccurately positioned central lumen line introduces a pseudo-stenosis. When us-
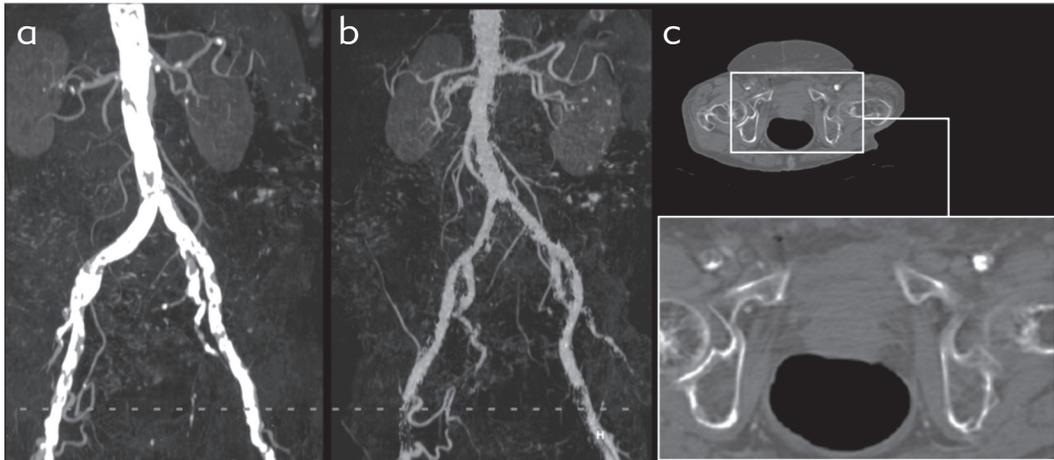
Figure 8. Severe vessel wall calcifications in a 61-year-old man with left leg critical ischemia. (a) Vessel assessment with volume MIP image after only removal of the bones is hampered by extensive vessel wall calcifications. (b) Volume MIP after segmentation of bones and calcifications reveal a high grade stenosis in the left common femoral artery and an occluded right common femoral artery. (c) The transverse source images at the level of the common femoral artery (dashed line) is required to confirm the findings.

Figure 9. Results of semiautomated quantitative lumen assessment in aortoiliac arteries of a patient with in stent thrombosis. (a) Graph (upper section) displaying the maximum and minimum diameters of the lumen to quantify stenosis. CPR (lower section) through the aortoiliac arteries, which can be rotated around its longitudinal axis, depicts the luminal obstruction (asterisk) due to a thrombus inside an iliac stent.

(b) Corresponding transverse image confirms the occlusion of the iliac stent. (A full color version of this illustration can be found in the color section).

ing semi-automated tracing applications this risk is minimized. Multipath CPRs could enhance image evaluation and the technique is under development.

MIPs present a collapsed volume projected in a plane using the maximum Hounsfield

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value encountered in a line in that volume perpendicular to the plane. To solve the limitation of superimposing bone structures, thin-slab MIPs are used, to depict the vasculature by scrolling through the stack without superimposing structures since the volume is divided in thinner subvolumes and the arteries are evaluated by scrolling through the stack (Figure 6). The thickness of the slab is variable and depends on the size of the vessel and on the distance of the vessel and the bones. Another option to remove the superimposed bony structures in MIPs is to use thresholding, region-growing, and selection and subtraction algorithms. Using a threshold value, bone and arteries are selected as objects. The arteries are deselected by placing a
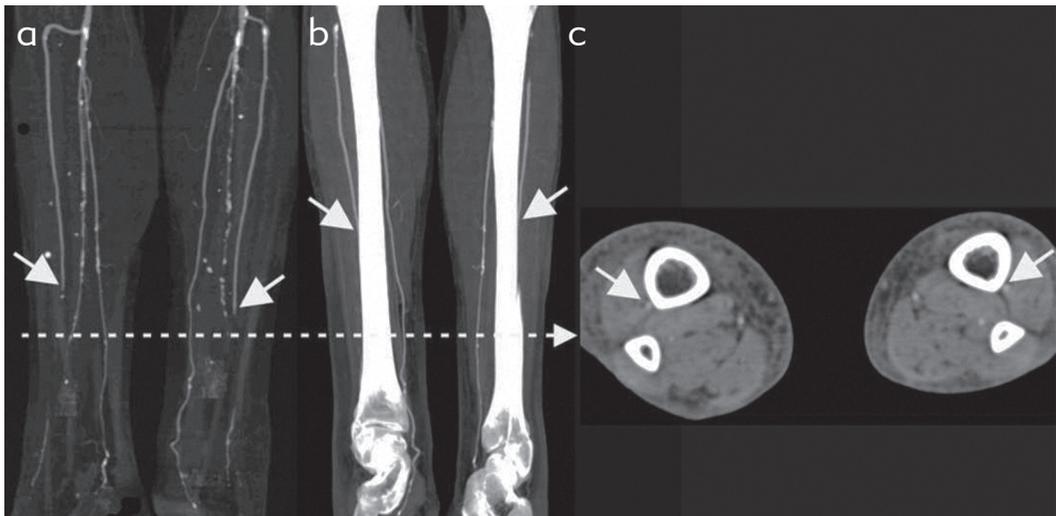

Figure 10. *Images of segmentation artifacts due to bone removal in 16D-CTA. (a) Volume MIP after bone segmentation of the lower legs showing a pseudo-occlusion of both distal anterior crural arteries (arrows) which is caused by segmentation of the bones. (b) MIP of the lower legs showing the anterior tibial arteries in close proximity to the tibia (arrows) which is the cause of the false positive pseudo-occlusion (c) Axial image of the lower legs just caudal from the pseudo-occlusion showing the patency of both anterior tibial arteries of both legs in close proximity of the tibia (arrows).*

region-growing seed. The bone-selection is inverted to display the data set without the bones to create an angiogram-like image (Figure 5). Contrary to the removal of the bones, can the removal of the numerous arterial wall calcifications be very time consuming. First, a higher threshold value needs to be used to select the cortical bone and the calcifications without the enhanced lumen. This selection is merged with the previous bone-selection. Subsequently, inverting this combined selection leads to the display of the arterial roadmap without bones and arterial wall calcifications (Figure 5). Readers should be aware of misinterpretation when performing data segmentation. Pseudo-stenosis or occlusion can be suggested by the image by inadvertent removal of voxels that represent lumen, in particular when in close contact with the bones (Figures 10, 11). Artificial stenosis or occlusions can also be introduced by using a too low threshold value. Our experience suggests that threshold values should be chosen so that some rest voxels of the burden of calcifications are just visible as

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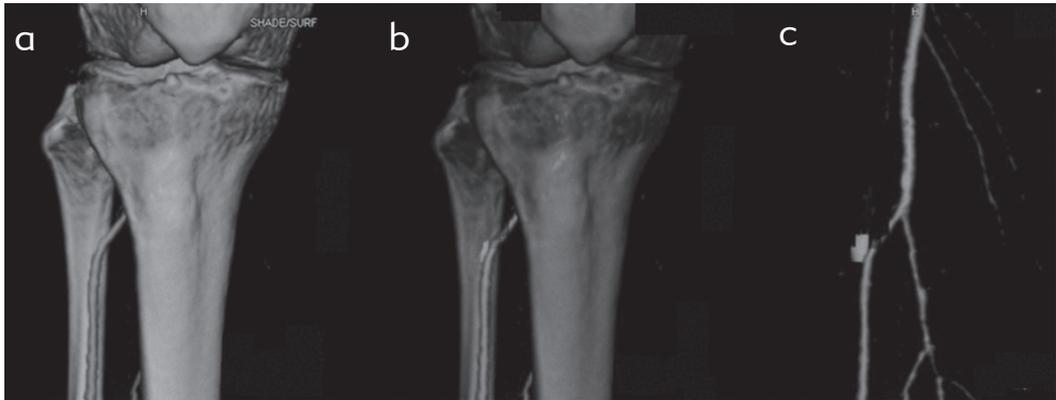
Figure 11. Applying blue color to the voxels selected for removal helps to identify the sites of segmentation artifacts in VRT images. (a) VRT image before bone segmentation of the lower legs showing patent proximal anterior tibial arteries. (b) VRT with blue bones to indicate the voxels to be removed shows the voxels of the bone which are in contact with the proximal anterior tibial artery are not selected for removal and shows the voxels of the artery which are selected for removal. (c) Segmented VRT image showing the pseudo-occlusion of the anterior tibial artery.(A full color version of this illustration can be found in the color section).
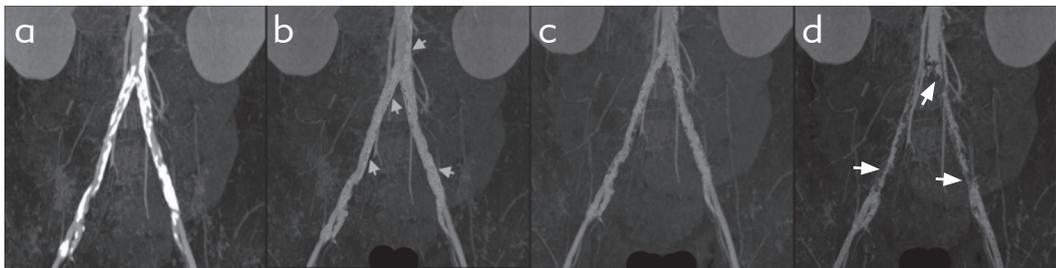

Figure 12. Volume MIP images in anteroposterior projection show the result of three different threshold levels used for the segmentation of arterial wall calcifications. (a) Volume MIP before removal of the calcifications shows that the lumen is not visible. (b) Volume MIP after removal of the calcifications shows that still many voxels of calcification are present hampering lumen assessment (grey arrow). (c) Volume MIP shows angiogram after calcium segmentation using a correct threshold level allowing lumen assessment. Rest voxels of the burden of calcifications are just visible as unesthetical noise, which is, however, preferable to introducing pseudo-stenoses (d) (white arrow) by using a too low threshold level.

unesthetical noise, which is preferable to introducing pseudo-stenoses by using a too low threshold level (Figure 12).

The volume rendering technique (VRT) depicts structures that are interactively coded with different colors and opacity. Using the angiography presetting, it provides an easy and interactive overview of arteries and bones. Bone editing is possible but often not necessary and preserves the perception of depth (66). Projections from different angles can be created for presentation to clinicians, who normally do not have the possibility to review the dataset interactively (Figure 2). Limitations of VRT are that circumferential wall calcifications could hide stenoses and that VRT settings could be

too narrow suggesting stenoses. Therefore, VRT should be preserved for rapid overview or for presentation purposes and not for the assessment of stenosis (Figure 5).

Tabel 3a. *Validity of CT angiography in peripheral arterial disease*

Author*	No. of Patients	No. of Analyzed Segments	No. of Detectors	Reported Sensitivity (%)§	Reported Specificity (%)§	Assessed Segments	Stenosis Category (%)‖
Richter et al 1994	32	NA	1	84	NA	Iliac	>50
Lawrence et al 1995	6	134	1	93	96	Femorocrural	>50
Raptopoulos et al 1996	39	624	1	93	96	Aortoiliac	85-99
Rieker et al 1996	50	400	1	73-88†	94-100†	Femorocrural	75-99
Rieker et al 1996	30	210	1	93	99	Aortoiliac	75-99
Kramer et al 1998	10	NA	2	94	NA	Iliocrural	>90-99
Ishikawa et al 1999	49	NA	1	97	95	Bypass grafts	NA
Bourlet et al 2000	22	318	1	95	90	Aortoiliac	>50
Puls et al 200	31	186	4	89	86	Total tree	50-99
Willman et al 2003	46	769	4	91	99	Aortoiliac grafts	NA
Ofer et al 2003	18	410	4	91	92	Total tree	>50
Heuschmid et al 2003	18	568	4	91#	92#	Total tree	>50
Martin et al 2003	41	1312	4	92	97	Total tree	75-99
Catalano et al 2004	50	1148	4	96	93	Total tree	>50
Mesurolle et al 2004	16	168	2	91	93	Total tree	>50
Ota et al 2004	24	470	4	99	99	Total tree	>50
Poletti et al 2004‡	12	144	4	82/86**	NA	NA	>50
Portugaller et al 2004	50	740	4	92	83	Total tree	area >70
Romano et al 2004	42	3402	4	93	95	Total tree	NA
Romano et al 2004	22	1782	4	92	94	Total tree	NA
Stueckle et al 2004	52	NA	4	82	100	Total tree	NA
Edwards et al 2005	44	1024	4	79	93	Total tree	50-99
Fraioli et al 2005	75	1425	4	96-99¶	94-96¶	Total tree	50-99
Schertler et al 2005	17	170	16	96	90	Popliteocrural	>50
Willmann et al 2005	39	1365	16	96	96	Total tree	>50
Mean				91	94		

*Note. - NA = not available. * Based on references (1-6, 8-10, 13-24, 32, 36, 77, 78)*
†For various anatomic levels. # Calculated from the data. ‡ Based only on subtracted MDCTA images the positive predictive value was 95%. § Sensitivity as published or calculated overall mean.
*‖ Diameter stenosis is mentioned unless specified (>50 means stenosis more than 50% including occlusion). ** For subtracted and nonsubtracted segments, respectively. ¶Depending on the MDCTA protocol with varying mAs.*

Table 3b. *Intertest agreement between CT angiography and digital subtraction angiography in peripheral arterial disease*

Author[*]	No. of Patients	No. of Assessed Segments	No. of Detectors	Reported Inter-test Agreement[§]	Assessed Segments
Raptopoulos et al 1996	39	624	1	90%	Aortoiliac
Beregi et al 1997	20	52	1	100%	Popliteal
Tins et al 2001	35	219	1	84%	Aortoiliac
Walter et al 2001	22	456	4	K = 0.68 (0.50-0.97)[‡]	Total tree
Rubin et al 2001	18	351	4	100%	Total tree
Heuschmid et al 2003	23	1136	4	86%	Total tree
Ofer et al 2003	18	444	4	78%	Total tree
Romano et al 2004	42	3402	4	K = 0.68; 90%	Total tree
Romano et al 2004	22	1782	4	K = 0.68; 90%	Total tree

[*] *Based on references (3, 7, 12, 14, 16-18, 37, 76).*

[†] *Based on 97% of the segments.* [‡] *Average of the reported kappa values (ranges) of the individual anatomical segments.* [§] *An unweighted kappa statistic (K) is reported or percentage agreement*

Wall calcification problem
The depiction of vessel wall calcifications using MDCT can be valuable since severely calcified arteries may have consequences when bypass surgery is contemplated. On the other hand, these wall calcifications are known to hamper the assessment of the lumen (2,10,14,19). Approximately 20% to 50% of the vascular segments contain wall calcifications and in 10% the arterial segments are severely calcified (11,19). In particular, we found that patients with a history of diabetes mellitus, cardiac disease, or elderly age, are very likely to have extensive calcifications. Diabetes is most strongly associated with stenoses of the femoropopliteal and infrapopliteal segments. Furthermore, PAD in diabetics is more often more progressively and more severe with symptoms at rest and ulcers (classified in Fontaine stage III or IV) compared to in patients without diabetes (67,68).

How can we deal with the vessel wall calcifications depicted with MDCTA? Important is to use a wider window width (WW) and higher window center (WC) level settings from the usual CT angiography level of around 150 WC ± 250 WW to 200 WC ± 1000 WW, for a better differentiation of calcifications and stents from the enhanced lumen and to minimize the effect of blooming. A further minimization of blooming is reached by using a sharper reconstruction kernel and higher spatial resolution.

Especially in MIP images is the lumen hidden by the circumferential calcifications. In these circumstances transverse images, CPR images, and the digital removal of the

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Table 3c. *Interobserver agreement of CT angiography in peripheral arterial disease*

Author[*]	No. of Patients	No. of Assessed Segments	No. of Detectors	Reported Inter-test Agreement[§]	Assessed Segments
Raptopoulos et al 1996	30	210	1	K = 0.95	Aortofemoral
Walter et al 1997	22	456	4	K = 0.71-0.76[‡]	Total tree
Tins et al 2001	35	219	1	78%	Aortofemoral
Martin et al 2001[***]	41	1312	4	K_w = 0.84	Total tree
Romano et al 2001	42	3402	4	K = 0.84;0.86[§]	Total tree
Romano et al 2003	42	1782	4	K = 0.85;0.88, K = 0.80[ǁ]	Total tree
Catalano et al 2003	50	1137	4	K = 0.80	Total tree
Ota et al 2004	24	470	4	K = 0.88	Iliac
Portugaller et al 2004	50	740	4	K = 0.81	Total tree
Kock et al (this thesis)[**]	73	2268	4	K_w = 0.84	Total tree
Ouwendijk et al 2005	79	2419	16	K_w = 0.85	Total tree
Willmann et al 2005	39	1365	16	K = 0.85–1	Total tree

Note. - [*] Based on references (4, 7, 9, 11, 15, 17-19, 21, 23, 37).

[†] An unweighted kappa statistic (K) is reported, unless indicated (K_w = weighted kappa statistic).

[***] A linear weighting was used except in one paper (15) where a quadratic weighting was used.

[‡] Range of kappa values of the individual anatomical segments.

[§] For reader one and two, respectively.

[ǁ] For intraobserver (two readers) and interobserver agreement, respectively.

