HEINI SÖDER

Restenosis after Infracubinal Artery Balloon Angioplasty for Chronic Limb Ischemia

Angiographic and Clinical Studies

Doctoral dissertation

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ABSTRACT

BACKGROUND: Restenosis is a major problem impairing the long-term results of endovascular interventions. Despite numerous attempts to prevent restenosis the problem still persists. The main purpose of this study was to evaluate restenosis and to obtain a tool for its prevention after intrainguinal angioplasty.

MATERIALS AND METHODS: Intrainguinal angioplasty was performed on 425 patients, 257 (60%) were claudicants and 168 (40%) suffered from chronic critical limb ischemia (CCLI). The follow-up angiographies of 52 patients with clinically suspected recurrent disease were analysed. Femoropopliteal angioplasty was performed on 112 limbs of 97 patients using prolonged balloon inflation in 93 of the limbs. The primary success and long-term patency, along with their predictors were determined. Infraopopliteal angioplasty was performed on 72 limbs of 60 patients with CCLI and the primary clinical and angiographic success as well as the long-term clinical success, limb salvage, and angiographic patency were determined.

MAIN RESULTS: The recurrent disease was longer than the original stenosis [3.9± 3.9 cm (mean ±standard deviation) vs 2.8 ± 2.7 cm, p=0.03] and half of the restenoses (22 / 44) extended beyond one or both ends of the original stenosis. The recurrent disease was more likely to be a stenosis when the original lesion was a stenosis rather than when the original lesion was an occlusion [92% (44 / 48) vs 59% (16 / 27), p<0.001]. The rate of major specific local vascular complications of intrainguinal angioplasty was 2.3% (5 / 214). Prolonged balloon inflation improved the angiographic result in 95% (37 / 39) of the treated lesions. The primary patency rate of femoropopliteal artery angioplasty according to Kaplan-Meier analysis was 42% ± 5%, (± standard error of the estimate, SEE) at one year and 39% ±5% at two and three years. In multivariate analysis, additional treated lesions, instead of only femoropopliteal lesion, was the strongest predictor for poorer long-term patency. The primary angiographic success rate for angioplasty of infrapopliteal stenoses was 84% (102 / 121) and that of occlusions 61% (41 / 67) with corresponding restenosis rates of 32% and 52% at follow-up angiography. The primary clinical success of 63% (45 / 72), the primary clinical patency of 48% (±6%) and the limb salvage rate of 80% (±3%) were registered at 18 months. Lack of angiographic improvement at the site of the most severe ischemia and renal insufficiency were independent predictors of poorer long-term clinical results after infrapopliteal angioplasty. Clinical patency was registered at the time of follow-up angiography in two thirds of those limbs with a primary clinical success even though there was angiographic evidence of restenosis.

CONCLUSIONS: The length and severity of recurrent disease after intrainguinal angioplasty depends on the original lesion type. The initial result of femoropopliteal angioplasty is improved by prolonged balloon inflation but this does not improve the long-term result. Infrapopliteal angioplasty is feasible primary treatment of chronic critical lower limb ischemia. Even though there may be angiographic restenosis after infrapopliteal angioplasty, the achieved clinical patency is preserved.

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Medical Subject Headings: angioplasty, balloon; ischemia; recurrence; popliteal artery; femoral artery; vascular patency; prospective studies
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Kuopio, April 2002

Heini Söder
ABBREVIATIONS

ATM = atmosphere
\( \beta \) = beta
\( \gamma \) = gamma
CI = confidence interval
DSA = digital subtraction angiography
ESRD = end stage renal disease
F = French (= 0.33 mm)
Ir 192 = Iridium-192
IVUS = intravascular ultrasound
P-32 = Phosphor-32
PTA = percutaneous transluminal angioplasty
PTCA = percutaneous transluminal coronary angioplasty
PTFE = polytetrafluoroethylene
SEE = standard error of the estimate
US = ultrasound
VEGF = vascular endothelial growth factor
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals.


III Söder HK, Manninen HI, Räsänen HT, Kaukanen E, Jaakkola P, Matsi PJ. Failure of prolonged dilation to improve long-term patency of femoropopliteal artery angioplasty: results of a prospective trial. JVIR, in press.


