Experimental therapeutic strategies in restenosis and critical limb ischemia

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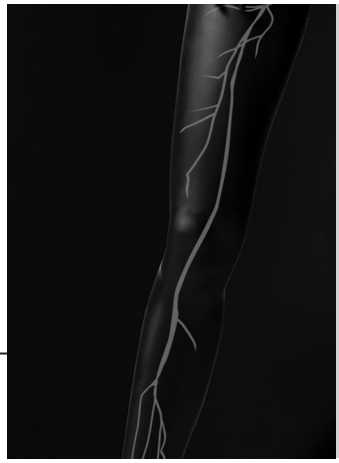


Chapter 01

General introduction

General introduction and outlines.

Peripheral arterial occlusive disease (PAOD) is a highly prevalent, age-related atherosclerotic phenomenon that affects 3% to 5% of the population. Several epidemiologic studies show that its incidence increases to 15% to 20% in persons over 70 years.[1,2] The most widely used examination to indicate the presence or absence of PAOD is the ankle-brachial pressure index (ABI) measurement. PAOD is therefore generally defined as a resting ABI value ≤0.90. PAOD may cause symptoms like intermittent claudication or critical limb ischemia however numerous patients with PAOD do not have symptoms. Using the criterion of ABI less than 0.90 for the presence of PAOD, the ratio between symptomatic and asymptomatic patients is in the range of 1:3 to 1:4.[3]

In case of symptoms, most patients suffer from intermittent claudication i.e. muscular leg pain on exercise that is relieved by a short period of rest. Although it is difficult to predict the risk of clinical deterioration of PAOD, approximately 5% to 10% of the patients with claudication will develop critical limb ischemia (CLI), defined as ischemic rest pain or tissue loss, over a 5-year period.[4] The large-scale longitudinal Framingham studies show that claudication results in less than 2% of the patients in a major amputation, i.e. above the level of the ankle.[5]

In symptomatic patients, revascularisation is considered in case of -severely- disabling intermittent claudication. The indication for intervention in CLI is regarded as more strict as if vascular reconstruction is not possible or attempts at reconstruction fails, about 30-40% suffers from limb loss within one year.[3,6] The classic armamentarium of the vascular interventionalist includes catheter intervention like angioplasty, and open reconstructions such as endarterectomy or bypass surgery. One of the major problems of both endarterectomy and bypass surgery is the complication of restenosis. Restenosis reduces the clinical effectiveness of these treatments and may even result in worsening of the clinical condition.

Problem of restenosis after intervention for PAOD

Angioplasty was introduced by Dotter and Judkins, using coaxial catheters to enlarge the obstructed lumen of an artery occluded by atherosclerotic disease.[7] Later, this technique was improved by introducing dilatating balloon catheters.[8] Percutaneous transluminal angioplasty (PTA) has been an evolving and highly valuable tool with a widespread use in the treatment of vascular obstructive disease ever since. Further technological advances resulted in continuously improved clinical results in the past decade. Along with patient preference related to the relatively non-invasiveness of these procedures, revascularisation strategies have shifted from first open surgical approaches towards first percutaneous endovascular treatments if feasible in e.g. the coronary, renal, iliac, and femoral arteries. In cardiothoracic surgery the result can be seen as over 9000 coronary artery bypass graft (CABG) operations were performed in the Netherlands in 2007. At

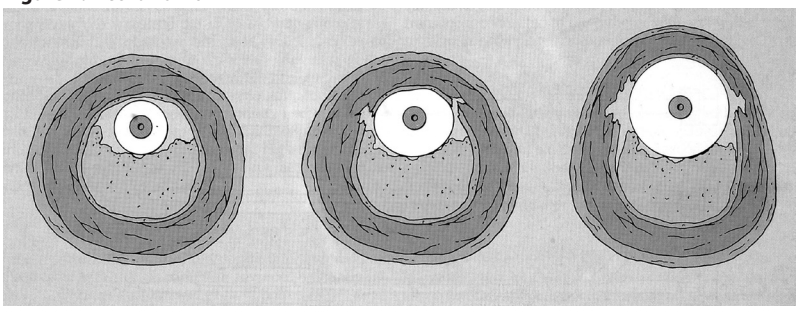
the same time more than the threefold PTCA interventions were carried out. [9] In general, results obtained with reconstructive surgery are superior as compared with those obtained after PTA however PTA is much less invasive as compared with reconstructive surgery. For example, randomised trials indicate that risk of death or heart attack following either treatment is alike, however patients undergoing bypass surgery are less likely to need re-intervention.[10-12]

In the treatment of peripheral vascular disease there also has been a shift towards an endovascular approach. Generally, open surgical reconstructions appear to have better long-term patency and clinical durability. On the other hand, this comes at the expense of higher procedural mortality and morbidity, longer hospital stay and higher costs. Therefore, both the patient's general condition and the extent of the obstructed arteries are essential in weighing the benefits and risks of PTA and reconstructive surgery. In general, these considerations apply for obstructions of visceral and renal[13], aorto-iliac[14,15] as well as infrainguinal[16,17] interventions for revascularisation.

As indicated, the long-term patency and efficacy is a major limitation of many catheter-based interventions. This is dependent on several factors among these are the length and type of obstruction as well as the arterie(s) involved. The long term patency is reduced by a phenomenon of re-narrowing of arteries which is called restenosis. This process of restenosis is complex and not fully understood. Current evidence suggests that it is a maladaptive 'response to injury'.[18] When the balloon is inflated, the lumen is forcibly dilatated and a part of the vessel wall that is relatively unaffected by the disease is expanded. As a result, cracks and tears develop in the atherosclerotic plaque, but particularly in the remaining part of the arterial wall. As a rule, the plaque becomes dissected from the arterial wall.