[**] Based on chapter 3

calcifications help to depict the lumen, at least for the larger arteries. Despite all the available tools, in particular in the smaller crural arteries, the concentric calcifications still hamper lumen assessment (Figure 5) (11). Recent publications showed that a subtraction technique using two acquisitions is feasible in some patients with PAD using MDCTA (24, 69). In the near future, automated 3D applications, such as multi-path CPR, and automated lumen measurements (Figure 9), could help to minimize the impediment of the calcifications (70). Whether dual energy CT angiography can improve this limitation of CT needs to be evaluated. With current technology, we have to accept this limitation and need to distinguish patients with intermittent claudication from chronic critical ischemia. We may justify a preferential indication for MDCTA in patients with intermittent claudication (Fontaine stage II). Patients with

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critical limb ischemia (Fontaine stage III or IV), are likely to have a history of diabetes mellitus, cardiac disease, or elderly age, and thus likely have extensive calcifications of the smaller arteries, could be better off undergoing contrast enhanced magnetic resonance angiography (CEMRA) or DSA.

Clinical Value

Because MDCT angiography for imaging of the peripheral arteries is a rather new non-invasive technique, there are a small number of studies published on its performance and reproducibility. The majority report on 4D-CT, three authors report on 16D-CT. There are no reports of the assessment of peripheral arterial disease using the 64D-CTA. The reporting quality of the published studies was fairly poor since because authors use various thresholds for categorizing significant stenosis, anatomical segment categorization, and different imaging projections, authors should take more into account the Standards for Reporting of Diagnostic Accuracy (STARD) checklist (71). However, combining all reported data on sensitivity and specificity for depicting vascular stenosis in PAD using CT angiography, results in a mean sensitivity and specificity of 92% and 94%, respectively (Table 3a). For multi-detector row CT angiography, where the entire arterial tree is visualized, this is 91% and 94% for 4D-CTA (13-23), and 96% and 93% for 16 DCTA (9, 10), respectively. Publications on reproducibility of CT angiography reported a good intertest agreement between MDCTA and DSA (Table 3b) and a good to excellent interobserver agreement for 4D-CTA (12,21,23,37), and 16D-CTA (9,11). Some authors reported kappa values for every individual segment and between different readers separately which makes comparison of the literature difficult (Table 3c). Only a few studies provide stratified data on the aortoiliac, femoropopliteal, and crural tract and show that the accuracy and reproducibility of the crural tract is lower than for the aortoiliac and femoropopliteal tract (9,11,20,22,23).
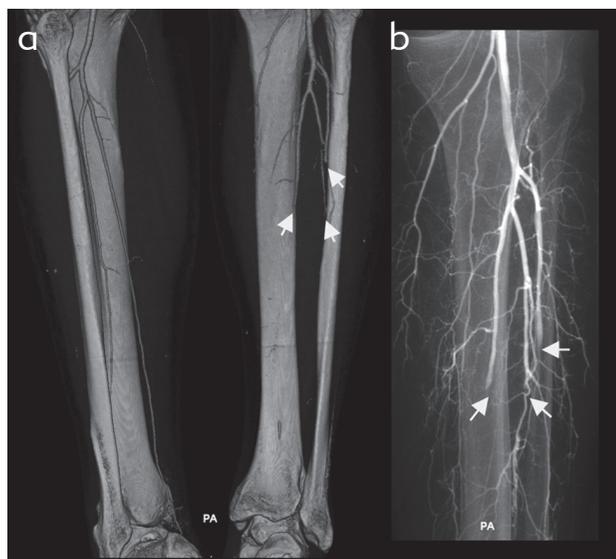

Figure 13. Acute thrombosis of the crural arteries in a 53-year-old woman with an acutely cold left leg after stopping anticoagulation therapy. The patient refused angiography. (a) VRT image (posteroanterior view) of MDCTA at the level of the crural arteries shows abrupt stop of arterial opacification in the left peroneal, anterior, and posterior tibial artery (arrow). The contralateral right crural arteries are patent. (b) Selective anterograde DSA image (posteroanterior view) confirms the occlusions of the three left crural arteries (arrow) due to thrombo-embolisms. (A full color version of this illustration can be found in the color section).

Table 4. *Advantages and limitations of multi-detector row CT angiography (MDCTA), contrast enhanced MR angiography (CEMRA), and digital subtraction angiography (DSA)*

Advantages and limitations	MDCTA	CEMRA	DSA
Intermittent claudication (Fontaine II)	+	+	+
Chronic critical ischemia (Fontaine III or IV)	-	+	+
Short examination time	+	-	-
Short postprocessing time	-	+	+
Outpatient setting	+	+	-
Availability	+	-	+
Non-invasive technique / patient comfort[†]	+	+	-
Low diagnostic imaging costs	+	-	-
Contrast media tolerance	-	+	-
Three-dimensional imaging	+	+	-
Noninterference of stents[‡]	+	-	+
Radiation/Radiation risk	+/-[§]	-	+/-[§]
Acute clinical setting	+	-	+
Haemodynamic assessment	-	-[*]	+
Extraluminal pathology visualization	+	-[*]	-

[*] *Is only possible when using additional sequences.*
[†] *From (79)*
[‡] *From (80).*
[§] *Radiation used (+) but the risk is negligible (-) in population with chronic obstructive PAD.*

Some authors reported that calcified plaques were the main reason for misinterpretations (mostly false-positive findings) on CT angiography (2,14) especially when blooming of the calcifications occurred in thicker slices (10). To our knowledge is, apart from our data, only one publication who reported in a stratified analysis that the reproducibility in calcified segments is lower than in non-calcified segments, especially of the crural tract (11).
Unfortunately, there is no specific data on the clinical value of MDCTA for the peripheral tree including smaller pedal arteries and for patients suffering chronic critical limb ischemia.

MDCTA has shown to lead to adequate decision making for treatment recommendations concerning both the anatomical level and the technique of revascularization (72). A cost-effectiveness study showed that MDCTA is a cost-effective diagnostic strategy in the work-up of PAD if the sensitivity is 85% or higher, the cost Euro 230 or lower, and the percentage of patients requiring additional imaging after MDCTA no higher than 35% (73,74). Randomized controlled trials confirmed that MDCTA in PAD is the optimal diagnostic imaging technique (25, 75). MDCTA leads to comparable therapeutic confidence, similar effectiveness, and less diagnostic costs when compared to DSA and CEMRA. All modalities have their advantages and limitations, clinical practice and health care makers need to decide which modality to use depending on local expertise, availability of image modality, and evidence based results (Table 4).

Finally, MDCTA is an accurate technique to evaluate the patency after revascularization procedures (39). The technique can be used in the evaluation of acute ischemia, e.g. after a revascularization procedure or in thrombo-embolic disease (Figures 2, 13). MDCTA can also be used to depict other non-atherosclerotic causes of PAD. In
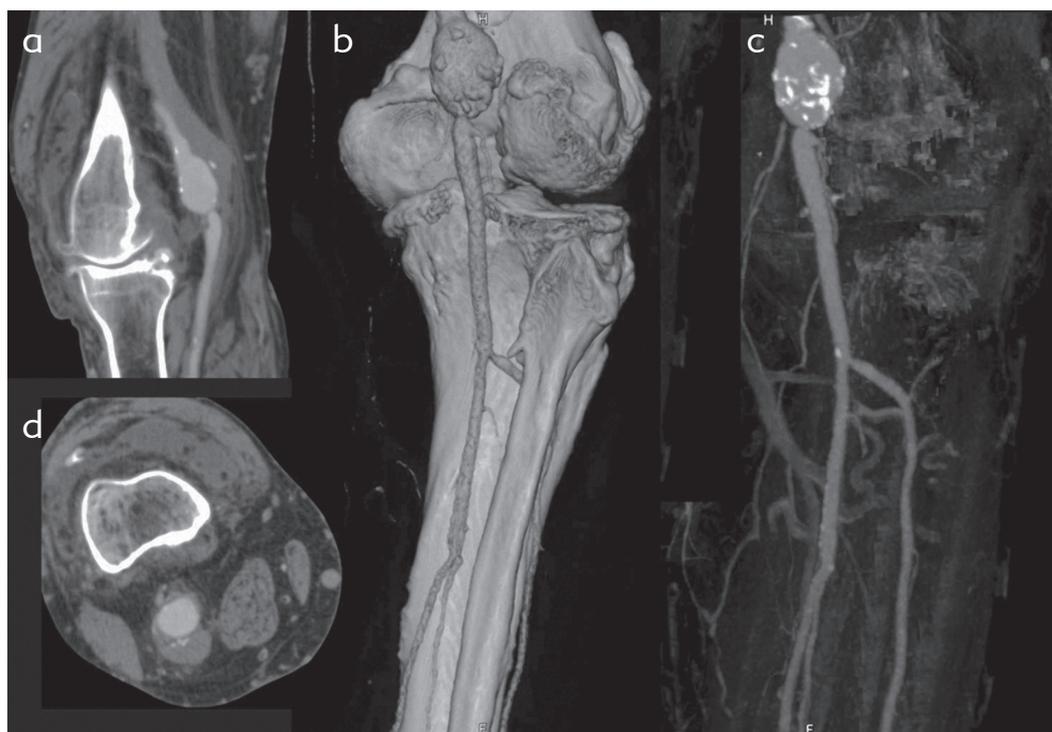

Figure 14. A 56-year old male patient who had a history of deep venous thrombosis with intermittent claudication of the right lower extremity. (a) Thin MIP image shows an aneurysmatic right popliteal artery with a tight stenosis distally. (b) VRT, volume MIP (c), and axial view (d) confirm these findings and show patent crural arteries. (A full color version of this illustration can be found in the color section).

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general, no specific adaptations of the MDCTA imaging protocol are necessary. Non-atherosclerotic causes of PAD includes peripheral (popliteal) aneurysmal disease (Figure 14) (76); external luminal compression such as popliteal entrapment syndrome, cystic adventitial disease, and compartment syndrome; arterial fibromuscular dysplasia; vasculitides, such as Takayasu's disease; other inflammatory disease, such as thromboangiitis obliterans (Buerger's disease); traumatic injury, such as AV fistula (Figure 15), dissection (Figure 16), pseudoaneurysm (Figure 17), drug induced, or radiation induced injury; infections; connective tissue diseases; vasospastic disorders such as Raynaoud's disease and Ergot toxicity; and other rare causes.

Figure 15. *Volume rendered image in MDCTA showing a post-traumatic AV fistula. The arterial phase shows enhancement of the right common, profound, and superficial femoral artery, and an immediate enhancement of the profound and common femoral vein. MDCTA shows the location of the AV fistula (arrow) at the origin of the profound femoral artery and vein.*
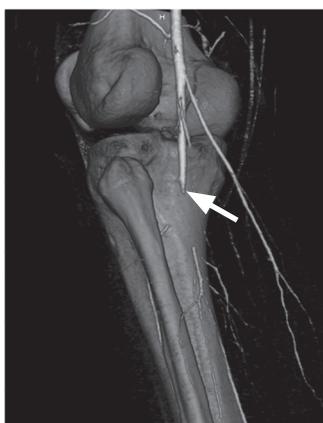
Figure 16. *Volume rendered image in MDCTA showing a dissection of the popliteal artery after repositioning of a luxated left knee. The popliteal artery is tethered distally from the joint (arrow). The run-off crural arteries show a faint enhancement.*

Figure 17. *Volume rendered image in MDCTA showing a post-traumatic pseudonaneurysm compressing and deviating the popliteal artery (solid arrow) and vein (dotted arrow). The tibioperoneal trunk show a very faint enhancement (dashed arrow).*

Conclusion

The submillimeter resolution of current multi-detector row CT scanners can display every detail of the peripheral arteries. Literature has shown that MDCTA has a high accuracy and good reproducibility for the assessment of stenosis and occlusion in the work-up of peripheral arterial disease and that it is a cost-effective modality when compared to other imaging techniques. The most important drawback is the limited lumen evaluation in smaller calcified arterial segments, which is associated with diabetics with PAD who suffer often from critical limb ischemia. Therefore, MDCTA seems currently the modality of choice in patients with intermittent claudication (Fontaine stage II) and appears clinically less valuable in critical limb ischemia (Fontaine III or IV).

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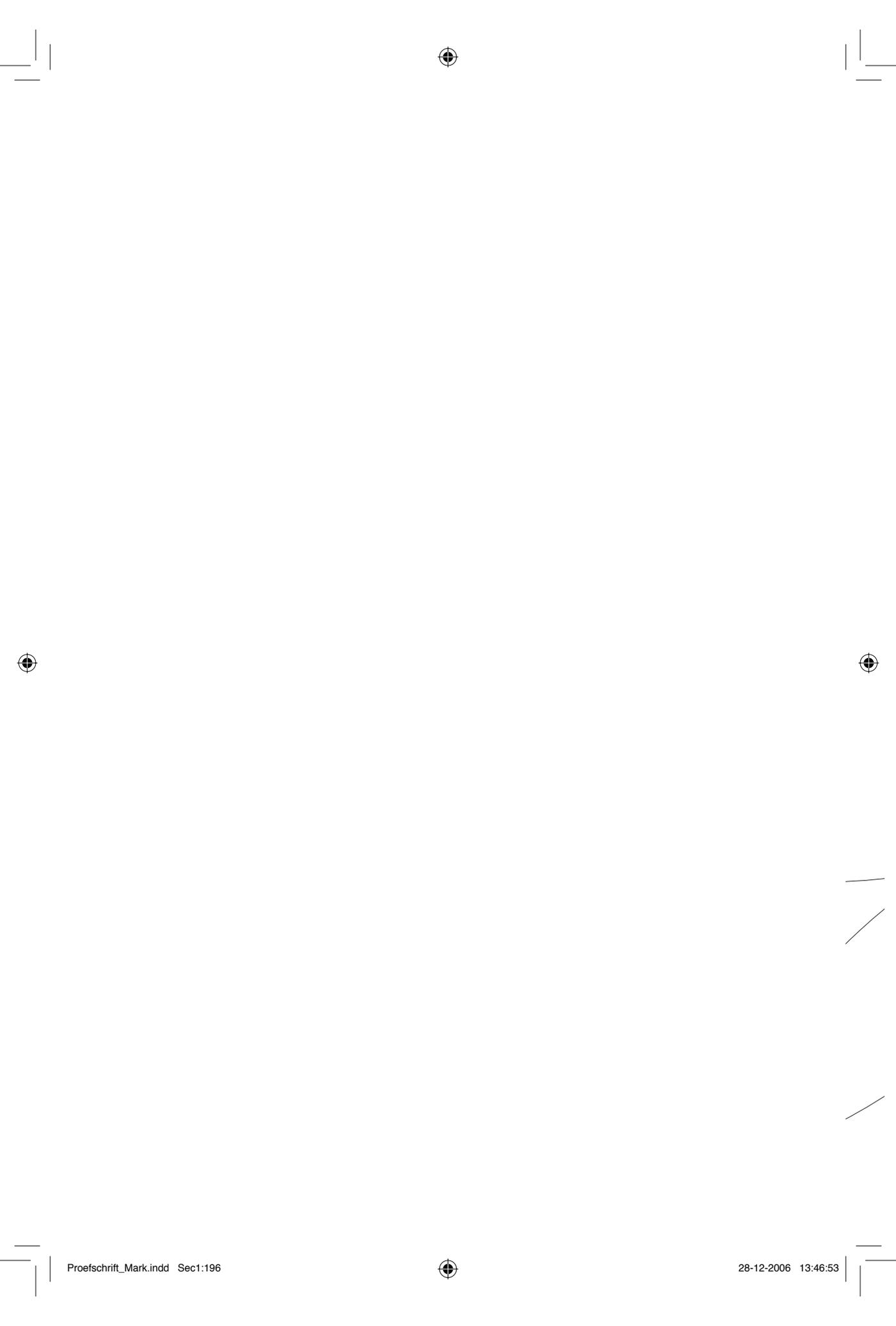
Chapter 10
Meta-Analysis of Multi–Detector Row CT Angiography

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Abstract

Background: Multi-detector computed tomographic angiography (MDCTA) is a rapidly evolving imaging technique that has been reported to be accurate for assessment of lower extremity arterial disease.

Purpose: To obtain the best available estimates of the diagnostic performance of MDCTA compared with digital subtraction angiography (DSA) for the assessment of symptomatic lower extremity arterial disease and to identify the most important sources of variation in diagnostic performance between studies.

Materials and methods: Studies published from January 2000 through April 2006 in English, German, French, or Spanish were searched from the Medline, Embase, and Cochrane databases. Studies were included that allowed construction of 2x2 contingency tables for detection of stenosis greater than 50% with MDCTA compared with DSA, the reference standard, in patients with claudication or critical ischemia. Two observers extracted data on study design, patient characteristics, arterial tract, and MDCTA technical protocols. Random-effects summary receiver operating characteristics analysis was performed to examine the influence of these data on diagnostic performance.

Results : Of 70 studies initially identified, 12 diagnostic studies were included that evaluated MDCTA in 436 patients, of which 9541 arterial segments were analysed. The pooled sensitivity and specificity for detecting a >50% stenosis per segment were 0.92 (95% CI, 0.89-0.95) and 0.93 (95% CI, 0.91-0.95) respectively. Only 3 studies provided data on the diagnostic performance of MDCTA in subdivisions of the arterial tract. Diagnostic performance of MDCTA in the infrapopliteal tract was lower but not significantly different from the aortoiliac or femoropopliteal tract. Regression analysis showed that the diagnostic performance was not significantly influenced by differences in clinical setting.

Conclusion: MDCTA is an accurate diagnostic test for assessment of arterial disease in the entire lower extremity.