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INTRODUCTION

Patients with claudication suffer high mortality rates due to the presence of other atherosclerotic manifestations. Therefore, the first priority should be to modify risk factors such as termination of cigarette smoking and decrease in obesity. This should be accompanied by long-term prescription of antiplatelet pharmacotherapy, usually low-dose acetylsalicylic acid. The second step is regular walking exercise training (1). In patients with chronic critical limb ischemia, the arterial disease is characterised by diffuse and multilevel involvement and the disease may be entirely infrapopliteal. These patients are mainly old and diseased. The development of limb ischemia to the stage of rest pain and / or ischemic ulcers or gangrene has an unfavourable prognosis with a high risk of limb loss. Amputation for chronic critical limb ischemia decreases patient mobility, increases costs and the need for institutional care (2).

A minority of patients with claudication will deteriorate and require some kind of local intervention, either endovascular or surgical. Patients with ulcers, gangrene or rest pain in the foot attributable to peripheral arterial disease should be considered as urgent cases. The primary invasive treatment for this patient population has so far been mainly surgical.

The role of balloon angioplasty (percutaneous transluminal angioplasty, PTA), and stent placement as a treatment modality in iliac arteries is well established. In infrainguinal arteries, the use of balloon angioplasty is more controversial. Although the initial success is high, restenosis seriously impairs the long-term efficacy of balloon angioplasty. Most attempts to overcome the
problem of restenosis have been unsuccessful. Even stents have not substantially improved the long-term results of femoropopliteal angioplasty. The experience with percutaneous PTA of infrapopliteal vessels is still very limited.
2. REVIEW OF LITERATURE

2.1. RESTENOSIS

2.1.1. Definition of restenosis

Most of the definitions used for restenosis are based on angiographic morphology, primarily from coronary angiography (3-7). The conventional definition of restenosis, >50% diameter stenosis at 6-month follow-up angiography (8), was based on prior data obtained from an animal model in which coronary flow reserve is limited beyond this value (9). This definition has not been uniformly endorsed since it failed to take into account whether the acute result itself was much better than a 50% residual stenosis. One study showed that by applying three different and widely used definitions, the greatest single determinant of restenosis was choice of definition (10). According to a quantitative angiographic study, there is a danger of misinterpretation of the results if observations are based solely on conventional restenosis criteria without knowledge of the actual changes in luminal dimensions during and after angioplasty (11). It has been demonstrated that the restenosis process takes place, at least to some extent, in most of the dilated lesions. Furthermore, there is a study suggesting that restenosis takes place not only in the stenotic portion of coronary artery, but also in the dilated but nonstenotic segments. As a consequence, the percent diameter stenosis measurements tend to underestimate the change when there is a simultaneous reduction in the reference diameter (12). The angiographic restenosis criteria should reflect the change in the minimal luminal diameter of the treated lesion immediately after
angioplasty and at follow-up, and the change in the minimal luminal diameter should be independent of the change in the “reference diameter” (10, 13).

The definition of restenosis is further complicated by problem of whether it is better to view luminal renarrowing as a dichotomous (“all or none”) outcome or as a continuous process. In the dichotomous outcome classification (8), a particular threshold of luminal renarrowing has to be reached before restenosis can be judged to have occurred. On the other hand, Holmes et al illustrated that the change in percent luminal diameter from immediately after PTCA (percutaneous transluminal coronary angioplasty) to follow-up angiography was a continuous, parametric distribution (3). Also a serial angiographic follow-up at one, two, three, four and six months revealed the luminal renarrowing of coronary artery to occur in some degree in all lesions and to be a continuous, time-related phenomenon which rarely occurs after six months (10, 14).

A study that used four angiographic definitions for coronary restenosis demonstrated that none of these angiographic definitions of restenosis correlated well with the clinical recurrence of angina (3). On the other hand, Gruentzig et al showed that most ischemic events due to target vessel renarrowing do occur within 6 to 8 months following coronary angioplasty (15). This correlates well with the time course of maximal angiographic luminal renarrowing, which occurs between 3 and 6 months after coronary balloon angioplasty according to other investigators (10, 14, 16).

There are few studies which have focused on the restenosis problem in lower limb arteries, for example it is not known if the principles outlined above from coronary studies can be simply extended to the peripheral circulation. “Clinical
restenosis is a concept that refers to the recurrence of symptoms or signs of ischemia following an initially successful procedure (17). However, recurrent signs and symptoms of ischemia may be due to progression of the disease elsewhere within the vascular system, and this definition may not distinguish such cases from those where there is in fact recurrent disease at the site of the previous intervention. New disease, not involving the site of the previous intervention, was reported to occur in 24% of cases in lower limb ischemia (18). On the other hand, in contrast to recurrent disease, new lesions appear later during the follow-up after femoral angioplasty (19, 20). So the clinical marker must distinguish between ischemic events related to significant target vessel renarrowing (restenosis) and irrelevant ischemic events due to significant luminal narrowing at other sites (21).