It is currently understood that there are three components that influence the mechanism of restenosis after PTA. First is the direct effect of early lumen loss due to elastic recoil. Thereafter intimal hyperplasia and subsequent constrictive arterial remodeling, being the two most important factors of luminal narrowing after percutaneous transluminal angioplasty.[19,20]

Figure 1. *Mechanism of PTA*



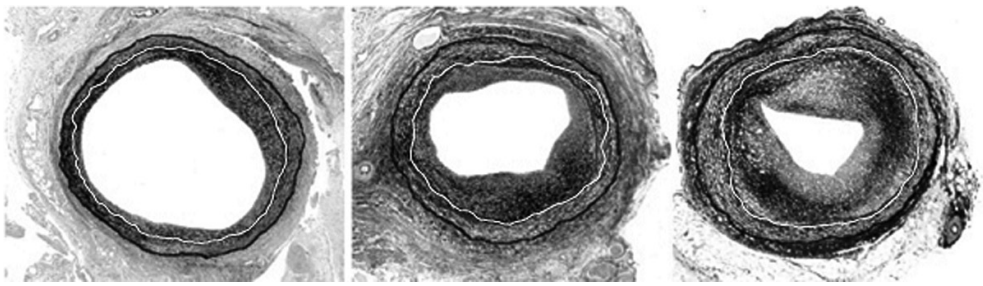
(a) positioning of the balloon catheter within the eccentrically occluded lumen. (b) Balloon inflation stretches the relatively normal portion of the arterial wall, not the inelastic plaque. (c) Asymmetrical stretching produces enlargement of the lumen and, as a rule, dissection of the arterial wall. (Adapted from Atlas of Interventional Radiology, Gowe Medical Publishing, 1990, NY)

Elastic recoil is a dynamic process that occurs directly after angioplasty and results in a prompt loss of lumen diameter. After coronary balloon dilatation, an acute recoil response can be responsible for some 30% immediate loss of the vessel lumen at the end of the procedure. [21] Elastic recoil might account for up to 50% of this acute lumen loss after angioplasty.[22] The other cause for early loss is flow-obstructing dissection of the vessel wall. Generally, dissection is an inevitable and usually essential element of angioplasty (Figure 1). However, extensive intimal dissection may result in significant obstruction or even occlusion of the artery. Stent implantation can reduce elastic recoil as well as redress dissections which are an inevitably effect of PTA.

Specific data on elastic recoil in peripheral arteries are limited. Residual stenosis (>30%) occurs in approximately 10% of the cases after PTA of the superficial femoral artery.[23,24] In the Dutch Iliac Stent Trial, primary stenting versus stent placement on demand (residual mean pressure gradient > 10 mmHg) was compared in patients with significant iliac lesions. In the group of selective stent placement, 65 of 169 (38%) lesions had to be treated with stent placement because of elastic recoil and/or dissection.[25]

The second component of restenosis after PTA is **intimal proliferation** resulting in new tissue growth covering the cracks and tears in the vessel wall and sometimes growing to produce severe reobstruction of the artery. Instantly after balloon dilatation, disruption of the atherosclerotic vessel wall in conjunction with a virtually complete denudation of the endothelial layer, exposes thrombogenic factors to the flowing blood, triggering platelet adhesion, activation, and thrombosis. Endothelial denudation also results in the loss of antithrombotic factors (e.g., nitric oxide, prostacyclin, and tissue plasminogen activator), further contributing to thrombus formation. In addition, forceful stretching by the balloon also causes disruption of the inner and outer lamina elastica in the tunica media.[18,26]

Figure 2. *Varying extent of neointima formation after angioplasty. The white and black lines represent the inner and outer lamina elastica.*



This early phase sets stage for regeneration consisting of proliferation of the remaining endothelium and smooth muscle cells (SMC). Additionally, smooth muscle cells and

myofibroblasts start to migrate from the media (and adventitia) towards the intima and are responsible for an increased amount of extracellular matrix synthesis. Simultaneously, the phenotype of local smooth muscle cells changes from contractile to synthetic. An enhanced proliferation rate results in an increase of 'neointima' volume (intimal hyperplasia) and in a gradually reduced luminal size.[18,27] This process starts within days after angioplasty and continues for weeks or months. SMC accumulation, inflammatory cell recruitment, and endothelial restoration are critical parts in vascular repair and it is widely appreciated that chemokines and growth factors regulate and control each step of the process.[28] These multiple chemokines act in a very complex network that is still largely to be elucidated. A more detailed description is given in chapter 5.