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Introduction

Digital subtraction angiography (DSA), the standard of reference for the evaluation of lower extremity arterial disease, is an invasive procedure with significant costs and a small risk of complications (1, 2). Non-invasive techniques for the anatomic assessment of the peripheral arteries that could replace DSA are therefore desirable. For this reason, non-invasive techniques, such as magnetic resonance angiography, and computed tomographic angiography are increasingly used for the assessment of lower extremity arterial disease.

Over the years, several studies have been published that validate contrast enhanced CTA as a non-invasive alternative against conventional DSA for imaging of the vascular tree. Studies that evaluated single-slice CTA reported high estimates of sensitivity and specificity for the assessment of lower extremity arterial disease, but also identified problems of limited scan coverage and resolution (3, 4). Since the advent of hardware with multiple detectors, the spatial and temporal resolution could be improved, which allowed the depiction of the entire vascular tree including the inflow and the runoff arteries. The first reports evaluating MDCTA showed that important disagreement between conventional DSA and MDCTA still occurred in the smaller arteries, in particular the arteries of the calves (5, 6). Further advances in CT angiography technology resulted in an increased number of detector rows allowing for thinner collimations, faster scan speed, and an improved tube capacity, which could improve its diagnostic performance.

The diagnostic performance of MDCTA for the assessment of lower extremity arterial disease has been evaluated in multiple relatively small studies from 2000 onwards. These studies report varying estimates of sensitivity and specificity, which are probably caused by advances in technology, differences in scan protocols, and heterogeneity in patient populations. The purpose of the current study was to obtain the best estimates of diagnostic accuracy of peripheral MDCTA through a systematic review and meta-analysis of all published studies, taking into account the heterogeneity between clinical settings, and to identify the most important sources of variation in diagnostic performance between studies.

Methods

Study selection
The Medline, Embase, and Cochrane database were searched from January 2000 through April 2006 using the following search terms: computed tomography AND (peripheral OR lower limb OR lower extremity) AND artery AND specificity NOT pulmonary embolism. A hand search of the reference lists of review articles and cited articles were used to locate additional studies.

Studies were included if they met the following criteria: The data were acquired with a MDCTA scanner with at least two detectors; DSA was used as the reference standard; clinical suspicion of peripheral arterial disease was the reason for referral; the

absolute numbers of true-positive, false-negative, false-positive, and true-negative test results were available or derivable from the available data to construct 2x2 contingency tables. Potential articles in the English, Dutch, French, German, and Spanish language were included in the search. Exclusion criteria were: single-slice CT studies, studies that concentrate on a part of the lower extremity, review articles or editorials, studies with potentially overlapping study populations.

Data extraction

Two independent readers (MHK, MK) evaluated the retrieved studies for possible inclusion in the meta-analysis and extracted the data using a standard data-extraction form taking into account the Standards for Reporting of Diagnostic Accuracy (STARD) checklist (7) Interobserver agreement for the data extraction was evaluated with Cohen's kappa test. Subsequently, a consensus decision was made in case of inconsistent findings.

The absolute numbers of false negative (FN), false positive (FP), true positive (TP) and true negative (TN) test results were retrieved or calculated from the published data. This was done separately for the total peripheral vascular tract (aorta through the ankles) and per anatomical area, namely aortoiliac, femoropopliteal, and infrapopliteal, if available. Significant disease was present if at least one stenosis of 50%-100% of the luminal diameter was present per arterial segment identified with DSA, the reference standard. If the imaging studies were evaluated by multiple observers, the data were extracted for the first observer reported.

The characteristics that were considered to be an indicator of advances in CTA technology were extracted from each included study, such as the number of detectors of the CTA scanner. The year of publication was considered to be an indicator of advances in technology and learning experience associated with the evaluation of MDCTA images. The slice thickness and table feed per second were extracted or derived from the protocol as indicators of spatial and temporal resolution. Also documented were scan coverage, reconstruction interval, and extent of image evaluation, that is, the number of postprocessing methods that are supplemented to review the axial source images. Contrast volume, iodine concentration, injection rate, and the method of acquisition timing were considered to be indicators of image quality. For each study population the following patient characteristics were extracted: mean age, prevalence of significant disease, proportion of men, proportion of previous revascularizations, proportion of patients with claudication and critical ischemia. The following characteristics of study design were extracted: number of patients, number of segments per patient, total number of segments analysed, exclusion of segments, and the proportion of non- assessable segments by MDCTA and by DSA.

Data synthesis and statistical analysis

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Publication bias

The main analysis was performed for the total peripheral vascular tree, which was defined as the anatomical area covering the abdominal aorta through the ankles. Secondary analyses were performed on available data specified for the aortoiliac, the femoropopliteal, and the infrapopliteal area.

First, sensitivity and specificity were pooled using a random effects model, which takes into account the variability between studies. Then, we performed a random effects summary receiver operating characteristic (SROC) analysis to estimate the relationship between sensitivity and specificity, taking into account potential differences in positivity criterion and other factors of heterogeneity between clinical settings.

In an SROC analysis the logits (log odds) of sensitivity and 1-specificity are summed to calculate D, the log of the diagnostic odds ratio, which represents a summary measure of the diagnostic performance or discriminatory power. These logits are subtracted to calculate S, a proxy for the positivity criterion of the diagnostic test. Different positivity criteria exist among studies when institutions use different thresholds for

scoring a test result as positive. Subsequently, a linear regression model $D = a + bS$ is estimated, weighted by the inverse of the variance of D (8-10). Additional covariates were added to the model to adjust for the indicators of advances in technology and image quality, and for differences in clinical settings and study design. Missing data were imputed with the mean of the variable, assuming that the data were missing at random. We evaluated the individual effect of each variable on the diagnostic odds ratio. Variables with a significance level of $p \leq 0.10$ were added to the model in a stepwise forward manner. A variable was kept in the model if $p < 0.05$.

Tau-squared, the residual between-study variance, was used as a measure of the model fit. A lower tau-squared indicates less residual between-study variance and therefore a better model fit and a better explanatory power by the model of the heterogeneity across studies. We used the meta and metareg commands of STATA 8.0 for all regression analyses.

Results

Study selection and data extraction
The Pubmed search and the manual search for original articles resulted in 70 articles. Forty-one articles were excluded on the basis of their title and/or abstract leaving 29 articles for further evaluation on the basis of the original publication. From these 29 articles 12 studies where finally included in the meta-analysis (5, 6, 13-22). One or more reasons for exclusion of an article were: single-slice CT in 5 studies, no reference test in 2 studies, not possible to reconstruct 2x2 contingency tables in 7 studies, only part of vascular tree studied in 5 studies, and potential patient overlap in 2 studies. All studies supplied data on the total peripheral vascular tree, of which 3 studies (33%) additionally supplied seperate data on the aortoiliac area, the femoropopliteal area, and on the infrapopliteal area.

Interobserver agreement for the data extraction between the two readers was excellent (Cohen's Kappa = 0.832). Consensus was reached between the two data extractors for all inconsistent data.

Data synthesis and statistical analysis
A total of 12 studies, including 436 patients and 9541 segments, were analysed. Study characteristics are shown in Table 1.
The mean sample size of the 12 studies was 31 patients (range 16 to 50 patients per study) and 682 segments (range 168-1365 segments per study). The number of segments per patient varied considerably among the studies (mean 23 segments/patient, ranging from 6 to 35 segments/patient per study). The mean age over all studies was 65 years (mean age per study ranging from 53 to 71 years) and 77% of the patients were men (mean proportion ranging from 55% to 96% men). On average, 75% of patients were referred for claudication (mean proportion ranging from 56% to 97%) and 25% for critical ischemia (mean proportion ranging from 3% to 44%).

The random effects pooled sensitivity and specificity of MDCTA for detecting at least

Table 1: *Selected characteristics of included studies*

Study, year	No. of Slices	Slice thickness (mm)	Arterial Tract	No. of patients (segments)	Mean age (y)	Men (%)	Sensitivity (% (n/N))*	Specificity (% (n/N))*
Puls et al, 2001	4	2.5	Aorta-ankles	31 (186)	53	55	89 (56/63)	86 (106/123)
Ofer et al, 2003	4	3.2	SMA-pedal arteries	18 (410)	64	83	91 (110/121)	92 (267/289)
Heuschmid et al, 2003	4	3	Aorta-ankles	23 (568)	66	65	91 (136/149)	90 (379/419)
Martin et al, 2003	4	5	Celiac artery - toes	41 (1312)	67	68	90 (327/365)	94 (886/947)
Catalano et al, 2004	4	3	Diaphragm-feet	50 (1137)	67	78	99 (251/254)	97 (860/883)
Mesurolle et al, 2004	2	5	Celiac artery -10cm below trifurcation	16 (168)	64	88	91 (52/57)	93 (103/111)
Ota et al, 2004	4	2	Second lumbar vertebra - calf	24 (470)	69	96	99 (121/122)	99 (345/348)
Portugaller et al, 2004	4	NA	Aorta-ankles	50 (740)	68	84	92 (240/261)	83 (399/479)
Bui et al, 2005	4	2	Celiac artery - toes	25 (718)	63	96	90 (159/177)	86 (466/541)
Edwards et al, 2005	4	3.2	Aorta-ankles	44 (1042)	68	68	79 (213/270)	93 (721/772)
Fraioli et al, 2005	4	3	Xyphoid-feet	25 (475)	59	72	93 (55/59)	94 (393/416)
				25 (475)	64	88	94 (47/50)	95 (405/425)
				25 (475)	71	68	91 (60/66)	96 (392/409)
Willmann et al, 2005	16	0.75	Aorta-ankles	39 (1365)	65	69	96 (350/363)	96 (960/1002)
Pooled RE [95% CI]							92 [89-95]	93 [91-95]

*For detection of a stenosis of 50% or more

SMA = superior mesenteric artery

Pooled RE = Pooled result from random effects meta-analysis

95% CI = 95% confidence interval

NA = not available

one significant stenosis (≥ 50%) per segment for the entire tract of the lower extremities were 0.92 (95% CI, 0.89-0.95) and 0.93 (95% CI, 0.91-0.95) respectively (Table 1). The published pairs of sensitivity and specificity and the estimated summary receiver operating characteristics curve are shown in figure 1.

Table 2 shows the diagnostic characteristics for the 3 subdivisions of the arterial tract in the 3 studies reporting these data. The pooled sensitivity and specificity of the infrapopliteal tract were lower compared with the aortoiliac and the femoropopliteal tract, although not significantly. The lower accuracy in the infrapopliteal tract is mainly caused by the results of the study of Mesurolle et al., who used a CT scanner with only 2 detectors and a slice thickness of 5mm, which could not depict the complete infrapopliteal tract through the ankles. The best results in the infrapopliteal tract were reported by Wilmann et al. who used a 16-slice CT scanner with only 0.75mm slice thickness.

The meta-regression analysis revealed that none of the indicators of advances in technology and image quality, and differences in clinical settings and study design significantly influenced the diagnostic performance of MDCTA.
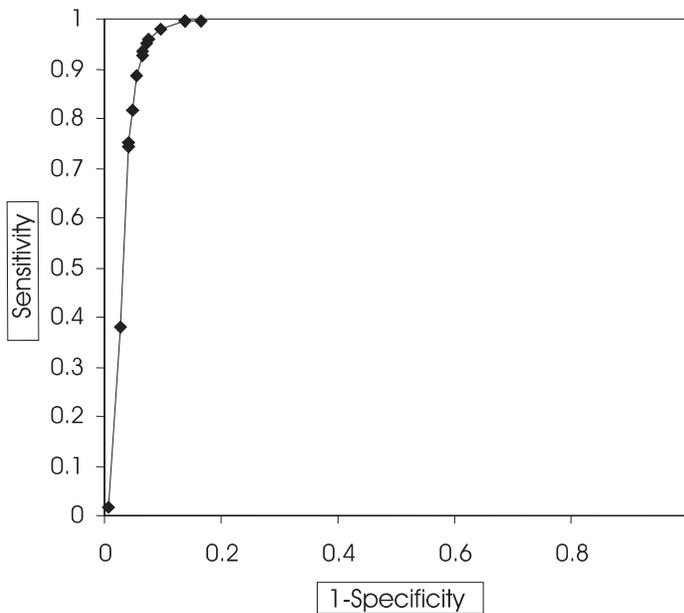

Figure 1. *Receiver operating curve of MDCTA for lower extremity arterial disease*
Published pairs of sensitivity and specificity (dots) of MDCTA for lower extremity arterial disease and the estimated summary receiver operating characteristics curve (line).

Publication bias
The funnel plot is shown in figure 2. Visual inspection revealed that the inverted funnel is not symmetric. The right tail, which represents the publication of small studies

with a high diagnostic performance, seems for the most part missing. The shape of the funnel implies that publication bias might be present. However, the figure indicates that the publication of small studies with low diagnostic performance is more common than small studies with high diagnostic performance. The diagnostic performance of MDCTA may thus be underestimated.

Table 2: *Pooled estimates of sensitivity and specificity for subdivisions of the arterial tract of the lower extremities. Differences between the subdivisions were not statistically significant.*

Author	Tract	Sensitivity (%)	Specificity
Mesurolle et al, 2004	Aortoiliac	100 (18/18)	97 (29/30)
Portugaller et al, 2004	Aortoiliac	92 (24/26)	95 (212/224)
Willmann et al, 2005	Aortoiliac	95 (74/78)	98 (267/273)
Pooled RE [95% CI]		96 [92-100]	97 [94-99]
Mesurolle et al, 2004	Femoropopliteal	97 (31/32)	93 (55/59)
Portugaller et al, 2004	Femoropopliteal	98 (62/63)	70 (26/37)
Willmann et al, 2005	Femoral	98 (99/101)	94 (199/211)
Pooled RE [95% CI]		98 [96-100]	89 [80-98]
Mesurolle et al, 2004	Infrapopliteal	43 (3/7)	86 (19/22)
Portugaller et al, 2004	Infrapopliteal	90 (154/172)	74 (161/218)
Willmann et al, 2005	Popliteocrural	96 (177/184)	95 (494/518)
Pooled RE [95% CI]		90 [81-99]	85 [69-100]

Pooled RE = Pooled result from random effects meta-analysis
*95% CI = 95% confidence interval*
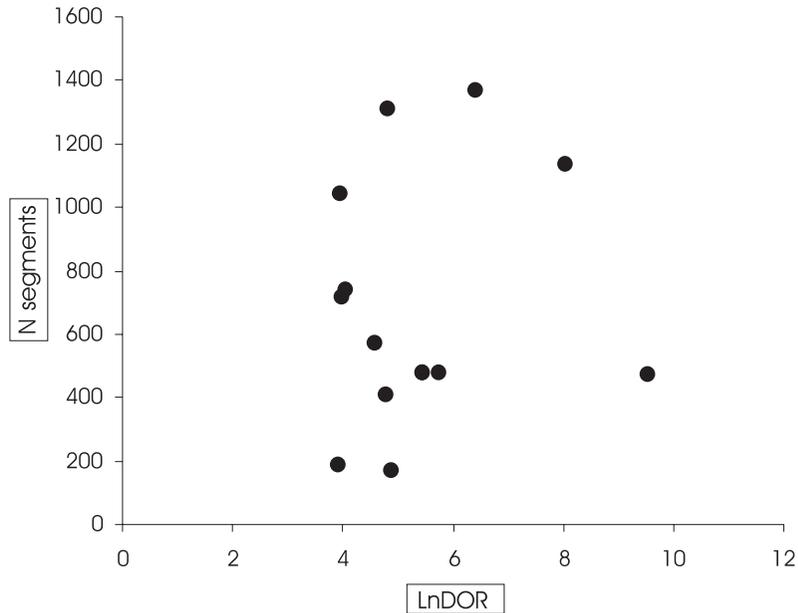
Figure 2. *Funnel plot*
Funnel plot demonstrating a measure of study size (number of segments) plotted as function of the natural logarithm of the diagnostic odds ratio (LnDOR). Asymmetry of the shape of the inverted funnel may indicate the presence of publication bias. Small studies with a high diagnostic performance are mostly underrepresented in this funnel plot, suggesting that the pooled diagnostic performance of MDCTA may be underestimated

Discussion

Our analysis of the available literature on MDCTA revealed that the pooled sensitivity and specificity of MDCTA for lower extremity arterial disease were 92% and 93% respectively. The funnel plot suggests that these estimates of diagnostic performance of MDCTA may be underestimated. Our results imply that MDCTA is a highly accurate diagnostic imaging tool for the assessment of ≥ 50% arterial stenosis in lower extremity arterial disease.

The published results of single-slice CTA studies for the assessment of lower extremity arterial disease showed that this imaging technique was insufficient to cover the entire vasculature of the lower extremity. Single-slice CT was limited to the evaluation of aortoiliac arteries or lower extremity arteries, separately. Lawrence et al described in 1995 that the helical system only allowed a spiral set of 60 seconds and 9 seconds was necessary between two spiral sets, which covered the upper and lower leg (3). Rieker et al published in 1996 a study using a single continuous acquisition of CTA for depiction of the lower extremities in 70 seconds (4). Because of the very slow scan speed they noticed a venous enhancement contamination in 13% of the patients.

Also, they reported poor longitudinal resolution for evaluation of the proximal part of the anterior tibial artery. The first multi-detector CTA of peripheral arterial disease was performed using the twin CTA of Elscinth which was able to cover a distance from the iliac bifurcation to 10 centimeters cranial of the ankle (23).