2.1.2. Mechanism of restenosis

The mechanism of restenosis is complex and not fully resolved. Hjemdahl-Monsen et al (22) showed that elasticity or recoil is responsible for the immediate loss in luminal diameter after coronary dilation. Other studies have confirmed that elastic recoil is a frequent phenomenon (23, 24). Elastic recoil was suggested as an explanation for the mechanism of restenosis (25, 26). The impact of elastic recoil as a mechanism of restenosis is somewhat conflicting. Elastic recoil did not correlate with restenosis measured as a continuous variable, whereas when restenosis was measured as a dichotomous variable, the greater the elastic recoil, the higher was the probability of developing restenosis (27).
Histopathological studies have suggested that the healing response to angioplasty induced vascular injury is the primary pathophysiologic mechanism of restenosis. According to this explanation, the balloon induces vascular injury and causes immediate, progressive release of thrombogenic, vasoactive, and mitogenic factors leading to platelet aggregation, thrombus formation, and inflammatory changes, causing activation of macrophages and smooth muscle cells. These events lead to production and release of growth factors and cytokines. A self-perpetuating cascade is initiated, which results in the migration of smooth muscle cells from their usual location in the media to the intima, where they undergo a phenotype change, produce extracellular matrix, and proliferate (28-38). However, therapies that inhibit intimal hyperplasia have not prevented restenosis after coronary artery balloon angioplasty in controlled clinical trials (39-41), suggesting that in humans, some additional mechanism may be possible for restenosis.

Arterial remodelling is an important determinant in vascular pathology. Histopathological studies indicated that human arteries enlarge in response to progressive atherosclerosis (42, 43). When there are de novo lesions, adaptive arterial remodelling (an increase in arterial cross-sectional area) may represent a compensatory response of the blood vessels to hemodynamic stress, arterial injury, and cellular proliferation. Adaptive arterial remodelling early in the coronary artery atherosclerotic disease process delays the development of focal stenoses despite significant plaque accumulation; functionally important lumen stenosis may be delayed until the lesion occupies 40 percent of the internal elastic lamina area (42). However, intravascular ultrasound (IVUS) imaging
studies have shown that pathologic arterial remodelling (a decrease in arterial cross-sectional area or chronic arterial constriction or shrinkage) contributes to lumen compromise in chronic local de novo stenoses in femoral arteries (44).

Adaptive and pathologic remodelling has also been recognised to be important in the development of restenosis after interventional procedures. In a histopathological analysis, the neointimal cross-sectional areas in the restenotic and nonrestenotic lesions after angioplasty of iliac arteries in an animal model were virtually identical; the differences in lumen areas resulted from significant differences in total arterial cross-sectional areas. In the nonrestenotic lesions, a given increase in intimal area was associated with a greater increase in the arterial cross-sectional area to preserve the lumen, whereas in restenotic lesions, there was a lesser increase in total arterial cross-sectional area indicative of inadequate adaptive arterial remodelling (45). Similar results have been obtained by other investigators (46). A study utilising IVUS revealed that adaptive remodelling can prevent restenosis; pathologic remodelling was the dominant mechanism of restenosis following coronary intervention. (47). Also in another IVUS study, the mechanism of lumen narrowing after coronary angioplasty appeared to be determined by unfavourable remodelling (48). However, variable patterns of remodelling may occur in individual injured coronary segments, which highlights the complexity and influence of local factors in the restenotic process. In an IVUS study, lumen narrowing at the most stenotic sites of the femoropopliteal artery was caused by plaque increase and vessel shrinkage (49).
Currently, the predominant cause of restenosis after angioplasty is thought to be remodelling, but the mechanisms responsible for remodelling are unknown. Several mechanisms have been postulated to explain the chronic decrease in arterial cross-sectional area following angioplasty. The potential role of adventitial fibrosis has been addressed (37). Also apoptosis may be exaggerated following catheter-based interventional procedures (50). An arterial wall response to shear stress is one explanation. When blood flows through a vessel, it exerts a physical force on the vessel wall. This force, shear stress, occurs in parallel to the vessel wall (51). The impact of blood flow suggests that evolution of the healing reaction is sensitive to wall shear stress. Low blood flow may promote restenosis after angioplasty because of its adverse effect on vessel remodelling after angioplasty (52). There is also data indicating that intimal hyperplasia is increased when flow is reduced (53).
2.2. PREVENTION OF RESTENOSIS

