Chapter 9

Summary and general discussion
Summary

In 1999 in the Netherlands 3769 percutaneous transluminal angioplasty (PTA) procedures, 1125 endarterectomies and 3332 peripheral bypass operations were performed in patients with symptomatic peripheral arterial occlusive disease (PAOD) (source: Prismand, Utrecht). Some 3628 patients were treated after diagnostic arteriography, the traditional reference standard for establishing the diagnosis of PAOD. Arteriography is invasive, has a low complication rate and frequently requires admission. Accurate non-invasive tests could obviate the need for arteriography. Diagnostic tests for PAOD can be divided in tests for screening for the presence of arterial disease and tests for localizing and grading the severity of atherosclerotic lesions, in order to plan an intervention. The aim of this thesis was to find scientific evidence for the use of non-invasive diagnostic tests for PAOD and to explore the possibility of a completely non-invasive work-up in patients with severe lower leg ischemia.

In the introduction in Chapter 1 the results of a systematic review of studies published between 1976 and 1993 comparing non-invasive tests for assessment of PAOD with arteriography as reference standard is described. Some 624 articles were retrieved, in which 697 times a test was evaluated. Independent judgement by three observers left 106 studies of satisfactory methodological quality for quantitative analysis. For medical history, physical examination, including pulse palpation, auscultation and Buerger's test, the sensitivity ranged between 64% and 96% with a specificity between 62% and 85% to identify the presence of any atherosclerotic lesion in the entire lower extremity. Ankle-Brachial Index (ABI) measurement is a useful test to confirm or refute peripheral vascular disease. A cut-off point < 0.97 was highly accurate with a sensitivity of 94% and specificity of 97% to determine a stenosis or occlusion. No comparative studies were found that confirmed the often held position that the ABI is falsely elevated in diabetics due to incompressible arteries. Exercise testing has no better discriminatory power than ABI, but may be helpful to determine the maximum walking distance, although this parameter was poorly reproducible. Segmental blood pressure measurements, Doppler waveform analysis and Pulse Volume Recordings are inferior to duplex scanning (DS) and Magnetic Resonance Angiography (MRA) for localization and grading lesions in the aortoiliac and femoropopliteal tract. The reliability of arteriography as reference standard was not often evaluated, but iaDSA techniques seem more accurate than conventional angiography for assessment of the lower extremity arteries. Disparities were found between arteriography and intraarterial pressure (IAP) measurements. Some prefer IAP as it provides functional information, but no evidence is available whether management based on IAP can influence the outcome of interventions.

By 1994 71 studies on DS for assessment of the lower extremity arteries had appeared in the literature. Chapter 2 is a systematic review and meta-analysis of 16 studies comparing DS to arteriography. The Peak Systolic Velocity (PSV) ratio is an accurate parameter to grade the severity of arterial lesions. The pooled estimates of sensitivity and specificity for detection of a stenosis greater or equal than 50% or occlusion in the aortoiliac tract were 86% (95% confidence interval (CI), 80-91) and 97% (95% CI, 95-99), respectively. For the femoropopliteal tract pooled sensitivity and specificity were 80% (95% CI, 74-
85) and 96% (95% CI, 94-98), respectively. Accuracy for detection of a stenosis greater than or equal to 50% or occlusion in the infrapopliteal arteries was lower with a sensitivity and specificity of 83% (95% CI, 59-96) and 84% (95% CI, 69-93), respectively. Due to its high accuracy for assessment of the aortoiliac and femoropopliteal tract, DS is a reliable alternative for routine diagnostic arteriography. Several management studies confirmed the potential of DS to guide PTA or surgical revascularization procedures in the aortoiliac and femoropopliteal arteries in patients with predominantly claudication.

The meta-analysis revealed that more work was needed to define the role of DS for assessment of the infrapopliteal arteries. Patients with severe lower limb ischemia usually have multilevel disease with extensively diseased superficial femoral and infrapopliteal arteries. Adequate assessment is technically demanding, both with arteriography and DS, but essential for percutaneous or surgical revascularization. Chapter 3 describes a pilot study of DS for evaluation of the popliteal and infrapopliteal arteries compared with arteriography. Pulse Generated Runoff (PGR) was also studied because it was reported to identify distal arterial segments not visible on conventional arteriography. After this pilot study, a prospective comparative study of DS, PGR and iaDSA for assessment of the lower leg arteries was started. This study is described in chapter 4 and comprised 120 consecutive patients with severe lower leg ischemia. Popliteal, tibial and pedal arteries were graded with B-Mode and Doppler parameters. Overall agreement, expressed as weighted \( \kappa \)-values between DS and iaDSA for grading popliteal and crural arteries was moderate, with good agreement within the popliteal and anterior tibial arteries. Agreement was moderate within the pedal arteries. The sensitivity for detection of occlusions in the popliteal and tibial arteries ranged between 53% and 81% and the specificity between 80% and 96%. In 74/126 (59%) limbs the proposed management with DS/PGR was identical to definitive management based on iaDSA. In 23/29 (79%) femoropopliteal and 15/37 (41%) femorocrural bypasses DS/PGR identified the same recipient artery and anastomosis site as iaDSA. The estimated two year primary and secondary patency and limb salvage rates for patients treated with femoropopliteal bypass were 58%, 80% and 92%, respectively. The one year primary and secondary patency and limb salvage rates after femorocrural bypass were 54%, 85% and 82%, respectively.