With the advances in CTA technology, especially the introduction of multiple detectors, the spatial resolution and scanning time have improved considerably. In single-slice CTA studies the table speed varied from 5 to 10 mm/s, which could be increased to 36 mm/s in a study using 16-slice CTA. A higher scan speed is technically possible to decrease the amount of contrast medium, but results in a decreased resolution and timing difficulties. The slice thickness has reduced from 5.5 mm in single-slice CTA to 0.75 mm in 16-slice CTA. These technological advances have led to improved diagnostic imaging covering the aorta through the ankles. The indicators of advances in technology and image quality, however, did not reach statistical significance for improvement of diagnostic performance in the current study.

The additional use of advanced post-processing techniques may also be important for the evaluation of lower extremity arterial disease. Ota et al. described that the use of curved planar reformats in iliac arteries will result in a higher sensitivity (97% versus 89%) and specificity (100% versus 96%) compared to axial images (17). However, the use of additional post-processing techniques neither influenced the diagnostic performance significantly in our analysis, which may be caused by the low number of studies included in our meta-analysis, and thus a low power to detect statistical differences.

A major drawback of multi-detector row CT angiography is the hampered vessel assessment due to the depiction of arterial wall calcifications. Several studies have reported a decreased accuracy in severely calcified arteries compared to arteries without severe calcifications (5, 17, 24). Only one of our included studies published results stratified for severe calcifications that significantly decreased the diagnostic accuracy (17).

The few studies that provided additional data on the aortoiliac, femoropopliteal, and infrapopliteal tract showed no significant differences in diagnostic accuracy among these areas. However, the subgroup results suggest that using a 2-slice CT scanner is insufficient for depiction of the entire vascular tree in the lower extremities (sensitivity 43% and specificity 86% in the first 10cm of the infrapopliteal arteries) (16). The best results in the infrapopliteal tract were obtained with a 16-slice CT scanner with 0.75 mm slice thickness (sensitivity 96%, specificity 95%) (22). The subgroup results suggest that especially 16-slice CT is an accurate diagnostic tool for the complete evaluation of lower extremity arterial disease. Unfortunately, only one study using 16-slice CTA for the entire lower extremity arterial tract could be included in the analysis. A recent report of Schertler et al. that evaluated diagnostic accuracy using a 16-detector row CTA with different section widths and increments showed that diagnostic performance improves when thinnest slice widths of 0.75 cm are used. However, the data of this study could not be included in our analysis since only the lower legs were

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scanned (24).

No studies have been published using 64-slice CT for the assessment of lower extremity arterial disease, but extrapolating the results of those studies evaluating arterial disease in other anatomical areas, we can expect that the sensitivity and specificity will improve if 16- or 64-detector CTA scanners will be used in future studies (25).

In comparison with other non-invasive diagnostic imaging technologies for lower extremity arterial disease, MDCTA showed similar pooled estimates of sensitivity and specificity. Meta-analysis on contrast-enhanced magnetic resonance angiography (MRA) for the diagnosis of lower extremity arterial disease reported a pooled sensitivity of 97.5 % and a pooled specificity of 96.2% versus 87.6% and 94.7% respectively for color guided duplex ultrasonography (26). Another meta-analysis estimated a 94% equal sensitivity and specificity for three-dimensional gadolineum-enhanced MRA (27). The advances of MDCTA over MRA are the relatively short scanning time and lower cost (28). Disadvantages of MDCTA include the use of radiation and the presence of severe calcifications that may cause overestimation of stenosis, especially in diabetic patients (29, 30).

Limitations of the present study were the relatively low number of published studies of MDCTA in this anatomical area and the relatively small study populations analysed which resulted in limited power to detect patient characteristics or technological details of the scan protocols that may significantly affect diagnostic accuracy. Furthermore, the number of publications reporting the results of the newest MDCTA scanners (16- and 64-detector CTA) for lower extremity arterial disease was almost nihil, precluding thorough evaluation of the most recent technological developments.

Furthermore, we found that the reporting quality of the published studies was fairly poor. We had to exclude several studies that did not satisfy the inclusion criteria and we had to impute some crucial data that were not reported in all studies. It was not possible to reconstruct 2x2 contingency tables in two studies, because contradicting results were reported (31, 32) and in one study because of incomplete results (33). In one study the reading was not performed independently (34) and in three studies no reference test was used for confirmation of the results (35-37), which are necessary conform the STARD guidelines for the conduct and reporting of diagnostic research to improve the quality of such studies (7). It is desirable that future studies adhere to this concept to make comparison of the results between studies possible and to improve the performance of systematic reviews, thereby facilitating the appreciation of new imaging techniques.

In conclusion: MDCTA is a highly accurate diagnostic imaging technology for the assessment of lower extremity arterial disease.

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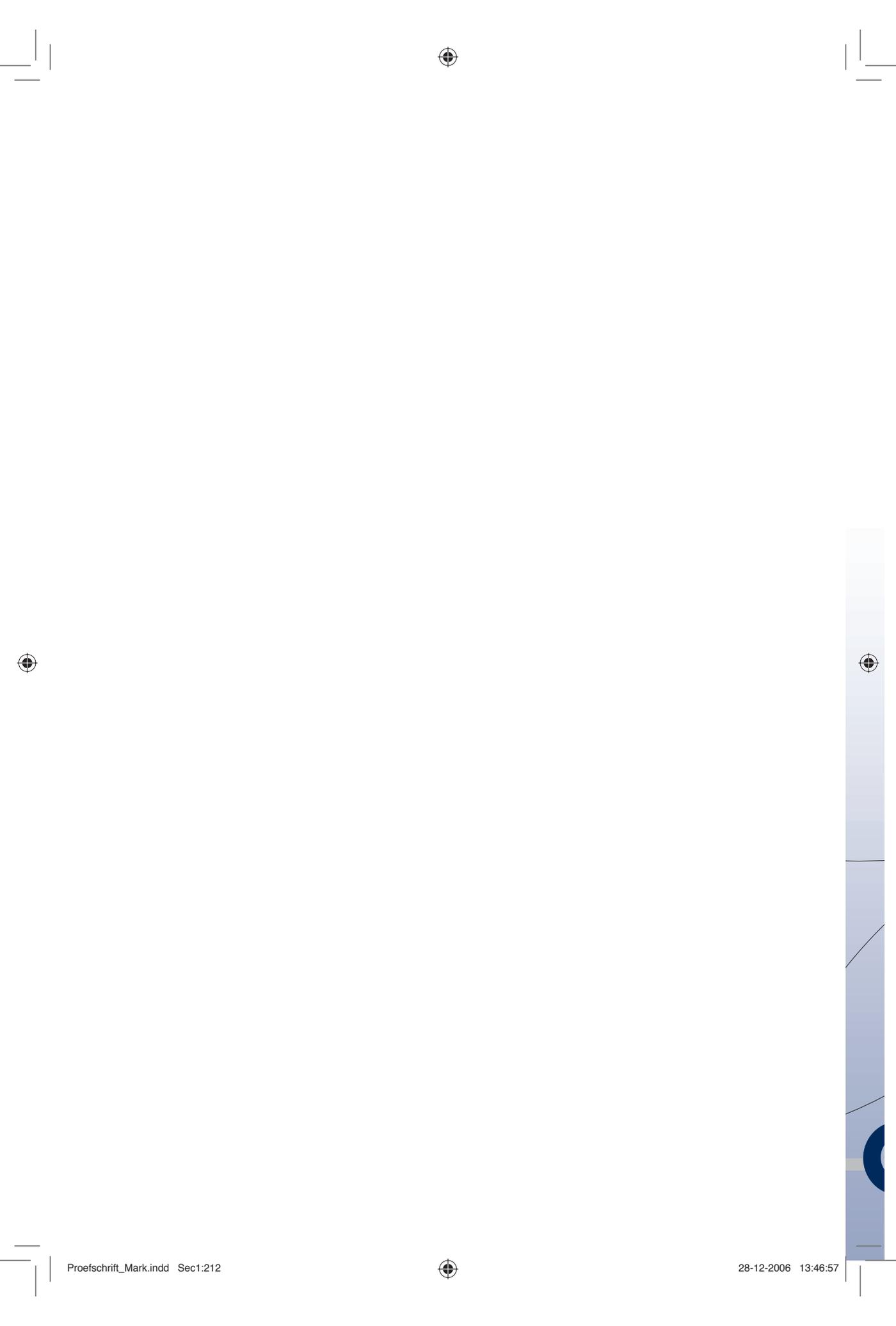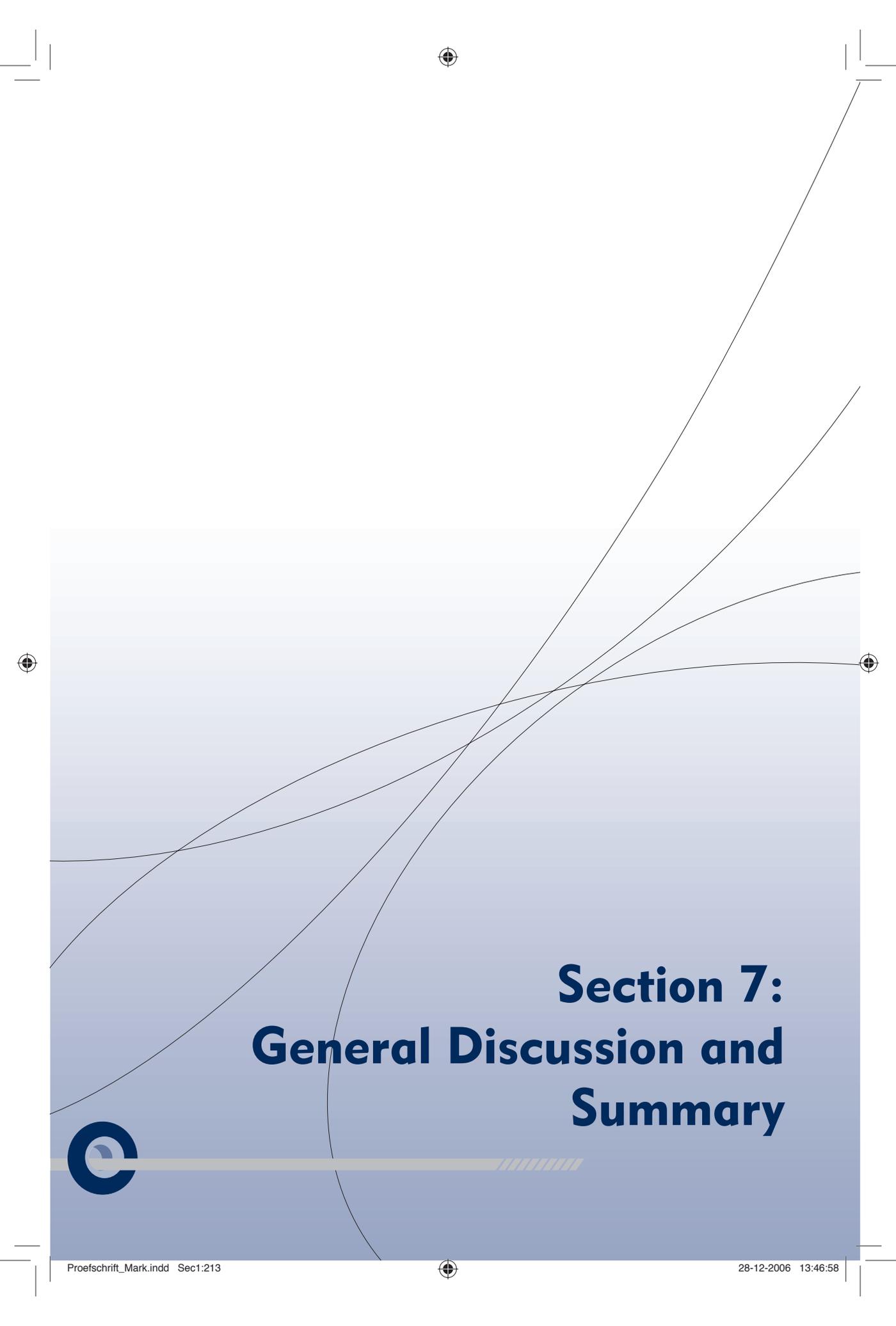
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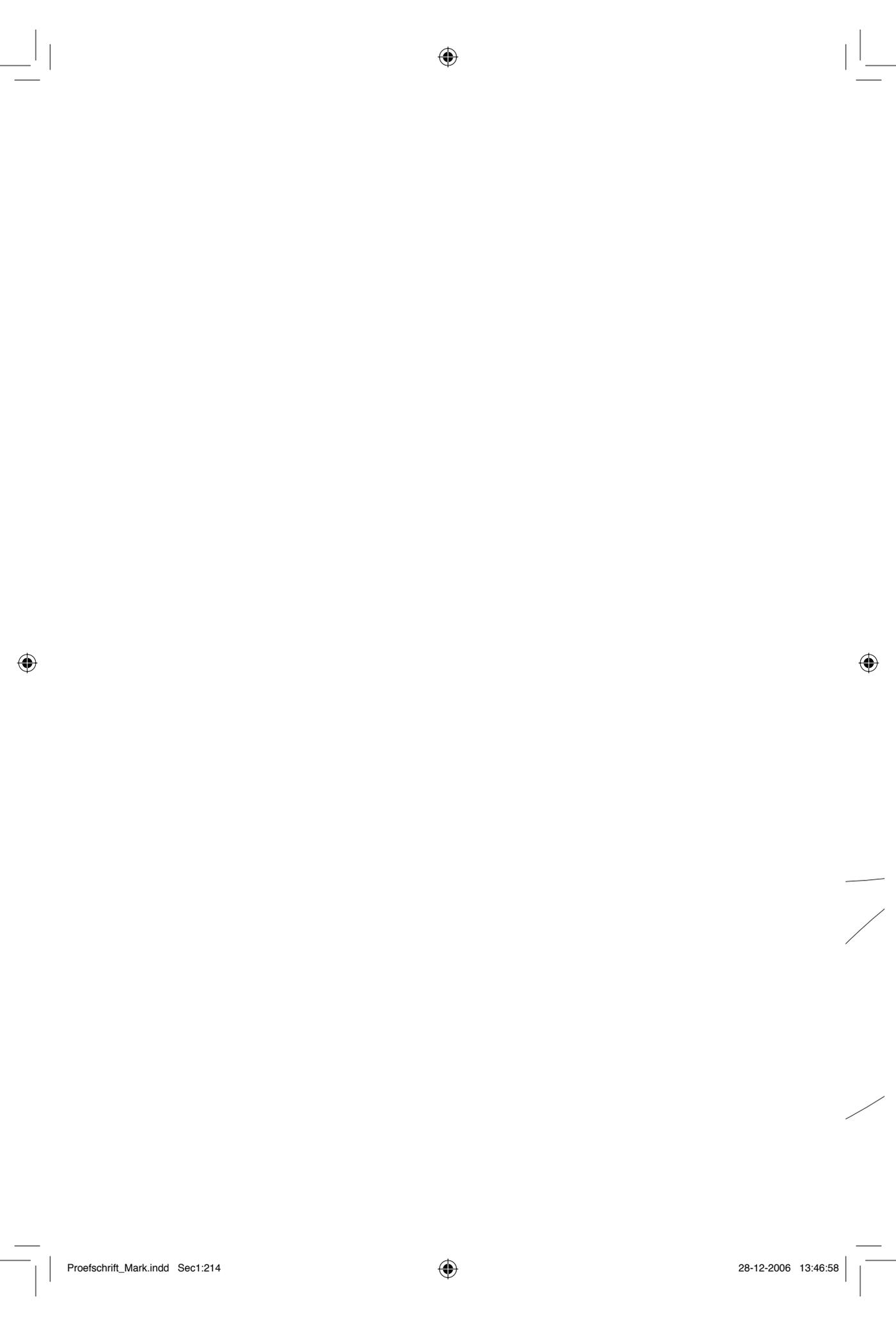
Chapter 11
General Discussion

General Discussion and Summary

Multi-detector row CT angiography (MDCTA) has met a widespread popularity in the radiological community in the past years. The multi-detector technique combines fast acquisition with high-resolution data sets that has resulted in new approaches for the assessment of various diseases. A relatively new application includes the evaluation of the aorta including the run-off vessels in patients with peripheral arterial disease (PAD) and its practice is increasing rapidly. When peripheral arterial disease becomes symptomatic patients will have symptoms of cramps and weakness in their legs during exercise, which is relieved after a period of rest. One-quarter of these patients will develop critical limb ischemia with pain that will not improve after a period of rest and results in tissue loss. Diagnostic imaging of the peripheral arteries is indicated when a revascularization procedure is considered, in patients with critical ischemia or with severe disabling intermittent claudication who are unresponsive to risk factor modification and exercise therapy. Diagnostic imaging indicates the level of disease, multiplicity, and severity of stenosis for planning an endovascular and/or surgical revascularization. Although, non-interventional imaging techniques such as contrast-enhanced magnetic resonance angiography (CEMRA) and MDCTA are increasingly performed to evaluate PAD, digital subtraction angiography (DSA) is still regarded as the reference standard. Important in the assessment of a new radiological technology is to evaluate the advantages as well as the potential disadvantages. The aim of this thesis was to evaluate MDCTA in the diagnostic work-up of patients with peripheral arterial disease. This thesis describes the targets that are necessary for a new imaging technique in the work-up of PAD to be cost-effective. Subsequently, it evaluates the reproducibility of MDCTA for the assessment of stenoses. Furthermore, it describes the results of the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) trial in which the costs and effects of the non-invasive MDCTA were compared with the reference test, DSA. In addition, the thesis evaluates potential disadvantages of MDCTA due to vessel wall calcifications and assesses the risk due to radiation. Finally, the technical aspects of performing MDCTA for imaging the peripheral arteries are reviewed and a systematic literature review summarizes the diagnostic performance of MDCTA for detecting significant stenosis in peripheral arterial disease.