2.2.1. Pharmacological therapy

As our knowledge of the pathophysiology of restenosis has increased, a number of targets have been identified for pharmacological intervention. Many pharmacological agents have been investigated in attempts to prevent restenosis. Even if an effective reduction in restenosis in some animal model has been observed with many agents (54-57), almost invariably the effect in clinical trials to prevent postangioplasty coronary restenosis has not been so efficacious (see Table 1).
<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration route</th>
<th>Study design</th>
<th>Clinical efficacy</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Antiplatelet agents</td>
<td></td>
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<tr>
<td>- acetylsalicylic acid</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Savage, -95 (58), Taylor, -91 (59)</td>
</tr>
<tr>
<td></td>
<td>Per oral</td>
<td>R, PC</td>
<td>Small beneficial effect</td>
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<tr>
<td>- dipyridamole</td>
<td>Intravenous</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Schwartz, -88 (60)</td>
</tr>
<tr>
<td>- cilostazol</td>
<td>Per oral</td>
<td>R</td>
<td>Effective</td>
<td>Tsuchikane, -99 (61)</td>
</tr>
<tr>
<td>- ticlopidine</td>
<td>Per oral</td>
<td>R</td>
<td>Effective</td>
<td>Nagaoka, -01 (62)</td>
</tr>
<tr>
<td>- selective thromboxane A2- receptor antagonist</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Serruys, -91 (63)</td>
</tr>
<tr>
<td>- selective thromboxane A2- synthetase inhibitor</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Hattori, -91 (64)</td>
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<tr>
<td>Anticoagulants</td>
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<tr>
<td>- warfarin</td>
<td>Per oral</td>
<td>R</td>
<td>Not effective</td>
<td>Thornton, -84 (4)</td>
</tr>
<tr>
<td>- heparin</td>
<td>Intravenous</td>
<td>R</td>
<td>Not effective</td>
<td>Ellis, -89 (65)</td>
</tr>
<tr>
<td>- low molecular weight heparin</td>
<td>Subcutaneous</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Faxon, -94 (41)</td>
</tr>
<tr>
<td></td>
<td>Method</td>
<td>Follow-up</td>
<td>Effect</td>
<td>Reference</td>
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<td><strong>Calcium channel blockers</strong></td>
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<tr>
<td>- diltiazem</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>O'Keefe, -91 (39)</td>
</tr>
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<td>- nifedipine</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Not effective</td>
<td>Whitworth, -86 (66)</td>
</tr>
<tr>
<td>- verapamil</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Beneficial effect</td>
<td>Hoberg, -94 (67)</td>
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<td><strong>ACE-inhibitors</strong></td>
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<td>Per oral</td>
<td>R, DB, PC</td>
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<td>No author list (40)</td>
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<tr>
<td>- fosinopril</td>
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<td>R, DB, PC</td>
<td>Not effective</td>
<td>Desmet, -94 (68)</td>
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<td><strong>Lipid lowering agents</strong></td>
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<tr>
<td>- fish oil</td>
<td>Per oral</td>
<td>R, DB</td>
<td>Not effective</td>
<td>Reis, -89 (69)</td>
</tr>
<tr>
<td>- lovastatin</td>
<td>Per oral</td>
<td>R, DB</td>
<td>Effective</td>
<td>Bairati, -92 (70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>Not effective</td>
<td>Kleemann, -99 (71)</td>
</tr>
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<td><strong>Corticosteroids</strong></td>
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<td></td>
<td>Intramuscular</td>
<td>R</td>
<td>Not effective</td>
<td>Stone, -89 (72)</td>
</tr>
<tr>
<td><strong>Antiproliferative agents</strong></td>
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<td></td>
</tr>
<tr>
<td>- angiopeptin</td>
<td>Subcutaneous</td>
<td>R, DB, PC</td>
<td>Effective</td>
<td>Eriksen, -95 (73)</td>
</tr>
<tr>
<td>- tranilast</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Effective</td>
<td>Tamai, -99 (74)</td>
</tr>
<tr>
<td>- trapidil</td>
<td>Per oral</td>
<td>R</td>
<td>Effective</td>
<td>Okamoto, -92 (75)</td>
</tr>
<tr>
<td>- pro buc ol</td>
<td>Per oral</td>
<td>R, DB, PC</td>
<td>Effective</td>
<td>Tardif, -97 (76)</td>
</tr>
</tbody>
</table>