The concordance between DS and iaDSA was substantial, but not perfect. Among other factors, interobserver variability could explain disparities between the two modalities. Chapter 5 describes a study on interobserver agreement on iaDSA and subsequent treatment plans. A random sample of 48 arteriograms was drawn from the patients participating in the comparative study and judged by 4 observers. The rate of non-diagnostic judgements ranged from 1% in the popliteal arteries to 22% in the pedal arteries. Overall agreement, expressed as \( \kappa \)-values was good for grading the popliteal, moderate for the tibial and fair for the pedal arteries. Agreement was good to excellent for grading occluded or fully patent popliteal and tibial artery segments, and fair to moderate for grading severe disease. In 55% of cases at least 3 (out of 4) observers (\( \kappa \)-value 0.33) and in 75% at least 2 (out of 3) vascular surgeons proposed identical treatment plans. It was concluded that using our grading system, iaDSA is reliable for detection of occluded or fully patent popliteal or tibial arteries, but not for detection of severe
disease. In addition, evaluation of the performance of two diagnostic modalities as concordance in treatment plans may be flawed by interobserver variation.

DS is often criticized for being operator dependent. If DS is to be used to guide clinical decision making it has to have an acceptable interobserver variation. In the study in chapter 6 two vascular technologists independently recorded PSV and graded the lower leg arteries with B-Mode and Doppler parameters in 24 consecutive patients. The intraclass correlation coefficient (ICC) for PSV recordings in the popliteal and tibial arteries was 0.90 (95% CI, 0.86-0.93) which indicates good agreement. For the pedal arteries the ICC was 0.64 (95% CI, 0.37-0.81) indicating moderate agreement. Interobserver agreement on grading artery patency was good within the popliteal and tibial arteries with weighted κ-values between 0.60 and 0.80 and moderate within the pedal arteries (weighted κ-values between 0.49 and 0.54).

Chapter 7 describes a management study of 117 consecutive patients with severe lower leg ischemia who had treatment guided by DS/PGR and iaDSA performed on indication only. In 97/125 (78%) limbs management was based solely on DS. This included 83% of femoropopliteal bypasses and 38% of femorotibial bypasses. In the latter procedures PGR was of no additional value to identify the best recipient artery. Overall in-hospital mortality was 8/114 (7%) and the two-year survival rate was 83%. Estimated two-year primary and secondary patency and limb salvage rates after femoropopliteal bypass surgery were 75%, 93% and 93%, respectively and 35%, 73% and 74%, respectively, one year after femorocrural bypass surgery. There were no differences in patient characteristics, indication for treatment and immediate and one-year outcome between the patients included in the management study and the population of the comparative study described in chapter 4. It is concluded that in a vascular unit with expertise in DS of the lower leg arteries, management of patients with severe ischemia can be based on DS in a majority of patients, without negative effects on clinical outcome during admission and at one and two years follow-up.

Magnetic Resonance Angiography (MRA) is another rapidly evolving non-invasive imaging technique with great diagnostic potential. Chapter 8 is a systematic review and meta-analysis of the accuracy of MRA for assessment of lower extremity arterial disease compared with arteriography. As in the 34 included studies a large number of different MRA protocols were applied, Summary Receiver Operating Characteristic curves were constructed to determine the diagnostic accuracy. It was shown that MRA is highly accurate for detection of stenosis >50% or occlusions in the entire lower extremity arterial tree. The application of 3-Dimensional MRA with Gadolinium contrast enhancement (3DGd) has significantly improved the diagnostic accuracy in the entire lower extremity compared to 2D MRA (relative diagnostic odds ratio 2.8 (95% CI, 1.2-6.4)). The estimated points of equal sensitivity and specificity were 94% and 90% for 3DGd MRA and 2D MRA, respectively. The majority of studied patients however, were examined for claudication and not for critical ischemia.
Implications for clinical practice

The results of the studies described in this thesis indicate that the initial assessment of patients with chronic lower extremity arterial occlusive disease can be simple. History taking, physical examination and Doppler ankle pressure measurement can accurately discriminate between the presence or absence of significant peripheral arterial disease. The cut-off point for a normal ABI can be chosen depending on whether the test is used to rule out or confirm the presence of PAOD. An exercise test may be performed to verify the patient’s pain free walking distance. Post-exercise ankle pressure measurements are not likely to further differentiate between normal and diseased peripheral arteries.

