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# Introduction and outline of this thesis

## General introduction

Lower extremity peripheral arterial disease (PAD) is the third leading cause of atherosclerotic vascular morbidity (after coronary heart disease and stroke) and is associated with significant morbidity, mortality and quality of life impairment.[1,2] Symptoms vary from reduced walking distance, to rest pain and tissue gangrene due to impaired blood flow to the extremities. Prevalence of symptomatic PAD is estimated at 202 million people around the world, and ranges from 2 to 6% in patients aged 40, increasing with age, to 8 to 12% in patients aged 70.[1] About 10–30% of people with PAD experience intermittent claudication[3,4] The prevalence of critical limb ischemia in patients older than 60 is 0.4%.[4–6]

Selecting the best treatment modality for patients with symptomatic PAD is determined by patient factors such as age, severity of disease and comorbidities, as well as lesion characteristics, such as location, lesion length and calcification.[7] Bypass surgery and endarterectomy provide excellent long-term patency. However, in the frail and aging vascular patients, endovascular treatment gains popularity because of its minimally invasive character, with increasing durability.[8,9] Improved outcomes after endovascular treatment of PAD are the result of technical innovations as well as optimized treatment strategies. This thesis aims to provide insight in these recent treatment strategies and the use of new devices. What are these improvements? How do they work? How to they compare to established treatment? Is their improvement only angiographic or do they improve clinical outcomes? While treatments and outcomes of importance differ between the different vascular territories, this thesis is divided in different parts.

## Part I. Stent placement in endovascular treatment of iliac artery occlusive disease

In part I the endovascular treatment of iliac artery occlusive disease is discussed. Open surgical procedures provide durable results, with high long-term patency rates, however with increased morbidity (such as cardiac arrest during procedure, hematoma, posthemorhagic anemia, infection) and mortality rates.[10,11] Endovascular treatment has good safety and short-term efficacy with decreased morbidity, complications and costs compared with open surgical procedures. Chapter 2 is a systematic review comparing the endovascular treatments of percutaneous transluminal angioplasty (PTA) with bail out stenting versus primary stenting in the iliac arteries.[12] Chapter 3 provides an overview of endovascular treatment options of aortoiliac occlusive disease.[13]

## Part II. Endovascular treatment of femoropopliteal artery occlusive disease

In Part II the endovascular treatment of the femoropopliteal arteries is discussed, especially the use of drug-eluting balloons (DEB). Similar as in aorto-iliac occlusive disease, endovascular treatment of femoropopliteal arteries has gained popularity due to decreased morbidity and mortality rates compared to bypass surgery, with good short term outcomes.

However, the major limitation of endovascular treatment is durability. The 1 year patency rate of uncoated balloon angioplasty (UCB) ranges between 40-60%.[7,14,15] These rates can be improved up to 70-90% with the use of a bare-metal stent.[16–19] However, intra-arterial stenting has its limitations, as stent thrombosis can occur, as well as flow pattern disruptions, which may result in stent fracture or in-stent restenosis.[20,21] Therefore there is a tendency to move away from stent based treatment.

Drug-eluting balloons (DEBs) were introduced to provide homogeneous transfer of the antiproliferative drug Paclitaxel to the arterial wall. Paclitaxel is a higly lipohilic broad-spectrum anti-mitotic agent, this combination allow rapid infiltration of tissues and reduces neointimal hyperplasia.[22,23]Paclitaxel is transferred to the vessel wall with the use of an excipient and various DEBs are available with different Paclitaxel dosages and excipients. Dosage as well as excipient used influence outcomes.

In the past decade DEBs have been evaluated in various randomized controlled trials. Chapter 4 is a systematic review with meta-analysis comparing DEBs with UCBs in patients with femoropopliteal arterial disease.[24] Chapter 5 consists of a retrospective analysis of a prospectively kept database and describes a series of 100 patients with femoropopliteal arterial disease treated with the Passeo-18 Lux DEB (Biotronik AG, Bulach, Switzerland).

The optimal endovascular treatment for femoropopliteal arterial occlusive disease has yet to be assessed. The arsenal of devices ranges from UCBs and DEBs to treatment with various types of stents (either bare-metal stents (BMS), drug-eluting stents (DES) or covered stents). The outcomes of femoropopliteal DEB RCTs and DES RCTs are largely comparable.[16,25] If the results after DEB and DES are indeed comparable, DEB angioplasty might be the preferred therapy as is restricts the limitations of the use of stents. However, up to now, no RCT has been published comparing these two devices. The FOREST trial aims to provide an answer to the abovementioned hypothesis. Two hundred and fifty-four patients with femoropopliteal arterial occlusive disease will be randomized to either treatment with a DEB with provisional stenting and primary DES placement. Chapter 6 is the study protocol for this multicenter RCT.