Note: R=randomised trial; DB=double blind; PC=placebo controlled
Since stents are widely used, and restenosis in a stent is mainly thought to be caused by neointimal hyperplasia (77, 78), most of the newer pharmacological agents have concentrated on preventing neointima formation. There are some investigations on antiproliferative agents with promising effects in reducing restenosis. Oral administration of tranilast (an antiallergic agent), in a multicenter, randomised, double blind trial, markedly reduced the restenosis rate after coronary angioplasty compared with placebo group (15% (10 / 68) vs 46% (33 / 71), p<0.0001) (74). The restenosis rate was lower in patients who received trapidil (an antiplatelet agent with growth factor antagonism and antiproliferative effects) compared to acetylsalicylic acid in a randomised double-blind study (24% (31 / 128) vs 40% (50 / 126), p<0.01) (79). Probufol (an antioxidant agent), that has also lipid lowering effects, has been shown to reduce coronary revascularization rates at one year follow-up. Its preventive effect was independent of the lipid lowering effects (76, 80). According to an IVUS-study, profubol exerts its antirestenotic effects after coronary angioplasty by improving vascular remodelling (81). In a randomised double-blind pilot study, subcutaneous infusion of angiopeptin (a somatostatin analogue) prevented restenosis in patients undergoing successful PTCA in a statistically significant manner (12% (5 / 41) vs 40% (21 / 53), p=0.003) (73).
2.2.2. Angioplasty techniques

2.2.2.1 Laser angioplasty and atherectomy

The application of laser systems have been disappointing. The restenosis rate at 6-month after laser coronary angioplasty was 54% (434 / 797 lesions) (82). In a randomised trial comparing laser guide wires and conventional guide wires for recanalization of a chronic coronary occlusion, no differences in the restenosis rate between these two groups at the 6-month angiographic follow-up were detected (45% (30 / 66) vs 38% (31 / 81), p=0.72) (83). Procedural complications occurred more frequently in a laser treated group compared with PTCA alone in a study of 215 patients with 244 lesions (18% (21 / 117) vs 3% (3 / 98), p=0.0004) (84).

The efficacy of different atherectomy devices to prevent restenosis have not revealed any one to be superior than balloon angioplasty. In a randomised study between directional coronary atherectomy (n=512) and coronary angioplasty (n=500), although atherectomy led to a larger luminal diameter (1.05 vs 0.86 mm, p<0.001) there was a higher rate of early complications with atherectomy (57 events (11%) vs 27 events (5%), p<0.001) and at the angiographic assessment at 6-month (826 patients with angiographic follow-up) the restenosis rates were almost equal (50% vs 57%, p=0.06) (85). After successful directional atherectomy for occlusive peripheral vascular disease, 77 limbs with angiographic follow-up revealed 38 recurrences (86). In a randomised study between balloon angioplasty (n=35) and directional atherectomy (n=38) in patients with short femoropopliteal lesions, the 2-year angiographic patency rates were 67% and 44%, (p=0.06) (87). The restenosis
rates at 6 months were similar between coronary balloon angioplasty and rotational atherectomy (35% (51 / 146) vs 37% (54 / 147), p=0.66) in a randomised trial (88). In a study with a very limited patient population (n=15), only one of the infrapopliteal lesions treated with rotational atherectomy, was patent at the 6-month follow-up angiography (assessment was possible in 12 of 19 treated lesions) (89).

2.2.2.2. Stents
2.2.2.2.1. Bare stents

One attempt to solve the problem of restenosis after balloon angioplasty is placement of metallic endovascular stents (90, 91) that almost completely eliminate the decrease in vessel dimensions caused by elastic recoil (92). Stents convincingly reduce also angiographically assessed (93, 94) and clinical restenosis (95) after coronary angioplasty. Introduction of new antiplatelet agents ticlopidine and clopidogrel have further improved results of coronary stent placement (96). Although these agents are increasingly used for one month after femoral artery stent placement (97) there is no firm evidence for the efficacy of this strategy from other vascular areas except coronary arteries. After implantation of stents in femoropopliteal arteries moderate restenosis rates, varying from 11% to 28% at one year follow-up, are reported but only a few studies performed extensive angiographic follow-up (98-101). However, in comparative studies between stent implantation and balloon angioplasty the restenosis rates were equally high. Ten of the 26 patients with stent installed in the femoropopliteal occlusion had a recurrent stenosis within 12 months, as had
10 of the 26 balloon angioplasty group patients (102). One limitation of this study was that the 6-month angiography control in the balloon angioplasty group was performed only when a clinical deterioration was observed. The restenosis rate was higher in the stent than in the balloon angioplasty group after femoropopliteal artery angioplasty (50% (6 / 12) vs 25% (2 / 8), p=0.033) in another randomised, angiographically controlled study (103).