The third mechanism for restenosis that has been elucidated more recently is **arterial remodeling**. In 1972 Mann et al. were the first to report arterial size changes associated with atherosclerosis.[29] African Masai maintained large coronary artery lumina despite substantial atherosclerotic plaque size. With age, the coronary arteries develop thicker atherosclerotic plaques, but their coronary arteries also enlarged to accommodate the obstructing atherosclerotic plaque. The net result was an actual luminal enlargement. Regardless of equivalent plaque size, the Masai maintained larger lumina than their American counterparts. This compensatory enlargement of (coronary) arteries was further confirmed in autopsy studies.[30]

Vascular remodeling during atherosclerosis and restenosis following vascular injury however may differ. Not only outward (positive) remodeling, but also constrictive (negative) remodeling is observed in atherosclerosis and in restenosis. As a result, the entire artery may become contracted. The mechanisms of the both remodeling modes are largely unknown however hemodynamic stimuli like flow and circumferential stress seem to induce arterial remodeling to maintain a balanced level of shear stress and wall tension, respectively.[31] This is important since these local hemodynamic factors, and endothelial shear stress (ESS) in particular, play a major role in the regional localization of atherosclerosis. ESS is caused by the friction of flowing blood on the endothelial surface. Low ESS modulates endothelial gene expression through complex processes, inducing the formation of an early atherosclerotic plaque.[20,31]

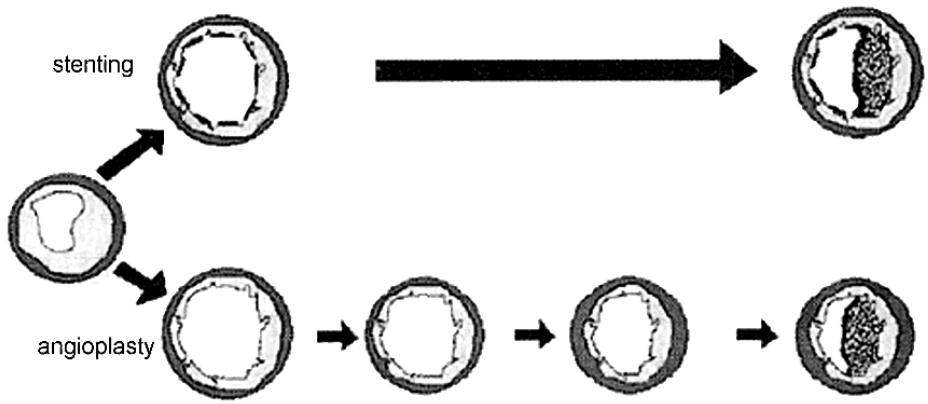
In a study conducted by Mintz and colleagues, serial intravascular ultrasound imaging was used to study constrictive remodeling in a series of 209 patients undergoing simple angioplasty. In this study, lumen loss was largely attributable constrictive vessel-wall remodeling rather than neointimal thickening.[32] Other data from directional atherectomy samples and post-mortem histology suggest a larger contribution to restenosis from intimal hyperplasia.[33,34]

Intimal hyperplasia resulting in restenosis contributes to failure to maintain patency after intervention. In reconstructive surgery, early thrombosis, occurring after days to weeks, is mostly due to technical problems. Intermediate (6-24 months) and late (>2 years) failure however is primarily caused by intimal hyperplasia and accelerated atherosclerosis, respectively.[36]

An other area for development of restenosis are arteriovenous (AV) fistulas constructed for hemodialysis. These are a clinical entity being studied in this thesis where the problem of (re)stenosis is obvious; in fact, it serves as a model for developing and treating intimal hyperplasia. An increasing and significant number of patients with end-stage renal disease require chronic hemodialysis. With an estimated incidence of 150–200 individuals per million in the western population, maintenance of vascular access is crucial in the care of these patients. Although an autologous radiocephalic fistula is the method of first choice, polytetrafluoroethylene (PTFE) grafts are frequently used due to failure or the inability to create an autologous fistula. In the United States over 70% of the accesses placed in the were prosthetic grafts.[37] In The Netherlands, prosthetic grafts, mostly PTFE grafts, account for approximately 30% of the access placements.[38] The patency rates for PTFE grafts are inferior to those of autologous fistulas, mainly because of the development of stenosis due to intimal hyperplasia. Such a stenosis preferably develops at the venous anastomotic site, or close by in the efferent vein.[39,40,41]

It is believed that the high blood flow velocity in AV-fistulas generates excessively high shear stress and turbulence causing damage to endothelial cells. The intimal proliferation that subsequently occurs is analogous to process outlined above. There is no consensus regarding the contribution to intimal hyperplasia of a compliance mismatch between PTFE grafts and the vein. Although numerous studies have found that compliance mismatch increases intimal hyperplasia in peripheral bypass surgery, it may have a less important role in high-flow systems such as AV-fistulas.[42]

Figure 3. *Mechanisms responsible for restenosis after balloon angioplasty.(adapted from Am J Med.[35])*



Phenomenon	**elastic recoil**	**negative remodeling**	**neointima formation**
Pathophysiology	passive recoil of elastic media-	increased collagen in extra-cellular matrix and adventitial thickening	proliferation and migration SMC's and extracellular matrix formation
Time course	within one hour	one to six months	one to six months

Attempts to control restenosis after angioplasty

Pharmaceutical:

Many strategies have been designed to influence the processes involved in restenosis after angioplasty. The first agents that were tested were anticoagulants and antiplatelet agents. Studies were carried out comparing coumarin derivates to aspirin,[43] and heparin administration of various duration.[44] Additionally, the effect of antiplatelet agents including aspirin and persantine,[45] plus antispasmodics such as nifedipine[46] and diltiazem[47] were assessed as well as agents felt to be important in the atherosclerotic process such as lipid-lowering medication including lovastatin[48] and omega-3 fatty acids (fish oil).[49] Most studies were single center trials and in the early 1990s several trials were initiated using agents that had been found to inhibit intimal proliferation in animal models. Although powerful effects in some animal models were observed, results in the human trials were universally disappointing. The anti-inflammatory component of restenosis has been clinically studied with the use of steroids[50,51] and antioxidants[52] with varying results. In spite of some encouraging outcomes, no drug has yet been identified or generally recommended for the uniform prevention of restenosis after angioplasty.