## Part III. Endovascular treatment of autologous bypass grafts

In complex infrainguinal vascular disease (TASC C & D lesions), bypass grafting remains the gold standard.[7] Autologous grafts show excellent long-term patency rates (up to 80% after 5 years).[26,27] One third of the patients treated with an autologous infrainguinal bypass will develop a significant stenosis in the graft.[28,29] Significant stenosis may lead to bypass occlusion, which is associated with poor outcomes. Therefore, bypass surveillance using duplex ultrasound imaging is widely accepted,[30,31] as well as treatment of an autologous bypass at risk for occlusion.

Part III is divided in two chapters. Chapter 7 contains the outcomes from a retrospective data cohort, reporting endovascular treatment of significant stenoses in infrainguinal autologous bypasses at risk with UCB angioplasty.[32] In Chapter 8 a comparison is made on the endovascular treatment of significant stenoses in autologous bypass grafts with UCB angioplasty versus DEB angioplasty.[33]

## Part IV. Angiosome concept theory

Critical limb ischemia (CLI) is the most advanced stage of PAD. The prognosis is poor, with amputation rates up to 30%, and mortality up to 25% after 1 year.[7,34] Treatment of patients with CLI is aimed at wound healing, improvement in quality of life, limb salvage and prolonged survival.[35] Patients often have multilevel and multivessel disease. When attempting infrapopliteal revascularization, current strategies propose open or endovascular revascularization of arteries with runoff through the ankle, but not specifically targeted to the location of the ischemia.[36–38]

Nearly thirty years ago, Taylor and Palmer introduced the angiosome concept to provide a basis for planning of incisions and flaps in reconstructive surgery.[39] An angiosome is a three dimensional unit of tissue fed by a source artery. In the foot and ankle six angiosomes have been identified. Revascularization of the feeding artery of an affected angiosome is called direct revascularization (DR) and is expected to improve outcomes such as wound healing and limb salvage compared to revascularization of an artery feeding an adjacent angiosome (indirect revascularization, IR). Part IV (chapter 9) is a systematic review with meta-analysis comparing angiosome directed revascularization with indirect revascularization in patients with CLI.[40]

## REFERENCES


1. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. Lancet. 2013;382(9901):1329–40.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2016 update a report from the American Heart Association. Vol. 133, Circulation. 2016. 38-48 .
3. Dormandy J, Heeck L, Vig S. The natural history of claudication: risk to life and limb. Semin Vasc Surg. 1999;12(2):123–37.
4. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. J Vasc Surg. 2007;45(6):1185–91.
5. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. J Am Med Assoc. 2001;286(11):1317–24.
6. Stoffers HEJH, Rinkens PELM, Kester ADM, Kaiser V, André Knottnerus J. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. Int J Epidemiol. 1996;25(2):282–90.
7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-Society Consensus for the management of peripheral arterial disease (TASC II). Int Angiol. 2007;26(2):82–157.
8. Jens S, Conijn AP, Frans FA, Nieuwenhuis MBB, Met R, Koelemay MJW, et al. Outcomes of Infrainguinal Revascularizations with Endovascular First Strategy in Critical Limb Ischemia. Cardiovasc Intervent Radiol. 2014;552–9.
9. Bradbury AW, Adam DJ, Beard JD, Cleveland T, Forbes JF, Fowkes FGRR, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): Multicentre, randomised controlled trial. Lancet. 2005;366(9501):1925–34.
10. Timaran CH, Prault TL, Stevens SL, Freeman MB, Goldman MH. Iliac artery stenting versus surgical reconstruction for TASC (TransAtlantic Inter-Society Consensus) type B and type C iliac lesions. J Vasc Surg. 2003;38(2):272–8.
11. Kashyap VS, Pavkov ML, Bena JF, Sarac TP, O'Hara PJ, Lyden SP, et al. The management of severe aortoiliac occlusive disease: Endovascular therapy rivals open reconstruction. J Vasc Surg. 2008;48(6).
12. Bekken J, Jongsma H, Ayez N, Hoogewerf J, Van Vincent W, Fioole B. Angioplasty versus stenting for iliac artery lesions. Cochrane database Syst Rev. 2015;5(5).
13. Bekken JA, Jongsma H, de vries JPPM, Fioole B. Self-expanding stents and aortoiliac occlusive disease: A review of the literature. Med Devices Evid Res. 2014;7(1):99–105.
14. Johnston KW. Femoral and popliteal arteries: Reanalysis of results of balloon angioplasty. Radiology. 1992;183(3):767–71.
15. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv. 2007;69(6):910–9.
16. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol. 2013 Jun;61(24):2417–27.