In-stent restenosis was observed to be a result of neointimal hyperplasia, which tended to be uniformly distributed over the length of the stent in a serial IVUS study of coronary arteries (77). Also, a histopathological study of in-stent restenosis of peripheral arteries demonstrated that the cause of the restenosis was smooth muscle cell proliferation (104). There did not appear to be any differences in neointima formation after insertion of three different types of stents (low-profile Nitinol stent, Palmaz stent and Wallstent) in an animal model (105). Clinical and angiographic outcomes were similar between self and balloon-expandable stents in coronary arteries (106). However, the structure of the stents may have some impact on restenosis. In a recent study the incidence of angiographic restenosis after coronary angioplasty was 15% in the thin-strut group (n=326) and 26% in the thick strut group (n=325) (p=0.003) (107). Also, the vessel size can influence the restenosis rate. The restenosis rate was lower in stented vessels with a diameter of minimum 3 mm than in vessels with a diameter of < 3 mm (20% vs 30%, p<0.01) in a study containing 911 coronary lesions (108). Only 7 out of 13 stents of 3mm in diameter remained patent compared with all of the 20 stents with a diameter of 4-5 mm in an animal model (109). The restenosis rate of iliac stenting is considerably smaller than that after
femoropopliteal stent placement (110, 111). Furthermore, an inadequate stent deployment carries the risk of creating turbulent flow, leading to residual pressure gradients and these may have an influence on neointima formation and subsequently on the development of restenosis as was seen in an animal model study (112). Compression of balloon expandable stents, especially in the adductor canal, was identified as the principal cause of restenosis in femoropopliteal arteries in an IVUS study (113).

2.2.2.2. Covered stents

A covered stent is thought to function as a mechanical barrier between the blood flow and the vessel wall (114). In supported devices, the purpose of the cover in stent-grafts is to prevent or limit myointimal ingrowth along the length of the treated segment. However, all current stent-grafts seem to induce an inflammatory vessel wall reaction with neointimal hyperplasia, though graft material placed outside stent structure showed less intimal hyperplasia than a graft placed inside (115, 116). In an animal model neointima formation proceeded from the ends towards the centre (117). The healing in human aortoiliac and femoral arteries was also found to begin from the ends (118), but tissue ingrowth was also noted through the graft (119). In an animal model, neointimal thickening was more pronounced with covered stents compared with non-covered stents (120).

Few preliminary clinical reports are available about the use of covered stents. Some of the study populations have been very small, with quite high restenosis rates. In one study, only three of nine patients did not have restenosis after
placement of Dacron-covered nitinol stent in femoropopliteal obstructions at angiography after 6 months (eight patients were angiographically controlled) (121). In another study, after placement of polytetrafluoroethylene (PTFE) covered stent-graft, occlusion was observed in 13 of 18 patients (72%) and intimal hyperplasia at the distal or proximal end of the stent-graft in seven patients (39%) (122). After implantation of a PTFE covered stent-graft in coronary artery, restenosis was detected in 2 of the 10 patients in proximal and/or distal parts of the stent which were not covered by the graft; in one patient restenosis was found outside the stent (123). Fourteen superficial femoral arteries were successfully treated with a PTFE covered stent-graft in which nitinol stents were sited at either end. One late occlusion was detected and three grafts developed hemodynamically significant stenosis also in the proximal and distal stents and the adjacent artery (124). There are also some promising results. In a prospective study with rather large patient population, a self-expanding PTFE covered stent-graft was placed in 80 femoropopliteal arteries. Restenosis or reocclusions were observed in 14 of the limbs within the first year (125).
2.2.2.3. Local drug delivery

2.2.2.3.1. Catheter based delivery systems

In effort to attain high concentrations of some agent at the site of injury without systemic side effects, attention has been focussed on the potential of localised therapies in the prevention of restenosis. A spectrum of catheters have been developed to deliver a variety of agents to the intervention site. The systems based on passive diffusion include double-occlusion balloon (126) and spiral infusion-perfusion balloon catheters (127). Micro-porous balloons (128), hydrogel-coated balloons (129), channel balloon catheters (130) and infusion-sleeve catheters (131) are based on pressure-augmented diffusion. Finally, systems based on mechanically or electrically enhanced delivery include infiltrator balloon catheters (132) and iontophoretic balloons (electrical current enhances drug infusion) (133).

Some reports in animal models have been published, such as local administration of heparin (134, 135) or r-hirudin (136) These were shown to prevent thrombus formation. Similarly, iloprost was shown to suppress smooth muscle cell proliferation (137).