Debulking strategies:

Treatment modalities such as atherectomy catheters are designed to remove a large bulk of atherosclerotic plaque, thereby creating a larger lumen with the expectation that the patency could be improved. In the mid 90's this strategy was evaluated in controlled clinical trials as compared to balloon angioplasty. Various generations of atherectomy catheters continued to fail in demonstrating substantial benefit over the less-expensive PTA alone.[53-55] Since no evident antirestenosis effect was found in large-scale cardiac trials as well,[56-58] there is currently no convincing evidence that directional or laser atherectomy has significant benefit over standard angioplasty.

Cryoplasty:

Cryoplasty proposes a new approach by combining balloon angioplasty with the delivery of cold thermal energy to the vessel wall. Hereby, it is hypothesized that apoptosis rather than necrosis is induced in the arterial smooth muscle cells. Thus is has the theoretical advantage of increasing long-term patency by inhibiting the biological processes involved in intimal hyperplasia. Large series form registries have demonstrated by duplex ultrasound a high restenosis rate of 30% at 9 months.[59] Cryoplasty devices, however, have not been studied in any comparative manner despite its commercial availability for several years. Because the claims to efficacy are not supported by controlled studies, it remains difficult to justify the technique and its significant associated costs.

Stenting:

Endovascular stents can mechanically prevent elastic recoil and flow-limiting dissection

after PTA. However, numerous studies found increased intimal hyperplasia that frequently result to in-stent restenosis, and randomised trials failed to demonstrate any benefit of stenting the iliac or femoral artery over angioplasty alone.[60,61] Therefore, as in the iliac segment, it is recommended that stents should be reserved for use in patients with suboptimal results of balloon angioplasty including complications like dissections. Recently however a randomised controlled trial demonstrated a better outcome for primary SFA stent placement than a strategy of provisional stent placement. Restenosis was not only significantly lower in the stent group at 6 and 12 months, but there was also better functional improvement and walking distance in the primary stent group.[62] As an explanation for their positive results, the authors hypothesize that the use of a nitinol (nickel-titanium) stent might be superior to the commonly used stainless-steel stents.

The most recent development in this field are drug-eluting stents. Although successful after coronary PTA, the use of drug-eluting stents in peripheral arteries should still be considered experimental. Early trials have not shown a significant difference in comparison with bare metal stents.[63]

In the cardiology field the initial enthusiasm is somewhat tempered since late clinical events related to stent thrombosis due to delayed arterial healing may limit the benefit of drug-eluting stents.[64]

Attempts to control stenosis in PTFE dialysis fistulas

Pharmaceutical:

There are few clinical trials available using agents to study a specific inhibiting effect on intimal hyperplasia in AV-fistulas for hemodialysis. Thoughts on medicament preventive strategies have been adopted from the cardiology field. A number of approaches were used to limit the incidence of vascular access thrombosis with anticoagulants and antiplatelet agents. A meta-analysis performed by the Cochrane Collaboration confirmed the beneficial effect of anti-platelet treatment as an adjuvant used to increase the patency of AV fistulas and grafts in the short term.[65]

One trial compared fish oil versus placebo with 24 participants during a 12 months follow-up. The overall result favored treatment (OR 0.07, 95% CI 0.01 to 0.49), despite the small number of patients.[66] Bowden and colleagues on the other hand, could not demonstrate a significant improvement in primary patency rates between the experimental fish-oil and control groups in their study.[67] Currently, a larger sized multicenter trial is ongoing that randomizes over 230 patients who require a new graft access.[68]

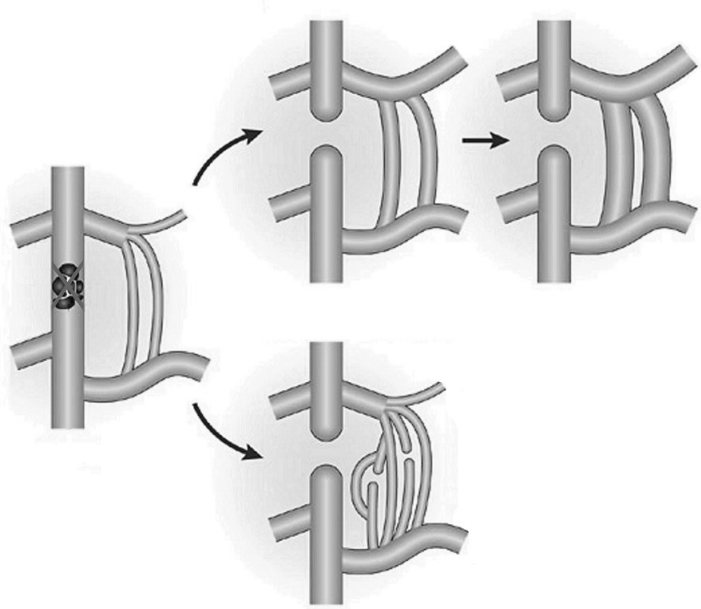
Results of a study in which vascular endothelial growth factor D (VEGF-D) gene in an adenoviral vector was delivered locally to the adventitial surface of a graft-vein anastomosis by means of a collagen collar device, were never published for unclear reasons. The proposed effect was the prevention of intimal hyperplasia at the distal anastomosis of the AV-fistula.[69]