The next question is how to proceed. Arteriography has been used successfully for decades to establish a definitive diagnosis and guide treatment, and it will be used as such in the near future, despite the rapid development of DS and MRA. Ideally, arteriography is performed only if an intervention is intended and the same point of view must be held for non-invasive imaging and functional tests. The fact that non-invasive tests are “patient-friendly” should not imply their unrestricted use, because diagnosis cannot be regarded separately from therapeutic options.

The choice to use DS for non-invasive assessment requires close cooperation between vascular technologist, vascular surgeon and interventional radiologist. First of all, the vascular technologist must be a certified professional with ample experience in assessment of the lower extremity arteries with DS. To guarantee reliable DS examinations and to gain mutual confidence, continuous feedback is necessary. Technologists must discuss difficult examinations together, and receive information about findings during arteriography and operation from radiologist and surgeon. In our practice such meetings were held every week, and helped to better understand the possibilities and pitfalls of lower leg artery DS. The results of the interobserver study of DS in chapter 6 indicate that good interobserver agreement can be achieved in this way. When high quality DS studies are obtained, a strategy of DS as first examination with selective use of arteriography is safe for management of patients even with severe lower extremity ischemia, as was shown in chapter 7. In several other, mainly retrospective, studies the safety of DS to guide femoropopliteal and femorocrural bypass surgery with good short and intermediate term results was reported.15 Despite this evidence many surgeons and radiologists will hesitate to rely on the information provided by a vascular technologist to plan an intervention. An explanation may be that although the information of DS is recorded on anatomical charts or videotapes, DS cannot compete with the psychological advantage of arteriography and MRA that they produce visual information that can be reviewed at any time, independent from the person who performed the examination. However, one must realize that interindividual variation in image acquisition during arteriography and MRA also induces subjective judgement.

A large number of studies have shown that MRA is highly accurate for assessment of the lower extremity arteries. However, only few management studies have been published to date. In two studies MRA was successfully used to guide endovascular interventions.
Some early studies on 2D MRA provided anecdotal evidence that it could detect more runoff vessels than arteriography and changed intervention plans accordingly. These studies were not rigorous evaluations. However, one management study confirmed the ability of MRA to replace arteriography before infrainguinal bypass surgery. It is expected that more such studies will appear in the near future so that the role of MRA in clinical practice can be fully appreciated.

From our management study it became clear that PGR did not have the ability to help identify the best suited recipient artery for distal bypass surgery. In addition, in a follow-up study on femorocrural bypass surgery not included in this thesis, we could not reproduce the observation from previous studies that PGR can predict the success of distal bypass surgery. This implies that PGR has no clinical value at all and should not be used for patient management.

**Suggestions for research**

The scientific evidence for the use of tests to confirm or refute chronic peripheral arterial occlusive disease is well established. It is not to be expected that other, simpler tests than ABI measurement will become available in the near future.

A more important question may be which imaging or functional modality is to be regarded as reference standard to localize disease and establish a definitive diagnosis. In all comparative studies performed and analyzed in this thesis arteriography was used as reference standard. The possibilities and limitations of arteriography need not to be repeated here, but modalities compared to a reference standard will always perform second best. For assessment of the aortoiliac and femoropopliteal arteries both DS and MRA could serve as reference standard as both modalities showed a high concordance with arteriography within these tracts. This does not apply to the infrapopliteal arteries where significant disparities were found when DS and MRA were compared to arteriography. It has been suggested that arteriography is not appropriate for evaluation of these arteries and that intra-operative angiography (IOA) is the preferred reference modality. However, studies using IOA as such will suffer from verification bias, because IOA can only be performed in patients treated surgically. On the other hand such studies provide the possibility to gain information on the reliability of diagnostic arteriography as reference standard.