Local drug delivery has also been used for direct arterial gene transfer in animal models (138-140). There are many potential targets of gene therapy. Most gene therapy strategies have been directed towards inhibition of smooth muscle cell migration and proliferation, formation of connective tissue, and effects of undesirable growth factor (141). A cytotoxic gene therapy demonstrated reduction in the intima-to-media ratio (142). Vascular endothelial growth factor (VEGF) plasmid accelerated re-endothelialization, reduced mural
thrombus formation and decreased neointima formation (143). Selective blockage of transforming growth factor resulted in inhibition of neointima formation (144). Two study groups examined the benefits of gene therapy based on nitric oxide metabolism (145, 146). Further, an apoptosis inducer (Fas ligand) in the vessel wall after injury has been reported to prevent intimal hyperplasia (147).

Vaso-occlusive diseases, thromboangiitis obliterans (Buerger's disease) and chronic critical limb ischemia were treated by intramuscular gene transfer VEGF, a total of 15 patients with 17 treated limbs (148, 149). Ulcers healed or were markedly improved in 7 out of the 12 limbs and an improvement was reported by all patients suffering from rest pain. DSA (digital subtraction angiography) showed newly visible collateral vessels and improved flow was registered also in magnetic resonance angiography. The feasibility and safety of catheter-mediated (VEGF) gene transfer in human coronary arteries after coronary angioplasty and lower limb arteries of patients with chronic critical limb ischemia are now established (150, 151).

2.2.2.3.2. Coated stents and drug-eluting stents

Local drug delivery via stents either with immobilised drug or coated with a drug-releasing polymex matrix offers the possibility to focal therapeutic drug effect within target tissue without serious side-effects such as those encountered from systemic drug administration. Heparin coated stents were shown to be effective in prevention of restenosis in an animal model (152), but no impact was seen on the restenosis rate when compared with uncoated
stents in a clinical coronary artery trial (153). In a randomised coronary artery trial, which compared gold-coated stents with uncoated steel stents, the incidence of angiographic restenosis was higher in the gold coated stents, 50% (157 / 316) vs 38% (123 / 323) (p=0.003) (154). Some promising results in diminishing the restenosis rate was seen in a pilot study consisting of 100 consecutive patients treated with phosphorylcholine coated stents. Phosphorylcholine reduces platelet and protein adhesion to the surface of metal. Primary coronary stenting with this stent was associated a restenosis rate of 12% (8 / 65) (155).

Early experiences suggest that local therapy achieved with drug eluting stents may be effective in reducing neointimal hyperplasia and clinical restenosis. In an animal model dexamethasone coated stents reduced neointimal hyperplasia compared with non-coated stents (156). However, there are also contradictory results where there has been no decrease in the incidence of neointimal hyperplasia (157). Therapy with agents, such as abciximab, sirolimus and paclitaxel have potential in preventing restenosis since they have reduced the extent of myointimal hyperplasia in animal models (158-161). Only some preliminary reports in human coronary artery have been published (162).
2.2.2.4. Brachytherapy

Inhibition of the in-stent restenosis by endovascular irradiation was first shown by Böttcher et al (163). There is evidence that the mechanism is inhibition of neointima formation (164), but also remodelling plays a role (165, 166). Both gamma (γ)-and beta (β)-irradiation delivered via a radioactive catheter-based line source (afterloading method) have been shown to reduce in-stent coronary restenosis (167-169). Beta particles penetrate at most 1 cm in tissue and the effective radiation dose is insufficient for treatment of large peripheral arteries. Tissue penetration of gamma rays is much more effective (170, 171). In a randomised clinical trial, including 113 patients, femoropopliteal angioplasty and brachytherapy with Iridium-192 (Ir-192) source was performed on 57 patients and femoropopliteal angioplasty without irradiation on 56 patients. At the 6-month follow-up, recurrences were observed in the control PTA group more frequently than in the brachytherapy group (54% (29 / 54) vs 28% (15 / 53), p=0.008) (172). Endovascular brachytherapy with Ir-192 proved to be feasible for treatment of restenosis also after stent placement of failing Brescia-Cimino hemodialysis fistulas (173).