Technical strategies:
In efforts to improve clinical outcome of PTFE dialysis fistulas, several geometrical anastomotic modifications were evaluated aiming at reducing intimal hyperplasia by reducing shear stress at the anastomotic site: (1) a vein cuff at the ePTFE-venous anastomosis, and (2) cuffed ePTFE hemodialysis grafts. While successful in lower extremity bypass grafting (vein cuff)[70], the application these techniques at the distal anastomosis have been inconsistent in improving the clinical outcome of hemodialysis access.[71-73]

The second part of this thesis covers improving the peripheral circulation in patients with PAOD if intervention like percutaneous transluminal angioplasty or surgical reconstruction are not feasible. Currently, an alternative may become the stimulation of vascular growth by means of bone marrow-derived cell therapy ('*stem cell therapy*'). Peripheral therapeutic angiogenesis covers an emerging field of vascular regenerative medicine whereby new blood vessel growth is induced in order to supply oxygen and nutrients to the ischemic limb. Stem cells are characterized by two special qualities, i.e. their ability to differentiate into mature stages of various tissue cell types, and their potential of regenerating themselves "indefinitely" without losing their differentiation potential. Human stem cells are typed as embryonic or adult. Human adult stem cells have been identified in bone marrow, skeletal muscle, cornea and in various other organs as the heart, liver and brain.[74] As indicated in the first section, in the majority of patients symptoms of PAOD are mild or even absent. This can be explained by adequate functioning of a natural compensatory mechanism restoring distal blood flow if the occlusion is chronic / slowly progressing: collateral artery formation. Development of collateral formation is not entirely understood however it is now hypothesized that increased shear stress and overstretching of pre-existing interconnecting arterioles lead to endothelial cell activation and up-regulation of adhesion molecules.[75,76] Mononuclear cells adhere to the activated vascular wall, transmigrate into peri-vascular space and become activated. This process is further amplified by an ongoing cycle through release of proinflammatory cytokines from activated monocytes and macrophages. Under the influence of a multitude of released growth factors, cytokines and possibly also bone marrow-derived stem cells, arterioles increase in diameter by the process of outward remodeling. This ultimately results in formation of significant collateral vessels. Compared to its original size, the diameter increases approximately 40-fold however large individual variations have been noted.[77] Development of such natural bypass vessels is certainly insufficient in patients with PAOD who progress to critical limb ischemia. Advances in the field of vascular biology have led to the concept of stimulation of collateral formation (arteriogenesis) in situations in which revascularisation procedures have failed or were not possible. In an attempt to induce collateral formation, mononuclear cells and/or stem cells were to be auto-transplanted from the bone marrow into the limb. This hypothesis was confirmed in several animal models of limb ischemia,[78,79] and was clinically studied in clinical phase I-II studies. A

more detailed introduction to the mechanisms of vascular growth in ischemic limbs is, as known to date, is given in chapter 5. The principles of angiogenesis, vasculogenesis and arteriogenesis are discussed and the possible role of gene therapy, angiogenesis growth factors and cell-based therapy as a therapeutic stimulation strategy is summarised.

Figure 4. *Suggested working mechanisms of stem cell therapy: enlargement of pre-existing collateral arteries and/or true newly formed vessels.*



Outline of the research

This thesis is based on clinical research. The studies presented in the first part concentrate on the role of radiation therapy to reduce or to prevent (re)stenosis after percutaneous transluminal angioplasty and arteriovenous fistulas.

Chapter 2 reviews the concept of radiotherapy for inhibiting intimal hyperplasia and arterial remodeling in vascular surgery. The role of radiation biology, external beam radiation versus endovascular radiation and beta versus gamma radiation are discussed. Further, a concise overview of randomised clinical trials on peripheral vascular radiation therapy is presented. In **chapter 3** a multicenter study is reported in which the efficacy of endovascular brachytherapy (EBT) for prophylaxis of restenosis after femoropopliteal percutaneous transluminal angioplasty is evaluated. **Chapter 4** presents a randomised trial which was designed to assess the presumed preventive effect of external beam radiation therapy on anastomotic intimal hyperplasia in prosthetic arteriovenous fistulas constructed to obtain access for chronic hemodialysis in patients with renal failure.

The second part of this thesis focuses on the experimental therapeutic strategy of cell therapy in patients with severe limb ischemia who are without regular surgical or endovascular treatment options. **Chapter 5** addresses the molecular and cellular mechanisms of vascular growth in ischemic limbs. Basic conceptions of angiogenesis, vasculogenesis and arteriogenesis are considered and experimental therapeutic strategies as gene therapy, angiogenetic growth factors and cell-based therapy are outlined.

Chapter 6 describes a clinical study that evaluated feasibility and safety as well as efficacy of autologous cell-therapy in patients with severe peripheral arterial disease who were not candidates for surgical or endovascular treatment. For this purpose, bone marrow aspirated from the iliac crest, was filtered and concentrated at the stem cell laboratory of the Leiden University Medical Center and subsequently intramuscularly or combined intramuscular/intra-arterially re-administered to the patients. The angiographic results of this study and hypotheses on the clinical usefulness of digital subtraction angiography in the assessment of the effects on possible inducement of collateral circulation after cell-based therapy are separately considered in **chapter 7**.

Since angiography may not be a reliable assessment to identify improved collateral circulation while the "gold standard" functional test (ankle pressure) is often not reliable in patients with diabetes mellitus we study a new non-invasive test in **chapter 8**. Doppler derived maximal systolic acceleration is a parameter adopted from renal assessment with duplex and might be a useful tool in screening the lower limb for peripheral arterial disease in those patients where the ankle pressures are not reliable. Finally, **chapter 9** summarizes the results and conclusions of the studies presented in this thesis and discusses on the current and future clinical status of vascular radiotherapy and stem cell therapy for peripheral arterial disease.