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Main findings

The prevalence of symptomatic PAD in the Dutch population of 55 years and older is 1.6% and increases with age (1). In our aging western society approximately 24% of the total population is older than 55 years. Thus, the absolute prevalence of symptomatic PAD in the Netherlands is almost 61,000. Annually, approximately 13,000 patients in the Netherlands undergo a diagnostic imaging work-up for PAD with the goal of revascularization (2). Furthermore, PAD is associated with a high morbidity and mortality (3-9). The majority of the fatalities are due to cerebrovascular and cardiovascular events. Epidemiological studies have reported an annual hazard of mortality associated with PAD varying from 4 to 12% (5, 8, 9) and a 10-year survival ranging from 35% to 82% (4,9).

The main reason to image the aorta and the arteries that supply the legs is to find and define an arterial lesion that has a suitable morphology for some form of revascularization. For the work-up of PAD alternative imaging modalities have been developed. The development of new technology is also called phase one according to the traditional hierarchical model of evaluating strategies. Subsequently, the hierarchical approach advocates evaluating the technical and diagnostic performance of the new test. This is often called phase two, during which the reproducibility in terms of intra- and interobserver agreement and the validity in terms of sensitivity and specificity are evaluated.

DSA is regarded as the reference standard in the assessment of PAD with a high temporal and spatial resolution and can provide hemodynamic information. But, it requires catheterization of an artery, normally the common femoral artery, and intra-arterial injection of iodinated contrast agent. It also requires a 4-6 hour period of bed rest and observation and, sometimes, hospitalization. DSA has a higher morbidity risk of 1.7% (for femoral approaches), mortality risk ranging from 0.025% (10) to 0.3% (11). Therefore, alternative non-invasive techniques were developed including Duplex Ultrasound (DUS), CEMRA , and MDCTA.

In some centers, the traditional DSA is preceded by DUS to determine the therapeutic approach. DUS is a non-invasive technique that is completely safe that can provide stenosis assessment plus functional hemodynamic information, such as arterial blood flow velocities. However, DUS does not provide a roadmap of the arterial tree, which is preferred by most vascular surgeons before undertaking a vascular reconstruction (12). The sensitivity of DUS varies from 85-88% whereas the specificity varies from 95-97%, depending on the threshold of the velocity ratio used to define a positive test result (13-15).

CEMRA has proven to be an accurate non-invasive alternative to DSA as imaging strategy prior to a revascularization procedure. With the use of intravenously administered gadolinium contrast agent the accuracy of the technique was considerably improved with sensitivity and specificity ranging from 92-100% and 92-100%, respectively (13, 16, 17).

Currently, MDCTA also has proven to be an accurate new alternative to invasive im-aging as initial diagnostic imaging technique for peripheral arterial disease. For the evaluation of significant stenosis, MDCTA has a pooled sensitivity and specificity, for detecting a >50% stenosis per segment, of 92% and 93% (this thesis). Concordant to publications in the literature we found that MDCTA has excellent interobserver agree-ment (18-23). Important to note is that the accuracy and reproducibility of MDCTA for the vasculature of the lower leg is lower than the aortoiliac or femoropopliteal tract, especially when arterial wall calcifications are present.

Although it is valuable to know whether the estimate of a test corresponds to the truth, in order to answer the question whether the test does more good than harm, it is necessary to take the downstream consequences of the test into account. The results of estimates of comparative studies do not automatically translate into patient outcomes, costs, and clinical effectiveness. One would like to know how the new test influences subsequent decisions when implemented in clinical practice. This phase of evaluation is often called phase three. A cost-effectiveness analysis based on a decision model can give answer to these questions. The virtual world of these com-puter models attempt to reflect the real world. However, our real world is so wide and complex that assumptions have to be made to keep the model manageable. Another drawback of decision models is that various sources need to be consulted in order to provide input data. The models used in this thesis were derived from meta-analyses, published studies, and original patient data. Advantages of decision analyses are that many strategies can be modeled to compare the clinical impact of a diagnostic test and with sensitivity analysis the ''what if?'' questions can be addressed.

To determine the cost-effectiveness of a new diagnostic imaging modality in the work-up of PAD, targets were assessed based on a decision-analytic model. In this study DUS, DSA, and CEMRA were taken into account in the work-up for PAD. The model allowed 'additional imaging' if test results were equivocal and allowed 'incorrect treat-ment' if test results were incorrect. Target values for sensitivity and costs were estab-lished to evaluate the cost-effectiveness of a new non-invasive imaging modality com-pared to MR angiography. In a base-case analysis, a cohort of 100,000 60-year old men with severe unilateral claudication without a history of coronary artery disease, was simulated using a societal willingness-to-pay of $100,000 per quality-adjusted life year. For the base-case, if the new non-invasive imaging technique would have a sensitivity of 95% and 20% of patients require an additional DSA then the maximum acceptable cost of a new modality-examination would be $673. If, for example, then the new modality-test cost only $300, the sensitivity needs to be minimally 94%. At the time of evaluation, preliminary results showed that sensitivity was 90 – 95% and the cost of contrast-enhanced CT examination was estimated to be $237. Therefore, MDCTA in peripheral arterial disease can meet the required targets.

A drawback of decision analysis is that it is limited by using assumptions and second-ary data from the literature. Another disadvantage of cost-effectiveness analysis of radiological strategies is that only small differences between the imaging strategies are found because a new diagnostic test will yield only small benefits for the patients

and the differences in the costs are usually small.

The conflict of the hierarchical approach to the assessment of new diagnostic imaging is that it needs to be rigorous and valid. But when performed sequentially it is extremely time-consuming. With the rapid advances in radiological technology, a new imaging test is often implemented in practice after use in a limited number of cases, has shown promising results. The results of a rigorous traditional comparative study (performing the alternative test and the reference standard in all patients) is often too late to influence management and policy. Therefore, a new design has been suggested for the assessment of radiological technology (24). The design involves an empirically based pragmatic trial, which means that the trial is integrated into clinical practice rather than conducted in a strictly controlled experimental setting. The latter probably does not reflect real practice and is difficult to use for evaluating downstream effects when implementing a new test. At the same time, a pragmatic trial can deal with the development, assessment, and implementation of a new diagnostic imaging test. A randomized controlled trial of diagnostic strategies has been advocated to integrally assess these subjects (24, 25). Patients are randomized between different strategies to minimize bias introduced by extraneous factors resulting in an unbiased comparison between the groups. Measurements focus on the clinical decision-making process and trends in outcomes over time.

In this thesis we describe the DIPAD trial which used this design to evaluate the promising technique of MDCTA in comparison with the current reference technique, DSA, in patients with PAD who needed diagnostic imaging prior to a revascularization procedure. Primary outcomes evaluated were clinical utility, effectiveness, and economic consequences. Clinical utility was assessed with the physician's confidence in the treatment decision and recommendation for additional imaging. Effectiveness was evaluated as the change of quality of life measured with Euroqol-5D and Short Form-36 questionnaires. Economic outcomes were assessed by measuring actual costs of the initial imaging test, additional diagnostic tests, and of therapy. The DIPAD trial described in this thesis (chapter 5 and 6) demonstrates a lower therapeutic confidence, which increased over time, a similar effectiveness, less total diagnostic costs although more additional imaging tests were performed, and similar therapeutic costs for the MDCTA strategy compared to the DSA strategy. These results suggest that MDCTA can replace DSA for the initial evaluation of peripheral arterial disease.

Randomized controlled trials are seldom used to compare diagnostic tests (26-34, 35). Jarvik (36) stated that conducting a randomized controlled trial could be more time-consuming than cohort studies and therefore, more labor-intensive and expensive, because referring physicians could hesitate to randomize and eligible patients may not consent to being randomized. However, we found this pragmatic randomized trial to be both feasible and inexpensive (24, 36). Compared to performing both the new diagnostic test as the reference standard in all patients, randomization between the two diagnostic tests necessitates only one test per patient. One limitation of randomization is generalizability—a trial provides a test under strictly specified conditions, whereas clinical practice may be more disorganized. We believe that the results

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of the DIPAD trial are generalizable to other settings since an empirical pragmatic approach was chosen which was interwoven in current clinical practice allowing a wide range of clinical scenarios.

Although, MDCTA has shown to be a good alternative imaging modality it is also associated with disadvantages. The major drawback is the misinterpretation of the degree of stenosis in the presence of circumferential calcified arteries. We found significantly lower interobserver agreement in arterial segments with calcifications compared to segments without calcifications (chapters 3 and 4). We used data of these two randomized controlled trials to evaluate the impact of arterial wall calcifications on the clinical utility of MDCTA and to identify predictors for the presence of these calcifications (chapter 7). The results showed that calcified vascular segments are associated with lower therapeutic confidence and higher need for additional imaging. Furthermore, diabetes mellitus, cardiac disease, and elderly age (age above 84 years) were independently predictive for the presence of arterial wall calcifications.

In our clinical practice we have empirically encountered that patients suffering chronic critical limb ischemia have relatively more mural calcifications in the crural arteries compared to patients with intermittent claudication. To test this hypothesis we performed a pilot analysis to evaluate the proportion of vessel wall calcifications per anatomical station on MDCTA images in intermittent claudication compared with chronic critical ischemia. We included patients from the first DIPAD study (DIPAD I) where 72 of the 145 randomized patients underwent MDCTA. For analysis purposes, the arterial vascular system was divided into 3 anatomic region of in total 32 segments, namely the aortoiliac, femoropopliteal, and infrapopliteal region. If vascular wall calcifications were present in an arterial segment, this was noted down. The proportion of arterial wall calcifications was calculated per anatomical region. An independent t test was used to evaluate the difference in the proportion of arterial wall calcifications between the two groups of patients. Table 1 and figure 1 show the preliminary results from this analysis.

Table 1. *Proportion of arterial wall calcifications per anatomical region*.

Region	Intermittend Claudication		Chronic Ischemia		p
	Calcified (n/N)		Calcified (n/N)		
Aortoiliac	53 %	321/495	52 %	203/308	0.70
Femoropopliteal	46 %	248/540	51 %	171/336	0.93
Infrapopliteal	31 %	191/630	44 %	172/392	0.03

A statistically significant difference was found for the infrapopliteal region between the two groups. For the aortoiliac and femoropopliteal regions, no difference was found. Concordant with the findings of Chapter 7, for the total vascular tree including all three region and all vascular segments no statistically significant difference

was found between patients with intermittent claudication compared to chronic limb ischemia.
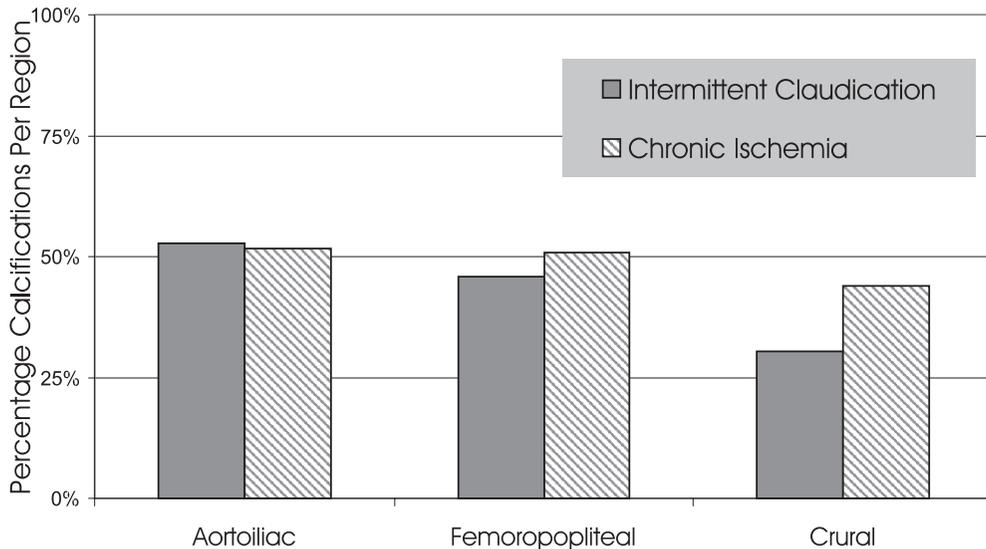

Figure 1. *Proportion of arterial wall calcifications per anatomical region*.

 These preliminary results show that patients with Fontaine stage III or IV have more arterial wall calcifications in infrapopliteal arteries compared to patients with a lower stage of PAD. Furthermore, these patients are known to be associated with stenosis and occlusions of the infrapopliteal segments. Since MDCTA depicts these vascular wall calcifications accurately, the lumen assessment can be very difficult in these arteries due to the blooming artifact and the small lumen caliber as shown in Chapters 3, 4 and 7. This implies that MDCTA has decreased clinical utility for patients with Fontaine stage III or IV. Thus, we have to accept this limitation and need to distinguish patients with intermittent claudication from chronic critical ischemia to decide which imaging modality would be appropriate. From these results can be concluded that for the evaluation of patients with intermittent claudication (Fontaine stage II) a preferential use of MDCTA seems justified when no contra-indications exist for the use of iodinated contrast agent. For the luminal assessment in patients with chronic critical limb ischemia, Fontaine stage III and IV, a technique that is not hampered by vascular calcifications, such as CEMRA, or DSA should be utilized.

Furthermore, the concern on radiation risk from MDCTA or DSA was concluded as a drawback in many reports in literature. This is partly due to the increasing contribution of CT examinations in total medical radiation (37, 38) which increasingly receives more attention in literature (37, 39-46). Up to now, risks due to radiation dose have always been calculated for the 'healthy' patient. Radiation dose must be viewed in context of the average annual background radiation (2.55 in the Netherlands, 2-5 mSv in the United States of America). An important perspective is the risk of inducing

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a fatal cancer due to radiation from an examination in a 'diseased' patient with his/ her specific risk from their disease. Therefore, we estimated the excess mortality risk of radiation induced fatal cancer in this specific patient population with symptomatic peripheral arterial disease (chapter 8). We measured radiation exposure at MDCTA and DSA, which was expressed as effective dose. The excess risk of radiation induced fatal cancer was estimated using a modified multiplicative model of the ICRP 60 in order to include the reduced life expectancy of patients suffering PAD as reported in various epidemiologic reports (3-9). We found that similar radiation doses are delivered at MDCTA (8.3 mSv [SD 1.3]) when compared with that of DSA (9.9 mSv [SD 4.9]). Our results showed that the excess mortality risk associated with radiation doses from a single MDCTA or DSA in these patients could be qualified as neglible when compared to the mortality rate from the underlying disease of PAD, atherosclerosis. To understand its perspective, the excess risk of radiation is comparable to the mortality risk associated with the use of low-osmolality contrast media (47). To summarize, the issue of radiation risk is not a major drawback of MDCTA in imaging PAD.

MDCTA is increasingly used to evaluate patients with peripheral arterial disease. Therefore, it is important to become familiar with the advantages and disadvantages of this new technology. In this thesis, the principles of scanning and injection technique for the 4-, 16-, and 64-detector CT scanners are explained. These large volumes of data need effective methods for archiving, evaluation, and presentation. The currently available reports in literature have shown that MDCTA has a high accuracy and good reproducibility for the assessment of stenosis and occlusion in the work-up of peripheral arterial disease and that it is a cost-effective modality when compared to other imaging techniques. MDCTA has shown to have an important clinical value for depicting chronic obstructive peripheral arterial disease, aneurysmatic arterial disease, e.g. popliteal aneurysms, acute peripheral arterial disease, e.g. in thrombo-embolic disease, and for evaluating the arterial vasculature after revascularization procedures.

In the meta-analysis, we pooled the available reports using a random effects model and found a sensitivity of 92 (95% CI, 0.89-0.95) and a specificity of 93% (95 CI%, 0.91-0.95) for detecting significant stenosis (≥ 50%) with MDCTA in the peripheral arterial tree. The results suggest that the estimates of diagnostic performance of MDCTA may be underestimated. In comparison with other non-invasive diagnostic imaging technologies for lower extremity arterial disease, such as contrast-enhanced MR angiography, MDCTA showed similar pooled estimates of sensitivity and specificity. The pooled sensitivity and specificity of MDCTA for interpreting images of the infrapopliteal tract was lower but not significantly different

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from the aortoiliac or femoropopliteal tract. The diagnostic performance of MDCTA was not significantly influenced by advances in technology or image quality or by differences in clinical setting or study design.

Future directions

Unless new CT techniques can solve the annoying calcifications in the vascular wall depicted with MDCTA, the diagnostic work-up of patients with critical limb ischemia (Fontaine stage III or IV) should be performed using contrast enhanced magnetic resonance angiography (CEMRA) or DSA.

The development of new and improved CT technology is proceeding. The increase in number of detector rows has resulted in higher image resolution which is important for the smaller, crural arteries. Currently, there is no longer a trade off between resolution and scan speed and submillimeter scanning is not limited in obese patients.