17. Dick P, Wallner H, Sabeti S, Loewe C, Mlekusch W, Lammer J, et al. Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. Catheter Cardiovasc Interv. 2009;74(7):1090–5.
18. Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: Twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010 Jun;3(3):267–76.
19. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006;354(18):1879–88.
20. Scheinert D, Scheinert S, Sax J, Piorkowski C, Bräunlich S, Ulrich M, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol. 2005;45(2):312–5.
21. Tortoriello A, Pedrizzetti G. Flow-tissue interaction with compliance mismatch in a model stented artery. J Biomech. 2004;37(1):1–11.
22. Finn A V., Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, et al. Vascular responses to drug eluting stents: Importance of delayed healing. Arterioscler Thromb Vasc Biol. 2007;27(7):1500–10.
23. Ng VG, Mena C, Pietras C, Lansky AJ. Local delivery of paclitaxel in the treatment of peripheral arterial disease. Eur J Clin Invest. 2015;45(3):333–45.
24. Jongsma H, Bekken JA, Vries JPM De, Verhagen HJ, Fioole B. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty in patients with femoropopliteal arterial occlusive disease. J Vasc Surg. 2016;64(July):1–23.
25. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. J Am Coll Cardiol. 2015;66(21):2329–38.
26. Londrey GL, Ramsey DE, Hodgson KJ, Barkmeier LD, Sumner DS. Infrapopliteal bypass for severe ischemia: Comparison of autogenous vein, composite, and prosthetic grafts. J Vasc Surg. 1991;13(5):631–6.
27. Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature. Eur J Vasc Endovasc Surg. 2004;27(4):357–62.
28. Mills JL, Wixon CL, James DC, Devine J, Westerband A, Hughes JD. The natural history of intermediate and critical vein graft stenosis: Recommendations for continued surveillance or repair. J Vasc Surg. 2001;33(2):273–80.
29. Wilson YG, Davies AH, Currie IC, Morgan M, McGrath C, Baird RN, et al. Vein graft stenosis: Incidence and intervention. Eur J Vasc Endovasc Surg. 1996;11(2):164–9.
30. Mofidi R, Kelman J, Berry O, Bennett S, Murie JA, Dawson ARW. Significance of the Early Postoperative Duplex Result in Infrainguinal Vein Bypass Surveillance. Eur J Vasc Endovasc Surg. 2007;34(3):327–32.
31. Golledge J, Beattie DK, Greenhaigh RM, Davies AH. Have the results of infrainguinal bypass improved with the widespread utilisation of postoperative surveillance? Eur J Vasc Endovasc Surg. 1996;11(4):388–92.
32. Jongsma H, Bekken JA, Van Buchem F, Bekkers WJJ, Azizi F, Fioole B. Secondary interventions in patients with autologous infrainguinal bypass grafts strongly improve patency rates. J Vasc Surg. 2016;63(2):385–90.

33. Jongsma H, Akkersdijk GP, de Smet AAEA, Vroegindeweij D, de Vries J-PPM, Fioole B. Drug-eluting balloons and uncoated balloons perform equally to rescue infrainguinal autologous bypasses at risk. J Vasc Surg. 2017;1–7.
34. Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: A supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II): The TASC steering commi. Catheter Cardiovasc Interv. 2015 Oct;86(4):611–25.
35. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic). Circulation. 2006;113(11):e463–5.
36. Bosanquet DC, Wright AM, White RD, Williams IM. A review of the surgical management of heel pressure ulcers in the 21st century. Int Wound J. 2016;13(1):9–16.
37. Frykberg RG. Diabetic foot ulcerations: Management and adjunctive therapy. Clin Podiatr Med Surg. 2003;20(4):709–28.
38. Romiti M, Albers M, Brochado-Neto FC, Durazzo AES, Pereira CAB, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg. 2008;47(5):20–2.
39. Taylor GI, Pan WR. Angiosomes of the leg: anatomic study and clinical implications. Plast Reconstr Surg. 1998;102(3):598–9.
40. Jongsma H, Bekken JA, Akkersdijk GP, Hoeks SE, Verhagen HJ, Fioole B. Angiosome-directed revascularization in patients with critical limb ischemia. J Vasc Surg. 2017;65(4):1208–1219.e1.