A second question is whether DS and MRA have significantly better accuracy over each other for assessment of the lower extremity arteries. A simple answer could be obtained by studying arteriography, DS and MRA simultaneously. However, investigators seem to “believe” in only one of both modalities: to date only 3 inconclusive studies are available that made such comparisons, if for the iliac arteries only. It will take years before this question will be resolved, provided more comparative studies will be conducted at all. A less time consuming alternative to make comparisons and generate hypotheses is the use of meta-analysis. A recent meta-analysis compared the diagnostic accuracy of 3DGd MRA and color DS for assessment of the lower extremity arteries with arteriography as reference standard. It was concluded that 3DGd MRA has better discriminatory power than color DS. As the authors note, such results cannot be
generalized without caution. Differences in study designs, study populations and setting and lack of transparency in the original publications may be responsible for the observed differences. Moreover, ongoing technical innovations will improve the diagnostic performance of MRA and DS. Our meta-analysis showed that Gd-enhanced MRA has significantly improved its discriminatory power. The possibly additional value of DS innovations such as power Doppler and contrast-enhanced DS need further investigation. Finally, DS and MRA need not necessarily be regarded as competitive, but the additional value of one modality to the other can be studied as well.

The third, and probably the key issue in future studies is that diagnosis must be regarded in relation to therapeutic options. Although more comparative studies are desirable, if only for continuous quality control, research should also incorporate the impact on clinical decision making and evaluate the outcomes of available treatment strategies. This can be done by means of decision analysis or in randomized trials.

De Vries and Hunink have presented an example of decision analysis for management strategies for patients with intermittent claudication.\textsuperscript{13} They concluded that the overall gain in effectiveness achieved with bypass surgery for intermittent claudication does not justify the additional costs over a strategy combining exercise and PTA. Unfortunately, differences in diagnostic work-up were not included in their analysis. In a comprehensive review, Mol and Bossuyt have proposed a suggestion for decision analysis in the evaluation of diagnostic test and treatment strategies.\textsuperscript{14} In brief, all relevant combinations of diagnostic and therapeutic options are used to construct a decision tree. Utilities must be assigned to each outcome in the decision tree to be able to compare the outcome of each diagnostic and treatment strategy. Sensitivity analysis allows one to explore the robustness of the outcome of the decision analysis.

The fact that our and other studies showed that diagnostic arteriography could be replaced by DS or MRA before bypass surgery merely indicates that these modalities can indeed be used to guide operations, but not that a non-invasive work-up is more beneficial to the patient's health than treatment based on arteriography. In addition, in the management study in \textit{chapter} 7 we showed that DS can safely guide treatment decisions in patients with severe lower leg ischemia without negative effects on outcome after two years. However, hypothetically the introduction of DS to guide patient management may have led to treatments for each individual patient, different from would have been done if they had diagnostic arteriography, but not to different outcomes for the whole population.

Randomized diagnostic trials might elucidate which diagnostic strategy is best. Several designs for such trials are available. Patients can be randomly allocated to one of the investigated diagnostic modalities and have subsequent treatment depending on the test result. Differences in outcome are measured after a specified period of follow-up. However, such a design does not offer an assessment of the test, but rather of a test and treatment strategy. A more informative design would be to submit patients to all test modalities under study (e.g. DS and arteriography) and to randomize only in case of discordant test results.\textsuperscript{15} The need for a large sample size, as only patients with discordant test results are randomized is a serious drawback of this method. Whichever design is
chosen, strict adherence is necessary to predefined indications for a specific treatment in order to be able to compare the relative contributions of both diagnostic modalities to observed differences in outcome.

Whether decision analysis is used or randomized trials, both methods require information on the benefits and harms of different treatments for chronic lower limb ischemia. This poses a challenge because the effectiveness of all treatment modalities has been demonstrated predominantly in case-series, and not randomized trials, and is therefore only best-evidence-based and not fully clarified. Maybe this may explain why decision making in vascular surgery is subject to significant interobserver variation like has been shown in chapter 5 and in other studies.

More evidence on the effectiveness of conservative treatment, PTA and surgery, may help to tailor treatment to the individual patient. An important issue is how the effectiveness of therapy should be measured. Whereas radiologists and vascular surgeons may be mainly interested in patency or limb salvage rates, quality of life may be more important to the patient. Assessment of quality of life in patients with critical limb ischemia has only recently gained much attention in vascular research and is not yet fully established.16-19

It is clear that in experienced hands non-invasive assessment and subsequent management of patients with symptomatic peripheral arterial occlusive disease is feasible and safe. The next step may be to find more evidence for the relative effectiveness of various treatment modalities for lower leg critical ischemia to provide a framework for future evaluation of different diagnostic (and thus) therapeutic strategies.

References