The main problem remains the depiction of vessel wall calcifications, which are present in approximately half of the patients. The improvement of resolution and the use of double longitudinal sampling in 64-DCT results in less blooming of calcifications, which improves lumen evaluation. Current solutions for the calcification problem can be found in postprocessing techniques, such as digital removal of the calcified voxels, central lumen projections, and subtraction techniques. Although, these techniques have an increasing (semi)-automated interface, it still requires a high degree of user interaction and, therefore can be quiet time-consuming, or it can introduce artifacts. Despite all these available tools, lumen assessment still is hampered by the circumferential calcifications in the crural arteries. A promising new generation of CT technology that uses dual energy will be introduced in the near future. It will utilize two X-ray sources that operate simultaneously at different kV levels. The result are two spiral data sets acquired in a single scan that contain spectral information, which allows differentiation and characterization of imaged tissue. For instance, direct bone or calcification subtraction can be performed. This could overcome the calcification problem without manual post processing steps and a reduced reading time. Whether dual energy CT will overcome the major limitation of CT angiography need to be evaluated.

Another solution to bypass the problem is not by improvement of the technology, but through selecting patients prior to the diagnostic imaging test. Patients who are likely to have extensive vessel wall calcifications, such as patients suffering from chronic ischemia, cardiac disease, and diabetes mellitus should be redirected to DSA or CEMRA. The majority of patients with intermittent claudication should preferably undergo MDCTA. More research is necessary to evaluate new CT technology, restricted in patients with a severe stage of PAD, to validate our clinical predictors of vessel wall calcifications, and to evaluate new fields of MDTCA in peripheral arterial disease.

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In summary, multi-detector row CT angiography is an outstanding non-invasive imaging test in the evaluation of patients with PAD. MDCTA has shown to have high diagnostic performance and reproducibility in evaluating PAD. MDCTA reduces diagnostic costs and provides sufficient information for decision making to replace DSA. The clinical utility decreases when extensive arterial wall calcifications are present. Patients with chronic critical limb ischemia have more arterial wall calcifications compared to patients with intermittent claudication which are predicted by diabetes mellitus, cardiac disease, or older age. MDCTA can replace DSA in the work-up of peripheral arterial disease, but the application in patients suffering chronic critical limb ischemia need be modest.

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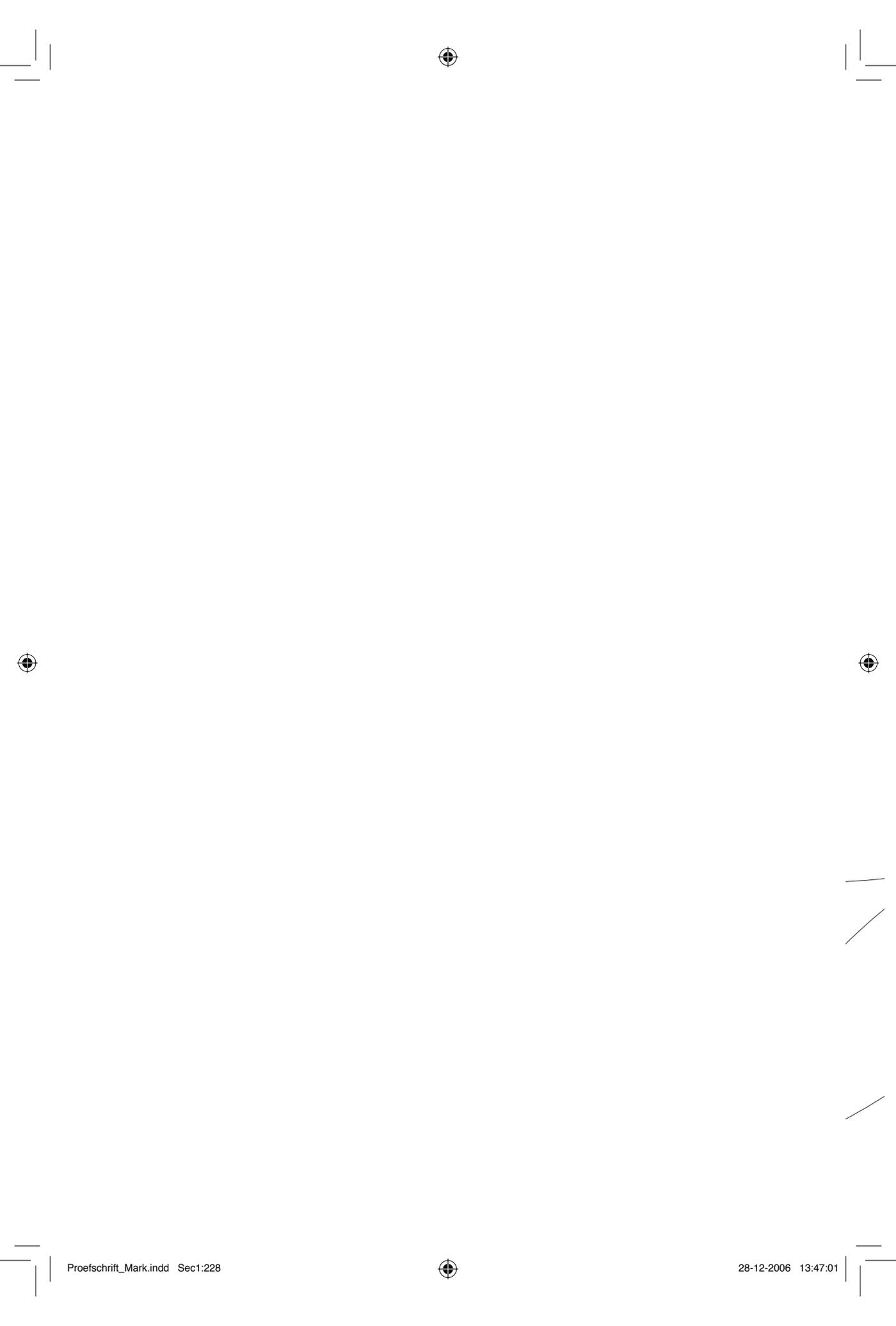
Chapter 12
Summary

General Discussion and Summary

This thesis describes studies on the evaluation of the non-invasive multi-detector CT angiography (MDCTA) for patients with peripheral arterial disease (PAD). In **chapter 1**, the motivation for this thesis is given. PAD is an important health care problem in western countries. Peripheral arterial disease results from atherosclerotic build-up in the peripheral arteries with clinical manifestations ranging from intermittent claudication (leg pain during exercise) to critical ischemia (pain at rest and tissue loss).

Diagnostic imaging in PAD is only indicated when revascularization is considered. It is important to evaluate the extent of the disease accurately when planning therapy. Traditionally, digital subtraction angiography (DSA) is used for the evaluation of PAD, but it is associated with risk of morbidity and mortality due to its invasive nature. Therefore, non-invasive techniques were developed to depict the arteries, such as duplex ultrasound (DUS) and contrast-enhanced magnetic resonance angiography (CEMRA). Helical CT equipment has advanced from the early method of a single-detector system to a multi-detector system which enables the depiction of the entire inflow and runoff arteries using one single acquisition and contrast bolus. Currently, multi-detector CT angiography (MDCTA) has entered the clinical practice for the evaluation of PAD. Important is to evaluate the advantages as well as the potential disadvantages of this new radiological technology. Therefore, the aim of this thesis was to evaluate MDCTA in the work-up of patients with PAD.

In **chapter 2**, target values, such as sensitivity and costs, were estimated to evaluate when a new imaging technique would be cost-effective when compared with the currently used non-invasive technique, MR angiography. The target values seemed achievable for a new imaging technique and MDCTA, as a new technique, can potentially meet these criteria.

Recent publications have reported a high diagnostic accuracy for MDCTA in the evaluation of PAD. In addition, it is important to evaluate the reproducibility, including interobserver agreement for interpreting the imaging test. In **chapters 3 and 4**, the interobserver agreement for the interpretation of MDCTA in patients with PAD was compared subsequently with DSA and CEMRA. The results showed that DSA, CEMRA, and MDCTA had excellent interobserver agreement for reporting the degree of stenosis in all segments. CEMRA has a higher interobserver agreement than MDCTA, and MDCTA had an interobserver agreement that was comparable with DSA. The two studies found that interobserver agreement for the interpretation of MDCTA decreased significantly, when calcified segments were present.

The findings demonstrated that MDCTA is a non-invasive imaging technique with good diagnostic performance for the evaluation of PAD. However, to decide whether this diagnostic test should be implemented in routine clinical practice for the work-up of PAD, other outcomes, such as the associated clinical utility, patient outcomes, and associated costs, need to be evaluated. **Chapters 5 and 6** describe the results of the Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) randomized controlled trial (RCT) on the effects and the costs of MDCTA as the initial test in the work-up of PAD. We found slightly lower therapeutic confidence but similar effectiveness and less di-

agnostic costs, and similar therapeutic, hospital, and outpatient costs for the MDCTA strategy when compared to the DSA strategy. Although, therapeutic confidence was lower for MDCTA, regression analysis showed a trend of increasing confidence during the trial. The MDCTA strategy resulted in more requested and performed additional imaging tests but the total diagnostic costs for the MDCTA strategy remained lower than that of the DSA strategy. These results suggest that non-invasive MDCTA can replace the reference test, DSA, as initial imaging test in the work-up of peripheral arterial disease.

Besides the assessment of the benefits, the potential limitations of MDCTA in PAD also need to be addressed. First, we encountered that in MDCTA extensively calcified vessels hamper the assessment of arterial luminal stenosis. Therefore, it is important to evaluate the impact of arterial wall calcification on the clinical utility of MDCTA measured as therapeutic confidence and number of additional imaging tests performed. In addition, it would be useful to identify clinical predictors for the presence of arterial wall calcifications in order to identify those patients where the clinical utility of MDCTA would be less than expected. We found that vessel wall calcifications decrease the clinical utility of MDCTA in patients with PAD and that diabetes mellitus, cardiac disease, and elderly age are independently predictive for the presence of arterial wall calcifications (**chapter 7**). In particular, diabetes mellitus is known to be associated with arterial disease of the lower legs and with severe form of peripheral arterial disease leading to symptoms at rest and ulcerations (Fontaine stage III or IV). This indicates that due to the calcification problem the clinical value of MDCTA in patients with chronic critical limb ischemia is limited. Whether new multi-detector CT techniques are able to solve this problem needs to be evaluated. Meanwhile, these results suggest that, depending on local expertise and availability of image modality, patients with chronic critical limb ischemia should undergo either CEMRA or DSA instead of MDCTA. Generally, patients with severe renal insufficiency will undergo CEMRA, since the use of large amounts of iodinated contrast agent is contra-indicated.

The second potential limitation is the issue related to radiation exposure from multi-detector row CT scanners. It is necessary to evaluate the dose and radiation-associated risks from MDCTA in relation to DSA to justify the application in the work-up of patients with PAD. Epidemiological studies have shown that patients suffering from PAD have a poor prognosis because they have an increased risk of fatal cardiovascular and cerebrovascular events. In **chapter 8** we evaluated the excess radiation risk of undergoing a MDCTA or a DSA examination in the work-up of PAD in relation to the increased mortality associated with the disease of these patients. We measured radiation exposure of MDCTA and DSA and calculated the effective dose. We used the multiplicative model of the International Commission on Radiological Protection (ICRP), which was modified in order to account for the reduced life expectancy of patients suffering from PAD, to estimate the associated excess risk of radiation induced fatal cancer. We found that MDCTA and DSA deliver comparable radiation doses in the evaluation of PAD. With the average published annual mortality rate of patients with PAD and mean age and dose as observed in our study, we found that the excess

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lifetime radiation-associated risk of fatal cancer would be less than 0.01% for both modalities. Therefore, we can conclude that the excess radiation-associated mortality risk from a MDCTA or DSA examination in the work-up of PAD can be qualified as negligible compared to the mortality rate from their underlying disease of PAD.

The technical review (**chapter 9**) explains the strengths and limitations of MDCTA and the principles of scanning and injection techniques. The properties of image postprocessing for effective evaluation and communication are provided and an over-view of clinical applications and of current literature of MDCTA of the peripheral vasculature is presented.

The meta-analysis (**chapter 10**) deals with overall diagnostic performance of MDCTA in the evaluation of peripheral arterial disease and the most important sources of variation in diagnostic accuracy between studies that were analyzed using summary operator characteristic analysis. We included 12 published studies that used DSA as the standard of reference and found that MDCTA has a high accuracy. The re-sults showed small differences in diagnostic accuracy that were not explained by the variables related to study design, patient population, or scanning technique. This indicates that MDCTA is a robust imaging test, which allows routine evaluation of peripheral arterial disease.

In **chapter 11**, the general discussion, the main findings described in this thesis are placed in a broader perspective and discussed with relevant methodological aspects.

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Samenvatting

Dit proefschrift beschrijft studies naar de evaluatie van niet-invasieve multi-detector CT angiografie (MDCTA) bij patiënten met perifeer arterieel vaatlijden (PAV). In **hoofdstuk 1** wordt de motivatie van dit proefschrift uiteengezet. PAV is een belangrijk probleem binnen de gezondheidszorg van westerse landen. Perifeer arterieel vaatlijden wordt veroorzaakt door arteriosclerose in de perifere slagaders. De ziekte manifesteert zich door de klinische symptomen variërend van claudicatio intermittens (pijn in het been tijdens lopen) tot kritische ischemie (rustpijn en weefsel verlies).

Beeldvormend onderzoek bij PAV is alleen geïndiceerd wanneer de patiënt voor een revascularisatie in aanmerking komt. Belangrijk is het dan om de uitgebreidheid van de ziekte nauwkeurig te identificeren om een adequate therapie te kunnen plannen. Digitale subtractie angiografie (DSA) is het traditionele onderzoek voor de anatomische beoordeling van PAV, maar is vanwege het invasieve karakter geassocieerd met een risico op morbiditeit en mortaliteit. Vanwege dit gegeven zijn niet-invasieve technieken ontwikkeld om de slagaders af te beelden, zoals duplex ultrageluid (DUG), contrastversterkte magnetische resonantie angiografie (CV-MRA). Spiraal CT technologie heeft zich ontwikkeld sinds de eerdere methode van een enkelvoudig detector systeem tot een meervoudig detector systeem. Door deze ontwikkeling is het nu mogelijk om met behulp van CT techniek de gehele instroom en uitstroom van de beenslagaders af te beelden met een enkele acquisitie en bolus contrastmiddel. MDCTA wordt in toenemende mate gebruikt in de klinische praktijk om PAV te evalueren. Het is hierbij van belang om zowel de voordelen als ook de potentiële nadelen van een nieuwe radiologische technologie te belichten. De doelstelling van dit proefschrift is om MDCTA te evalueren in de diagnostische voorbereiding van patiënten met PAV.

In **hoofdstuk 2** worden doelcriteria als diagnostisch onderscheidend vermogen en kosten van een beeldvormend onderzoek geschat waarmee een nieuw niet-invasief beeldvormend onderzoek kosten-effectief zou kunnen zijn in vergelijking met de huidig toegepaste niet-invasieve techniek, CV-MRA. De doelcriteria die aan het nieuwe beeldvormende onderzoek worden gesteld om kosten-effectief te zijn lijken haalbaar voor een nieuw te ontwikkelen niet-invasief beeldvormende techniek. MDCTA is zo'n nieuw alternatief en lijkt de potentie te hebben om aan deze criteria te voldoen.

Recent wetenschappelijk onderzoek rapporteert een hoge diagnostische nauwkeurigheid voor deze nieuwe niet-invasieve beeldvormende techniek, MDCTA, om PAV te evalueren. Het is tevens van belang om ook de reproduceerbaarheid, inclusief de interwaarnemer overeenstemming, te evalueren. In de **hoofdstukken 3 en 4** is de interwaarnemer overeenstemming onderzocht voor de beoordeling van perifere slagaders met MDCTA in vergelijking met DSA en van MDCTA in vergelijking met CV-MRA in patiënten met PAV. De resultaten lieten een excellente interwaarnemer overeenstemming zien van MDCTA als DSA en CV-MRA voor het rapporteren van de ernst van bloedvat vernauwingen. Met behulp van CV-MRA bleek een hogere overeenstemming bereikbaar te zijn dan met MDCTA en met MDCTA is een vergelijkbare overeenstemming haalbaar als met DSA. Beide studies vonden dat wanneer

verkalkte vaatsegmenten aanwezig waren dat de interwaarnemer overeenstemming voor de interpretatie van MDCTA significant lager is dan wanneer er geen vaatwand calcificaties aanwezig zijn.

Het is duidelijk dat MDCTA een niet-invasieve techniek is die een goede diagnostische prestatie levert om patiënten met perifeer vaatlijden te evalueren. Echter omdat de klinische bruikbaarheid, patiëntgerelateerde uitkomsten en de geassocieerde kosten nog niet zijn onderzocht blijft de vraag bestaan of MDCTA geïmplementeerd moet worden in de diagnostische voorbereiding van PAV. In de **hoofdstukken 5 en 6** worden de resultaten van de gerandomiseerde gecontroleerde trial van diagnostische beeldvorming van perifeer arterieel vaatlijden, de zogenaamde DIPAD studie, naar de kosten en effecten van MDCTA als initiële test in de diagnostische voorbereiding van PAV beschreven. We vonden tijdens de trial een stijgende trend over de tijd van de klinische bruikbaarheid, gemeten als het therapeutisch vertrouwen in MDCTA. Echter was het gemiddelde vertrouwen in MDCTA lager dan die in DSA. Tevens vonden we dat de patiëntgerelateerde uitkomsten gelijk waren voor MDCTA en DSA. Wanneer MDCTA het initiële beeldvormende onderzoek was resulteerde dat in meer aanvullend onderzoek dat werd aangevraagd en uitgevoerd. Toch bleek dat de diagnostische kosten lager waren voor de MDCTA strategie in vergelijking met de DSA strategie en dat de therapeutische kosten en kosten die gerelateerd zijn aan ziekenhuisbezoek of opname vergelijkbaar waren. Deze resultaten suggereren dat het niet-invasieve MDCTA onderzoek de referentie test, DSA, kan vervangen als initieel beeldvormend onderzoek in de diagnostische voorbereiding van perifeer arterieel vaatlijden.