References

1. Criqui MH, Denenberg JO, Langer RD, Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. Vasc Med 1997;2:221-226.
2. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. Arterioscler Thromb Vasc Biol 1998;18:185-192.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, Bell K, Caporusso J, Durand-Zaleski I, Komori K, Lammer J, Liapis C, Novo S, Razavi M, Robbs J, Schaper N, Shigematsu H, Sapoval M, White C, White J; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASCII). Eur J Vasc Endovasc Surg 2007;33 Suppl 1:S1-75.
4. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr., White CJ, White J, White RA, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463-e654.
5. Kannel WB, Skinner JJ Jr, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. Circulation. 1970;41:875-883.
6. Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, Keagy BA. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg. 2006;44:108-114.
7. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction: Description of a new technique and a preliminary report of its application. Circulation 1964;30:654-670.
8. Grüntzig A, Hopff H. Perkutane Rekanalisation chronischer arterieller Verschlusse mit einem neuen Dilatationskatheter: Modifikation der Dotter-Technik. Dtsch Med Wochenschr 1974;99:2502-2511.
9. Prismant. http://www.prismant.nl/Informatie-expertise/Thema's/Ziekenhuisstatistieken.
10. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schönberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA; Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease.New England Journal of Medicine 2001;344:1117-1124.
11. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention withstent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet. 2002;360:965-970.
12. Booth J, Clayton T, Pepper J, Nugara F, Flather M, Sigwart U, Stables RH; SoS Investigators. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation. 2008;118:381-388.
13. Bush RL, Najibi S, MacDonald MJ, Lin PH, Chaikof EL, Martin LG, Lumsden AB. Endovascular revascularization of renal artery stenosis: technical and clinical results. J Vasc Surg. 2001;33:1041-1049.
14. Tetteroo E, van der Graaf Y, Bosch JL, van Engelen AD, Hunink MG, Eikelboom BC, Mali WP. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. Lancet. 1998 ;351:1153-1159.
15. Murphy TP, Ariaratnam NS, Carney WI Jr, Marcaccio EJ, Slaiby JM, Soares GM, Kim HM. Aortoiliac insufficiency: long-term experience with stent placement for treatment. Radiology. 2004;231:243-249.
16. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H; BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005;366:1925-34.
17. van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. Eur J Vasc Endovasc Surg. 2004 ;28:132-137.

18. Weintraub WS. The pathophysiology and burden of restenosis. Am J Cardiol. 2007;100:3K-9K.
19. Haruguchi H, Teraoka S. Intimal hyperplasia and hemodynamic factors in arterial bypass and arteriovenous grafts: a review. J Artif Organs 2003;6:227-235.
20. Pasterkamp G, de Kleijn DP, Borst C. Arterial remodeling in atherosclerosis, restenosis and after alteration of blood flow: potential mechanisms and clinical implications. Cardiovasc Res. 2000;45(4):843-852.
21. Beyar R. Novel approaches to reduce restenosis. Ann N Y Acad Sci. 2004;1015:367-378.
22. Rodriguez AE, Palacios IF, Fernandez MA, Larribau M, Giraudo M, Ambrose JA. Time course and mechanism of early luminal diameter loss after percutaneous transluminal coronary angioplasty. Am J Cardiol 1995;76:1131–1134.
23. Mousa A, Rhee JY, Trocciola SM, Dayal R, Beauford RB, Kumar N, Henderson P, McKinsey J, Morrissey NJ, Kent KC, Faries PL. Percutaneous endovascular treatment for chronic limb ischemia. Ann Vasc Surg. 2005;19:186-191.
24. Vroegindeweij D, Vos LD, Tielbeek AV, Buth J, vd Bosch HC. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: A comparative randomized study.Cardiovasc Intervent Radiol. 1997;20:420-425.
25. Tetteroo E, van der Graaf Y, Bosch JL, van Engelen AD, Hunink MG, Eikelboom BC, Mali WP. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. Lancet. 1998;351:1153-1159.
26. Davies MG, Hagen PO. Pathobiology of intimal hyperplasia. Br J Surg 1994;81:1254-1269.
27. Schwartz SM. Perspectives series: cell adhesion in vascular biology. Smooth muscle migration in atherosclerosis and restenosis. J Clin Invest 1997;99:2814-2816.
28. Schober A. Chemokines in vascular dysfunction and remodeling. Arterioscler Thromb Vasc Biol. 2008;28:1950-1959.
29. Mann GV, Spoerry A, Gray M, Jarashow D. Atherosclerosis in the Masai. Am J Epidemiol. 1972;95:26-37.
30. Zarins CK, Weisenberg E, Kolettis G, Stankunavicius R, Glagov S. Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. J Vasc Surg. 1988;7:386-394.
31. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379-2393.
32. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C, Hong MK, Kovach JA, Leon MB. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94:35-43.
33. Gravanis MB, Roubin GS. Histopathologic phenomena at the site of percutaneous transluminal coronary angioplasty: the problem of restenosis. Hum Pathol. 1989;20:477-485.
34. Johnson DE, Hinohara T, Selmon MR, Braden LJ, Simpson JB. Primary peripheral arterial stenoses and restenoses excised by transluminal atherectomy: a histopathologic study. J Am Coll Cardiol. 1990;15:419-425.
35. Rajagopal V, Rockson SG. Coronary restenosis: a review of mechanisms and management. Am J Med. 2003;115:547-553.
36. Davies MG, Hagen PO. Pathophysiology of vein graft failure: a review. Eur J Vasc Endovasc Surg. 1995;9:7-18.
37. Gibson KD, Gillen DL, Caps MT, Kohler TR, Sherrard DJ, Stehman-Breen CO. Vascular access survival and incidence of revisions: a comparison of prosthetic grafts, simple autogenous fistulas, and venous transposition fistulas from the United States Renal Data SystemDialysis Morbidity and Mortality Study. J Vasc Surg 2001;4:694–700.
38. Blankestijn PJ, Smits JH. How to identify the haemodialysis access at risk for thrombosis? Are flow measurements the answer? Nephrol Dial Transplant 1999;14:1068–1071.
39. Ezzahiri R, Lemson MS, Kitslaar PJ, Leunissen KM, Tordoir JH. Haemodialysis vascular access and fistula surveillance methods in The Netherlands. Nephrol Dial Transplant 1999;14:2110–2115. Cinat ME, Hopkins J, Wilson SE. A prospective evaluation of PTFE graft patency and surveillance techniques in hemodialysis access. Ann Vasc Surg 1999;13:191–198.
41. Haruguchi H, Teraoka S. Intimal hyperplasia and hemodynamic factors in arterial bypass and arteriovenous grafts: a review. J Artif Organs. 2003;6:227-235.
42. Hofstra L, Bergmans DC, Leunissen KM, Hoeks AP, Kitslaar PJ, Daemen MJ, Tordoir JH. Anastomotic intimal hyperplasia in prosthetic arteriovenous fistulas for hemodialysis is associated with initial high flow velocity and not with mismatch in elastic properties. J Am Soc Nephrol 1995;6:1625–1633.
43. Thornton MA, Gruentzig AR, Hollman J, King SB 3rd, Douglas JS. Coumadin and aspirin in prevention of