Naast het bepalen van de voordelen van MDCTA is het ook van belang om potentiële beperkingen te onderzoeken. Ten eerste is tijdens de evaluatie van MDCTA geconstateerd dat wanneer er uitgebreide vaatwandverkalkingen aanwezig zijn de beoordeling van vernauwingen van slagaders bemoeilijkt wordt. Daarom is het van belang om de invloed van vaatwandverkalkingen op de klinische bruikbaarheid, gemeten als therapeutisch vertrouwen en het aantal aanvullende verrichtingen, van MDCTA te evalueren. Het is daarbij zinvol om klinische voorspellers van vaatwandverkalkingen te identificeren om te kunnen voorspellen bij welke patiënten de klinische bruikbaarheid van MDCTA minder zal zijn dan verwacht. We vonden dat vaatwandverkalkingen geassocieerd zijn met een verlaagde klinische bruikbaarheid van MDCTA en dat diabetes mellitus, hartziekte en oudere leeftijd onafhankelijke voorspellers zijn voor de aanwezigheid van deze vaatwandverkalkingen (**hoofdstuk 7**). Onder andere, diabetes mellitus is sterk geassocieerd met arteriële afwijkingen van de onderbenen en met ernstige vorm van perifeer arterieel vaatlijden met tekenen van ulcera en gangreen (Fontaine stadium III of IV). Dit geeft aan dat door het probleem van deze arteriële vaatwandverkalkingen de klinische waarde van MDCTA van patiënten met chronische kritische ischemie beperkt is. Of nieuwe multi-detector CTA technieken dit probleem kunnen oplossen dient te worden geëvalueerd. De resultaten wijzen uit dat tussentijds kan worden overwogen om patiënten te selecteren op basis van de gevonden voorspellers om een andere beeldvormend onderzoek te ondergaan, zoals CV-MRA of DSA, afhankelijk van lokale deskundigheid en beschikbaarheid. Omdat diagnostische beeldvorming met behulp van nefrotoxisch jodiumhoudend contrast-

middel een contraindicatie is bij patiënten met ernstige nierinsufficiëntie zullen deze patiënten over het algemeen een CV-MRA ondergaan.

De tweede potentiële beperking is de kwestie die gerelateerd is aan de blootstelling aan röntgenstralen van multi-detector CT scanners. Het is noodzakelijk om de dosis en de stralingsafhankelijke risico's van MDCTA in relatie tot DSA te evalueren en om de toepassing in de diagnostische voorbereiding van patiënten met PAV te justificeren. Epidemiologische studies hebben aangetoond dat patiënten die aan PAV lijden een beperkte levensverwachting hebben omdat zij een verhoogd risico hebben op een dodelijk hartinfarct of herseninfarct. In **hoofdstuk 8** evalueren we het toegevoegde risico van straling van een DSA of een MDCTA onderzoek in de diagnostische voorbereiding van PAV op het overlijdensrisico van de patiënt aan zijn ziekte. We hebben de blootstelling aan straling bij MDCTA en DSA gemeten en de effectieve dosis berekend. Vervolgens hebben we het toegevoegde risico van kankersterfte door straling bepaald met behulp van het multiplicatieve model van de Internationale Commissie van Radiologische Bescherming (ICRP). Het model hebben we aangepast om te corrigeren voor de beperkte levensverwachting van patiënten die aan PAV lijden. We vonden dat MDCTA en DSA in de evaluatie van PAV een vergelijkbare stralingsdosis geven. Uitgaande van een gepubliceerd gemiddelde jaarlijks sterfte binnen patiënten met PAV en een gemiddelde leeftijd en dosis zoals gevonden is in onze studie, hebben we een toegevoegd levenslange stralingsrisico op kankersterfte gevonden van 0.008% indien MDCTA is ondergaan en van 0.009% indien DSA is ondergaan. Hieruit kan geconcludeerd worden dat het toegevoegde levenslange stralingsrisico op kankersterfte door MDCTA of DSA onderzoek in de diagnostiek bij PAV als verwaarloosbaar klein kan worden beschouwd in vergelijking met de sterfte van deze patiënten aan hun ziekte.

In het technische review (**hoofdstuk 9**) worden de potenties en de beperkingen van MDCTA en de principes van scannen en contrast injectie uitgelegd. Het hoofdstuk behandelt de postprocessing van de beelden om effectieve evaluatie en communicatie te bewerkstellen. Verschillende klinische toepassingen van MDCTA van de perifere vasculatuur en de huidige literatuur worden besproken.

De meta-analyse in **hoofdstuk 10** behandelt de algemene diagnostische betrouwbaarheid van MDCTA in de evaluatie van perifeer vaatlijden en de belangrijkste oorzaken van variatie in betrouwbaarheid tussen studies door middel van summary receiver operating characteristic analyses. We includeerden 12 gepubliceerde studies die DSA als referentie standaard hadden gebruikt en vonden dat MDCTA een grote betrouwbaarheid heeft. Er waren geen variabelen die de kleine verschillen tussen de gepubliceerde diagnostische betrouwbaarheid van MDCTA kon verklaren. Dit wijst erop dat MDCTA een robuuste beeldvormende test is die gebruikt kan worden voor routinematige evaluatie van perifeer vaatlijden.

In **hoofdstuk 11**, de algemene discussie, worden de belangrijkste bevindingen van dit proefschrift geplaatst in een breder perspectief en besproken aan de hand van relevante methodologische aspecten.

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Abbreviations

16D-CT	=	sixteen–detector row computed tomography
2D	=	two–dimensional
3D	=	three–dimensional
4D-CT	=	four–detector row computed tomography
64D-CT	=	sixty–four detector row computed tomography
AUC	=	area under the curve
BEIR	=	Biological Effects of Ionizing Radiations committee
CEMRA	=	contrast enhanced magnetic resonance angiography
CI	=	confidence interval
CPR	=	curved planar reformat
CT	=	computed tomography
CTA	=	computed tomography angiography
CTDI	=	CT dose index
DAP	=	dose-area product
DDREF	=	dose–and–dose–rate effectiveness factor
DLP	=	dose length product
DSA	=	digital subtraction angiography
DUS	=	duplex ultrasonography
E	=	effective dose
EQ–5D	=	EuroQol–5D
EPA	=	Environmental Protection Agency
FOV	=	field of view
GEE	=	generalized estimating equations
ICRP	=	International Commission on Radiological Protection
LNT	=	linear extrapolation without threshold
MDCT	=	multi–detector row computed tomography
MDCTA	=	multi–detector row computed tomography angiography
MIP	=	maximum intensity projection
MPR	=	multiplanar reformat
MR	=	magnetic resonance
MRA	=	magnetic resonance angiography
NRPB	=	National Radiological Protection Board
p	=	p value
PACS	=	picture archiving and communication system
PAD	=	peripheral arterial disease
QALY	=	quality–adjusted life year
ROC	=	receiver operating characteristic
SD	=	standard deviation
SF–36	=	Medical Outcomes Study 36–Item Short Form Health Survey
SROC	=	summary receiver operating characteristic
STARD	=	standards for reporting of diagnostic accuracy
UNSCEAR	=	United Nations Scientific Committee on the Effects of Atomic Radiation
US	=	ultrasonography

VRT	=	volume rendering technique
WC	=	window center
WW	=	window width
K	=	kappa statistic
K_w	=	weighted kappa statistic

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List of Publications

Manuscripts based on studies described in this thesis

Chapter 2
Visser K, **Kock MCJM**, Kuntz KM, Donaldson MC, Gazelle GS, Hunink MGM. Cost-effectiveness targets for multi-detector row CT angiography in the work-up of patients with intermittent claudication. Radiology 2003; 227:647-656.

Chapter 3
Kock MCJM, Kuiper JW, Pattynama PMT, Hunink, MGM. Randomized controlled trial for imaging peripheral arterial disease: comparison of interobserver agreement of multidetector CT angiography with digital subtraction angiography. Submitted.

Chapter 4
Ouwendijk R, **Kock MCJM**, Visser K, Pattynama PMT, de Haan MW, Hunink MGM. Interobserver agreement for interpretation of contrast-enhanced three-dimensional MR angiography and multi-detector row CT angiography in peripheral arterial disease. AJR Am J Roentgenol 2005; 185:1261-1267.

Chapter 5
Kock MCJM, Adriaensen MEAPM, Pattynama PMT, van Sambeek MRHM, van Urk H, Stijnen T, Hunink MGM. Digital subtraction angiography compared with multi-detector row CT angiography in patients with peripheral arterial disease: a randomized controlled trial. Radiology 2005; 237:727-737.

Chapter 6
Adriaensen MEAPM, **Kock MCJM**, Stijnen T, van Sambeek MRHM, van Urk H, Pattynama PMT, Hunink MGM. Peripheral arterial disease: therapeutic confidence of CT versus digital subtraction angiography and effects on additional imaging recommendations. Radiology 2004; 233:385-391.

Chapter 7
Ouwendijk R, **Kock MCJM**, van Dijk LC, van Sambeek MRHM, Stijnen T, Hunink MGM. Vessel wall calcifications at multi-detector row CT angiography in patients with peripheral arterial disease: effect on clinical utility and clinical predictors. Radiology. 2006; 241(2): p. 603-608.

Chapter 8
Kock MCJM, Geleijns J, Kuiper JW, Pattynama PMT, Hunink MGM. Realistic effective dose and excess risk assessment in multi-detector CT angiography or digital subtraction angiography in patients with peripheral arterial disease. Submitted.

Chapter 9
Kock MCJM, Dijkshoorn M, Pattynama PMT, Hunink MGM. Multi-detector row CT angiography of peripheral arterial disease: a review. Accepted for publication in European Radiology.

Chapter 10
Heijenbrok-Kal M, **Kock MCJM**, Hunink MGM. Meta-analysis of multi–detector row CT angiography of peripheral arterial disease. Accepted for publication in Radiology.

Manuscripts not appearing in this thesis

Kock MCJM, Ijzermans JNM, Visser K, Hussain SM, Weimar W, Pattynama PMT, Krestin GP, Hunink MGM. Contrast-enhanced MR angiography and digital subtraction angiography in living renal donors: diagnostic agreement, impact on decision making, and costs. AJR Am J Roentgenol 2005; 185:448-456.

Hussain SM, **Kock MCJM**, Ijzermans JNM, Pattynama PMT, Hunink MGM, Krestin GP. MR imaging: a "one-stop shop" modality for preoperative evaluation of potential living kidney donors. Radiographics 2003; 23:505-520.

Liem YS, **Kock MCJM**, Ijzermans JNM, Weimar W, Visser K, Hunink MGM. Living renal donors: optimizing the imaging strategy--decision- and cost-effectiveness analysis. Radiology 2003; 226:53-62.

General Discussion and Summary

Curriculum vitae

Marcus (Marc) Cornelius Johannes Maria Kock was born on March 7, 1968 in Etten-Leur, The Netherlands. He attended secondary school "Katholieke Scholengemeenschap Etten-Leur" and graduated in 1986.

The national lottery system for allocating students to medical faculties retained him from studying medicine and he decided to start the study biology at the University of Leiden (RUL). The next year he began his medical study at same University and he graduated in 1994. During his study he was a member of the introduction committee for first year medical students, member of the medical student committee, NIKO, and member of the medical debating society "Cave Fungos". He also studied Philosophy and received his bachelor degree in Philosophy from the University of Leiden (RUL) in 1994. In 1994 he started internships and in the meantime taking elective courses "Health and Disease in Developing Countries" at the Nijmegen Institute for International Health and Spanish at the University of Leiden.

After obtaining his medical degree in 1996 he worked, on a voluntary basis, in a municipal public health centre as a family physician in collaboration with the School of Public Health of Nicaragua (CIES) in Managua, Nicaragua. When he returned in 1997, he started his training in tropical medicine at Netherlands Society of Tropical Medicine and International Health.

In 1999 he started his training in radiology at the Department of Radiology (head of department: Prof.dr. G.P. Krestin) of Erasmus MC in Rotterdam. One year later in 2000, he combined his clinical training with a research fellowship at the same department under the supervision of Prof.Dr M.G. Hunink, in collaboration with the department of Epidemiology and Biostatistics, and Prof.Dr. P.M.T. Pattynama. During his research he studied clinical epidemiology at the Netherlands Institute for Health Sciences (NIHES) from the Erasmus Universtity of Rotterdam for obtaining his Masters of Science degree. His research projects have resulted in several publications which are partly appearing in his thesis. For part of this work he was nominated for the Annual Ernst Schering Prize of the Dutch Radiological Society (NVVR). He has been awarded the Introduction to Research for International Young Academics stipend of the Radiological Society of North America in 2003. He has presented original research at international conferences and received funding to make this possible.

For 6 years he was a member of the Committee of Medical Ethical Questions (CMEV), as a representative of the residents of the Erasmus MC. Currently, he is completing his training in radiology.

General Discussion and Summary
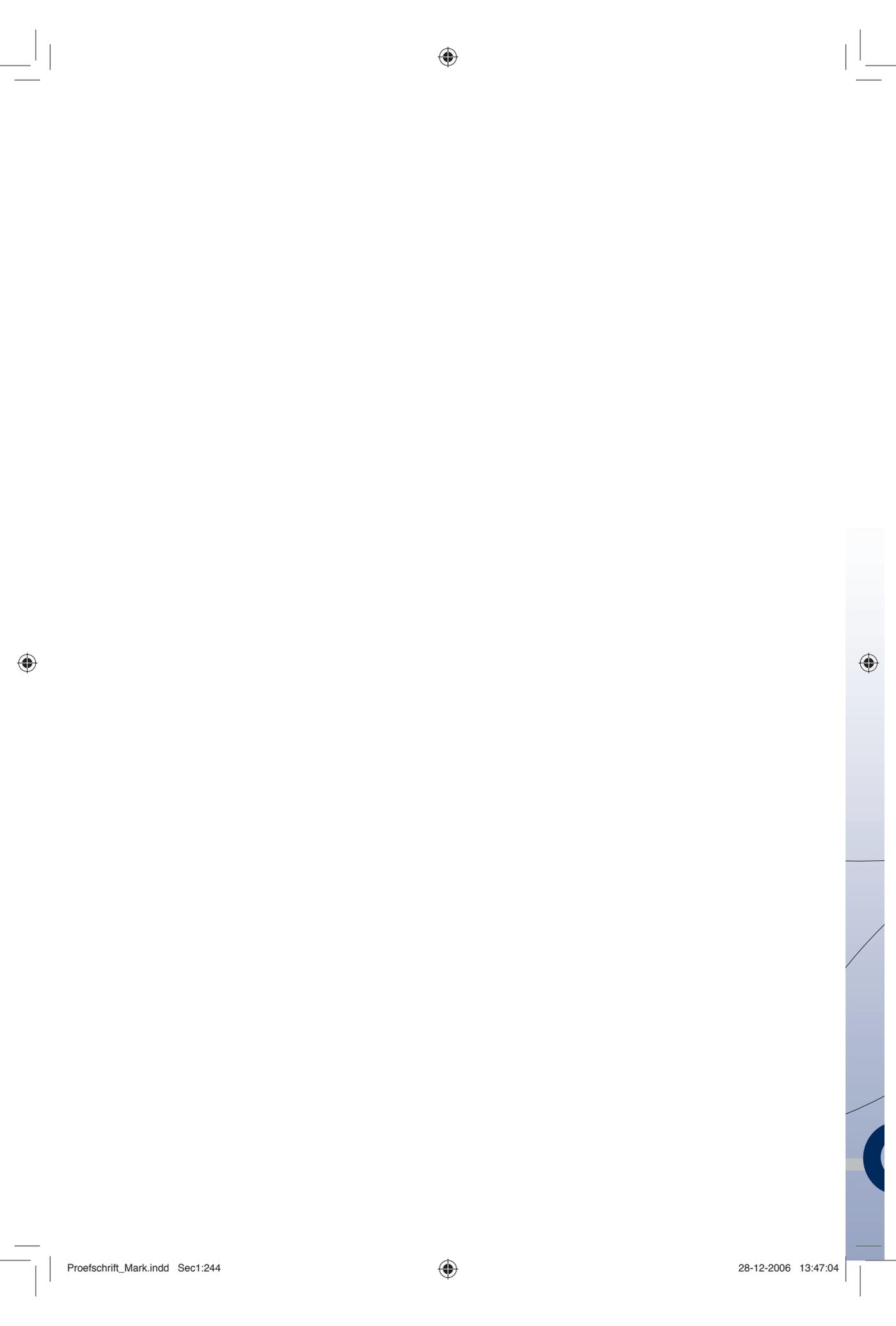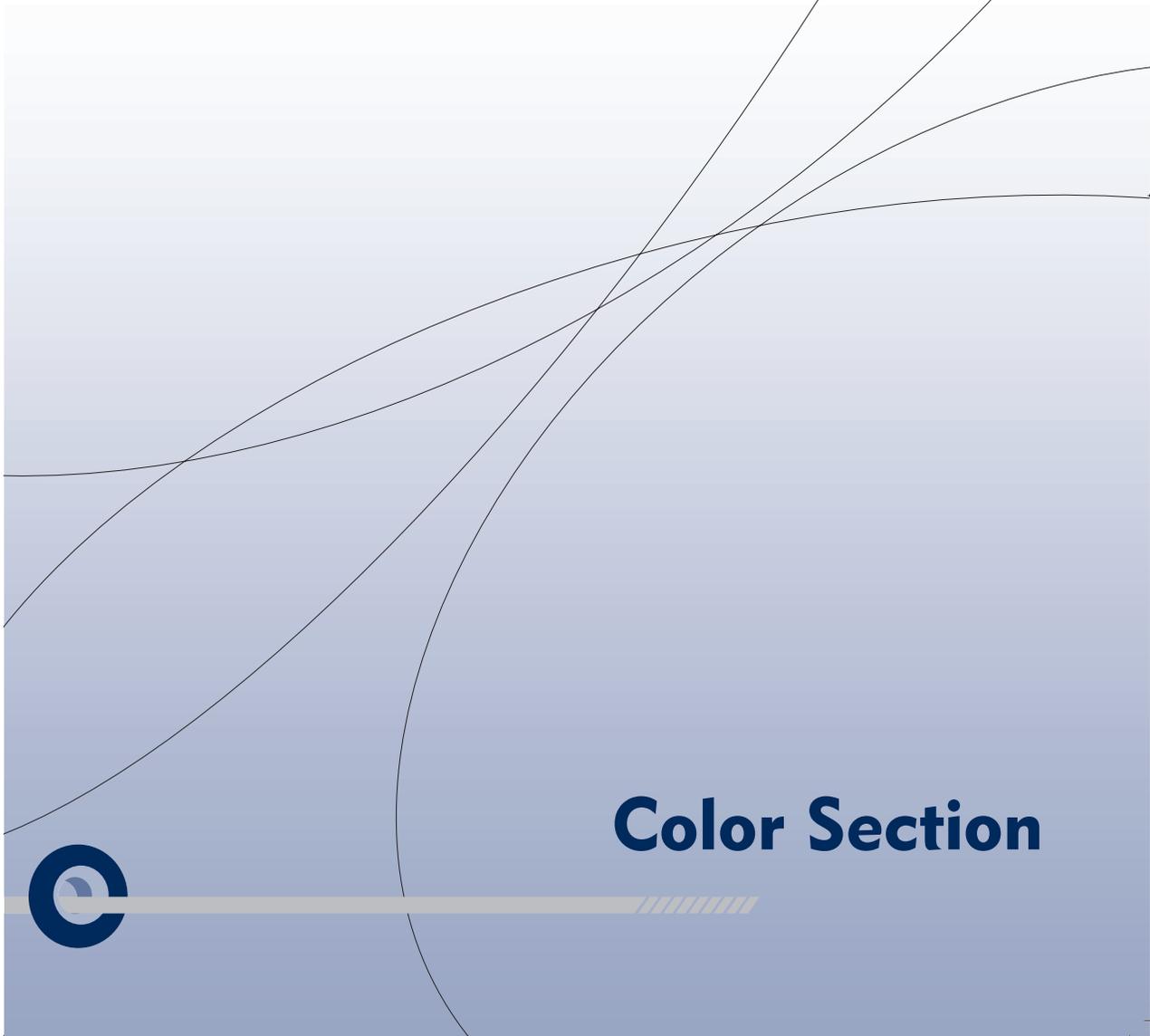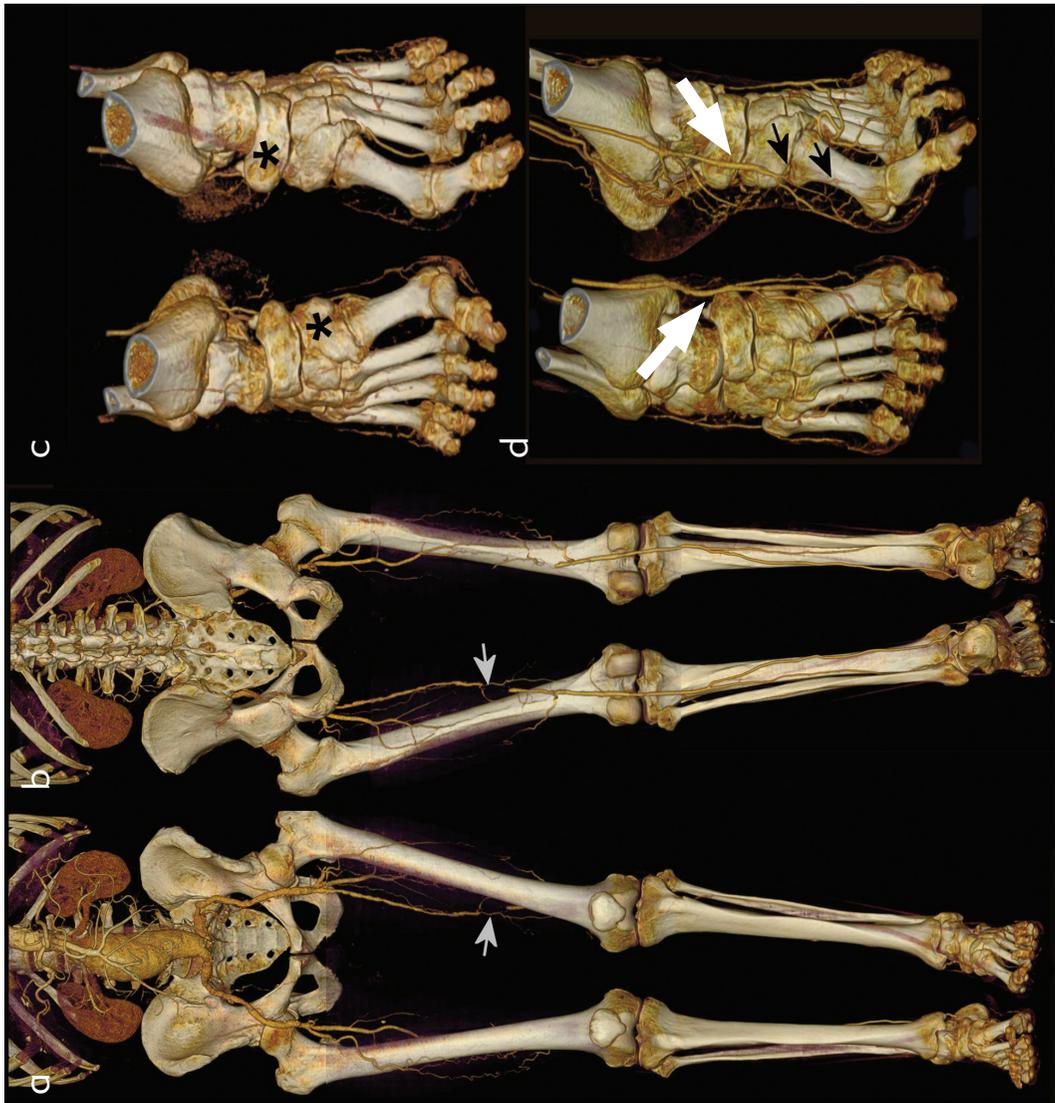
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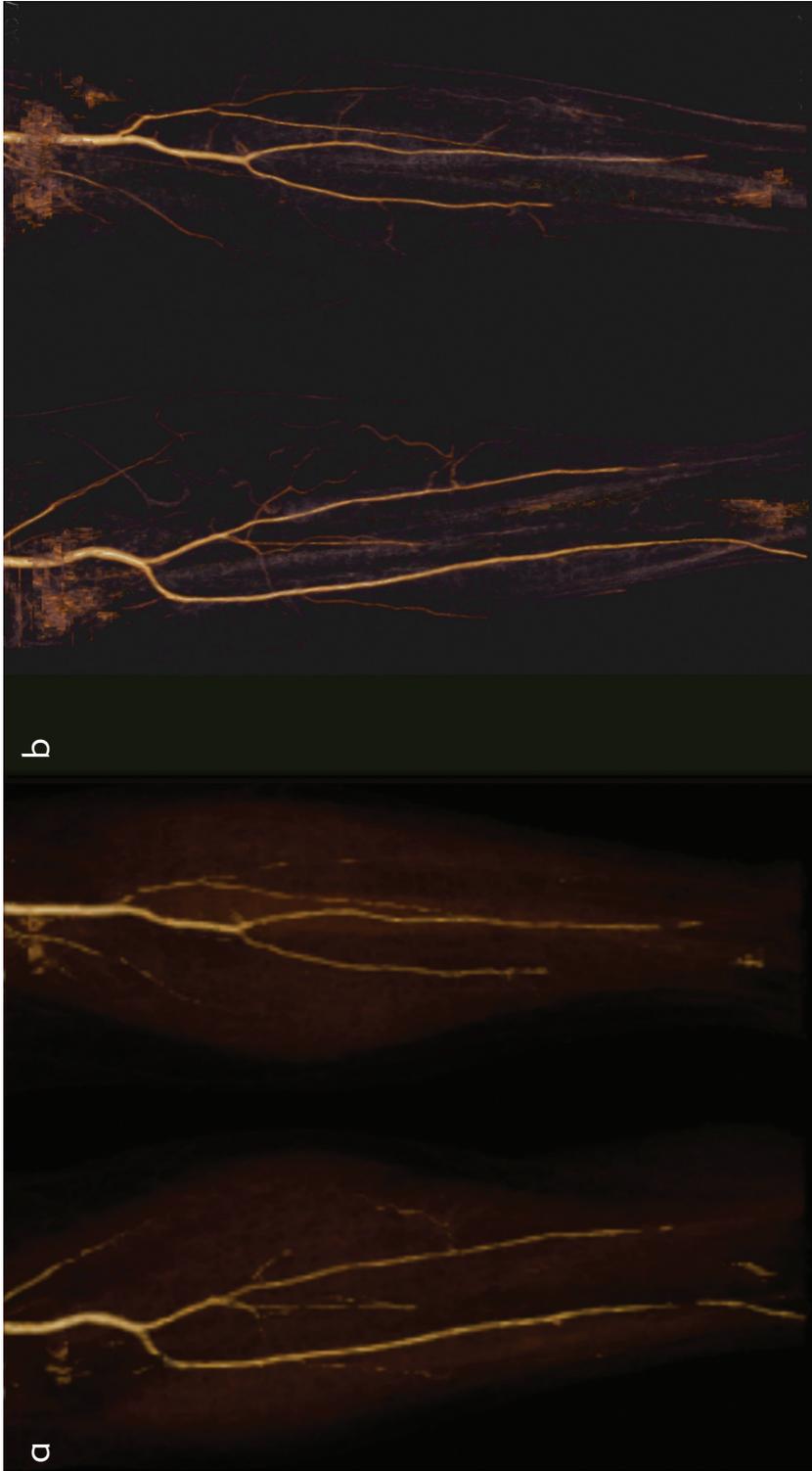
Chapter 9, Page 174; Figure 4.
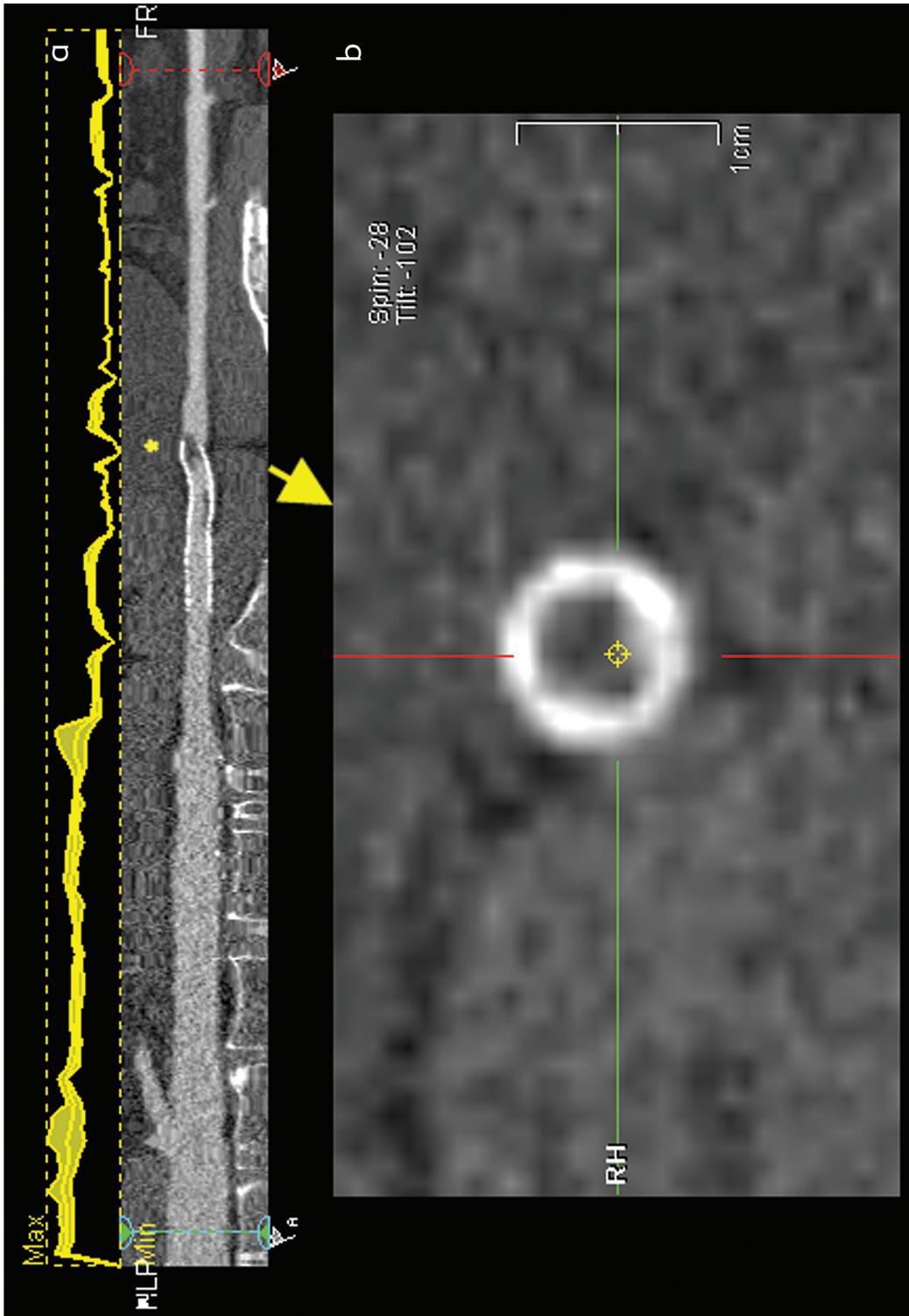
Chaper 9, Page 179; Figure 9.

*Chaper 9, Page 181; Figure 11.*

Chapter 9, Page 187; Figure 14.
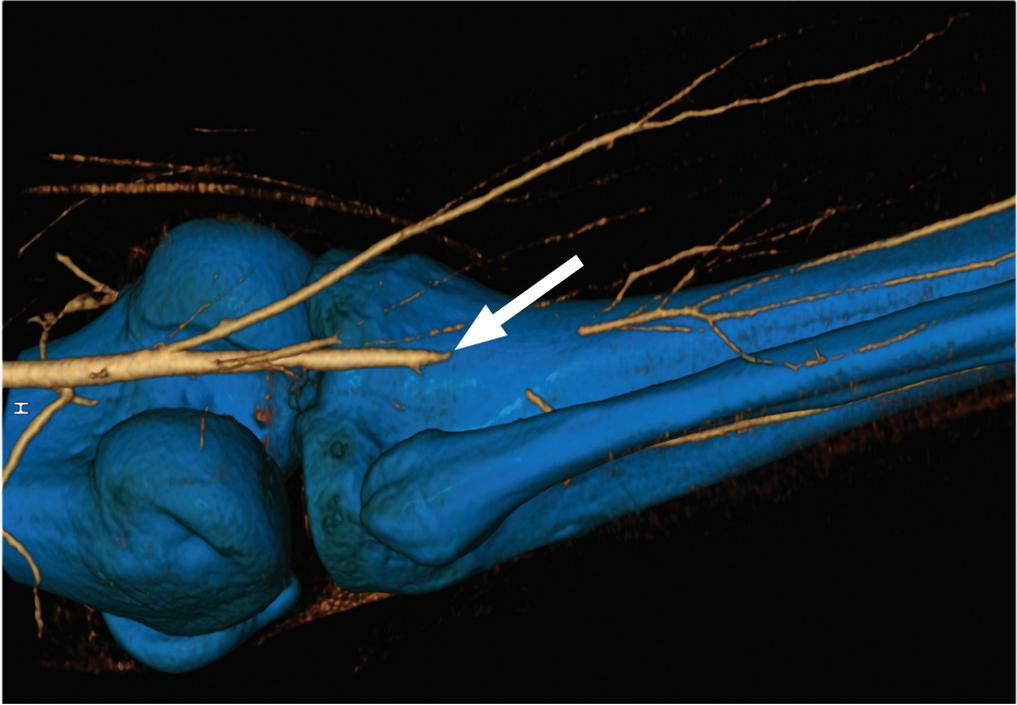
Chapter 9, Page 188; Figure 16.

Chapter 9, Page 188; Figure 15.

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Chapter 9, Page 188; Figure 17.