recurrence after transluminal coronary angioplasty: a randomized study.Circulation. 1984;69:721-727.
44. Ellis SG, Roubin GS, Wilentz J, Douglas JS Jr, King SB 3rd. Effect of 18- to 24-hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. Am Heart J. 1989;117:777-782.
45. Schwartz L, Bourassa MG, Lespérance J, Aldridge HE, Kazim F, Salvatori VA,Henderson M, Bonan R, David PR. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med. 1988;318:1714-1719.
46. Whitworth HB, Roubin GS, Hollman J, Meier B, Leimgruber PP, Douglas JS Jr, King SB 3rd, Gruentzig AR. Effect of nifedipine on recurrent stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol. 1986;8:1271-1276.
47. Corcos T, David PR, Val PG, Renkin J, Dangoisse V, Rapold HG, Bourassa MG. Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. Am Heart J. 1985;109:926-931.
48. Weintraub WS, Boccuzzi SJ, Klein JL, Kosinski AS, King SB 3rd, Ivanhoe R,Cedarholm JC, Stillabower ME, Talley JD, DeMaio SJ. Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group.N Engl J Med. 1994;331:1331-1337.
49. Reis GJ, Boucher TM, Sipperly ME, Silverman DI, McCabe CH, Baim DS, Sacks FM,Grossman W, Pasternak RC.Lancet. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. 1989;2:177-181.
50. Pepine CJ, Hirshfeld JW, Macdonald RG, Henderson MA, Bass TA, Goldberg S, Savage MP, Vetrovec G, Cowley M, Taussig AS. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. Circulation. 1990;81:1753-1761.
51. Kakio T, Matsumori A, Ohashi N, Yamada T, Saito T, Kawamoto A, Taguchi A, Morita Y, Takahashi M, Sasayama S. Hydrocortisone reduces restenosis after stenting of small coronary arteries. J Interv Cardiol. 2004;17:295-300.
52. Tardif JC, Côté G, Lespérance J, Bourassa M, Lambert J, Doucet S, Bilodeau L, Nattel S, de Guise P. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. N Engl J Med. 1997;337:365-372.
53. Tielbeek AV, Vroegindeweij D, Buth J, Landman GH. Comparison of balloon angioplasty and Simpson atherectomy for lesions in the femoropopliteal artery: angiographic and clinical results of a prospective randomized trial. J Vasc Interv Radiol. 1996;7:837–844.
54. Vroegindeweij D, Kemper FJ, Tielbeek AV, Buth J, Landman G. Recurrence of stenoses following balloon angioplasty and Simpson atherectomy of the femoropopliteal segment. A randomised comparative 1-year follow-up study using colour flow duplex. Eur J Vasc Surg. 1992 ;6:164-171.
55. Steinkamp HJ, Rademaker J, Wissgott C, Scheinert D, Werk M, Settmacher U, Felix R. Percutaneous transluminal laser angioplasty versus balloon dilation for treatment of popliteal artery occlusions. J Endovasc Ther. 2002;9:882-888.
56. Whitlow PL, Bass TA, Kipperman RM, Sharaf BL, Ho KK, Cutlip DE, Zhang Y, Kuntz RE, Williams DO, Lasorda DM, Moses JW, Cowley MJ, Eccleston DS, Horrigan MC, Bersin RM, Ramee SR, Feldman T. Results of the study to determine rotablator and transluminal angioplasty strategy(STRATAS). Am J Cardiol. 2001;87:699-705.
57. Dietz U, Rupprecht HJ, de Belder MA, Wijns W, Quarles van Ufford MA, Klues HG, vom Dahl J. Angiographic analysis of the angioplasty versus rotational atherectomy for the treatment of diffuse in-stent restenosis trial (ARTIST).Am J Cardiol. 2002;90:843-847.
58. Mauri L, Reisman M, Buchbinder M, Popma JJ, Sharma SK, Cutlip DE, Ho KK, Prpic R, Zimetbaum PJ, Kuntz RE. Comparison of rotational atherectomy with conventional balloon angioplasty in the prevention of restenosis of small coronary arteries: results of the Dilatation vs Ablation Revascularization Trial Targeting Restenosis (DART). Am Heart J. 2003;145:847-854.
59. Laird J, Jaff MR, Biamino G, McNamara T, Scheinert D, Zetterlund P, Moen E, Joye JD. Cryoplasty for the treatment of femoropopliteal arterial disease: results of a prospective, multicenter registry. J Vasc Interv Radiol. 2005;16:1067–1073.
60. Vroegindeweij D, Vos LD, Tielbeek AV, Buth J, van de Bosch HC. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: a comparative randomized study. Cardiovasc Intervent Radiol 1997;20:420-425.
61. Becquemin JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic versus selective stent placement after superficial femoral artery balloon angioplasty: a multicenter prospective randomized study. J Vasc Surg 2003;37:487-494.

62. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, Schlager O, Cejna M, Lammer J, Minar E. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006;354:1879–1888.
63. Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Oliva V, Tielbeek A, Anderson J, Wiesinger B, Tepe G, Lansky A, Jaff MR, Mudde C, Tielemans H, Beregi JP. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther 2006;13:701-710.
64. Pfisterer ME. Late stent thrombosis after drug-eluting stent implantation for acute myocardial infarction: a new red flag is raised. Circulation. 2008;118:1117-1119.
65. Osborn G, Escofet X, Da Silva A. Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts. Cochrane Database Syst Rev. 2008;4:CD002786.
66. Schmitz PG, McCloud LK, Reikes ST, Leonard CL, Gellens ME. Prophylaxis of hemodialysis graft thrombosis with fish oil: double-blind, randomized, prospective trial. J Am Soc Nephrol. 2002;13:184-190.
67. Bowden RG, Wilson RL, Gentile M, Ounpraseuth S, Moore P, Leutholtz BC. Effects of omega-3 fatty acid supplementation on vascular access thrombosis in polytetrafluorethylene grafts. J Ren Nutr. 2007;17:126-131.
68. Lok CE, Allon M, Donnelly S, Dorval M, Hemmelgarn B, Moist L, Oliver MJ, Tonelli M, Stanley K. Design of the fish oil inhibition of stenosis in hemodialysis grafts (FISH) study. Clin Trials. 2007;4:357-367.
69. Fuster V, Charlton P, Boyd A. Clinical protocol. A phase IIb, randomized, multicenter, double-blind study of the efficacy and safety of Trinam (EG004) in stenosis prevention at the graft-vein anastomosis site in dialysis patients. Hum Gene Ther. 2001;12:2025-2027.
70. Stonebridge PA, Prescott RJ, Ruckley CV. Randomized trial comparing infrainguinal polytetrafluoroethylene bypass grafting with and without vein interposition cuff at the distal anastomosis. The Joint Vascular Research Group. J Vasc Surg. 1997;26:543-550.
71. Gagne PJ, Martinez J, DeMassi R, Gregory R, Parent FN, Gayle R, Meier GH 3rd, Philput C. The effect of a venous anastomosis Tyrell vein collar on the primary patency of arteriovenous grafts in patients undergoing hemodialysis. J Vasc Surg. 2000;32:1149-1154.
72. Lemson MS, Tordoir JH, van Det RJ, Welten RJ, Burger H, Estourgie RJ, Stroecken HJ, Leunissen KM. Effects of a venous cuff at the venous anastomosis of polytetrafluoroethylene grafts for hemodialysis vascular access. J Vasc Surg. 2000;32:1155-63.
73. Lumsden AB, Weaver FA, Hood DB. Prospective multi-center evaluation of VENAFLO ePTFE as compared to Impra ePTFE vascular graft in hemodialysis applications. In: Vascular Access for Hemodialysis, 4th ed. Henry ML, editor. Chicago, Precept Press 1997: 242-249.
74. Brehm M, Zeus T, Strauer BE. Stem cells-clinical application and perspectives. Herz 2002;27:611-620.
75. Pipp F, Boehm S, Cai WJ, Adili F, Ziegler B, Karanovic G, Ritter R, Balzer J, Scheler C, Schaper W, Schmitz-Rixen T. Elevated fluid shear stress enhances postocclusive collateral artery growth and gene expression in the pig hind limb. Arterioscler Thromb Vasc Biol. 2004;24:1664-1668.
76. van Weel V, van Tongeren RB, van Hinsbergh VW, van Bockel JH, Quax PH. Vascular growth in ischemic limbs: a review of mechanisms and possible therapeutic stimulation. Ann Vasc Surg. 2008;22:582-597.
77. Buschmann IR, Schaper W. The pathophysiology of the collateral circulation (arteriogenesis). J Pathol 2000;190:338-342.
78. Takahashi T, Kalka C, Masuda H, Chen D, Silver M, Kearney M, Magner M, Isner JM, Asahara T. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nature Med 1999;5:434-438.
79. Shintani S, Murohara T, Ikeda H, Ueno T, Sasaki K, Duan J, Imaizumi T. Augmentation of postnatal neovascularization with autologous bone marrow transplantation. Circulation 2001;103:897-903.