However, there are several problems inherent in endovascular brachytherapy. Centering of irradiation source is essential to improve the homogeneity of dose distribution along the cross-section of the vessel wall (174), this being especially the case with larger peripheral vessels. Some preliminary results after brachytherapy with a centering catheter are available. Brachytherapy with centering catheter after long-segment femoropopliteal stent is promising, only four (12%) of 33 arteries had in-stent restenosis (97). A low
angiographic restenosis rate of 17% (5 / 29) at 6 months and clinical restenosis rate of 13% (4 / 30) at 12 months was recently reported also after femoropopliteal angioplasty with a centering gamma emitter (175). When using gamma emitters, dwelling times may be as long as 30 minutes and special radiation protection has to be available, and inevitably the patient has to moved from the angio laboratory to the brachytherapy suite.

In an animal model severe luminal narrowing was seen in pig coronary arteries after irradiation with beta rays (176). In another study, adventitial fibrosis increased with increasing dose although severe adverse effects were not evident until 4-5 years after radiation (177). Intracoronary radiation (both $\beta$ and $\gamma$) for in-stent restenosis was associated with a significantly higher rate of late total occlusions (>30 days) than the placebo group: 9% (28 / 308) compared to 1% (2 / 165) ($p<0.0001$) (178). On the contrary, in a follow-up study of 40 patients no changes were seen in the tissue surrounding the lower limb artery in computed tomography, color Doppler, IVUS or magnetic resonance imaging following irradiation of gamma-emitter (179). Further, there was no evidence of a deleterious effect of gamma-irradiation on angiographically normal, uninjured reference segment in the first 6 months after the treatment of in-stent coronary restenosis in an IVUS study (180). A recognised limitation of endovascular radiation therapy is the development of a new stenosis at the edges of the irradiated area after both gamma and beta irradiation. The new stenosis develops in the area called the "geographic miss", that is not fully covered by the radiation source (181, 182).
Other irradiation techniques such as radioactive liquid filled balloons (183) and technique where the radioisotope is integrated into balloon material (184) have also been shown to reduce neointima formation in animal models. However, external beam radiation after stent implantation was not found to reduce myointima formation, but on the contrary, to increase it (185). Radioactive stents might be an alternative to vascular brachytherapy. Studies in animals about the effects of β-emitting stents have shown variable effects on neointima formation (186, 187), and the capability of the radioactive stents in reducing neointima formation was shown to be dose-dependent (188). Inhibition of intimal growth in animal model was maintained at 6 and 12 months after placement of Phosphor-32 (P-32) stents. Nevertheless, delayed arterial healing, incomplete endothelialization and the edge effect were present (189). After implantation of P-32 stents in patients with coronary artery disease, the extent of intra-stent neointimal hyperplasia was reduced. However at the stent-edges, the restenosis rate was high, about 50% at 6 months follow-up (190). From another study was the conclusion that neointimal proliferation is delayed rather than prevented by radioactive stent implantation in patients of coronary artery disease (191). The authors of a recently published trial concluded that the high incidence of edge restenosis 44% (16 / 36), predominantly observed to occur more often at the proximal edge compared distal edge (56% (9 / 16) vs 25% (4/ 6), p=0.02), makes implantation of radioactive stents in coronary arteries currently clinically non-applicable (192).
2.2.2.5. Prolonged dilation

Longer balloon inflation periods were proposed as being beneficial in a post-mortem pilot study that showed a reduction in atheromata volumes in arteries depending on the duration of the pressure applied (193). The technique of using a perfusion balloon angioplasty catheter that maintains blood flow to the distal coronary artery bed during balloon inflation, allowed markedly extended balloon inflation and was associated with less ischemia and myocardial damage (194-197). Prolonged dilation strategy resulted in improved luminal outcomes and fewer dissections in some PTCA trials (196, 198, 199) but also contradictory results have been reported (200). The potential of longer inflations to reduce restenosis have been investigated by several authors with the same conclusion that prolonged dilation does not reduce restenosis rates after coronary angioplasty (201-204). In these studies, the angiographic follow-up varied from 52% to 93%, and dilation times with the perfusion balloon catheter were from 4.8 minutes to a maximum of 15 minutes. The use of prolonged inflations with a perfusion balloon catheter has been proposed also for lower limb PTA (205).
2.3. CLINICAL AND ANGIOGRAPHIC RESTENOSIS

The reliance on clinical end points alone in determining restenosis is too vague to serve as the end point of a rigorous study (206). When arteriographic examination was considered as the gold reference standard, the diagnostic accuracy for the identification of recurrent lesions was 74% at clinical examination after femoropopliteal angioplasty (18). Investigators have therefore proposed that some objective measurement of luminal renarrowing has to be the only acceptable outcome for defining restenosis (207). Since no more than 50-80% of patients are willing to undergo follow-up angiography (208), most restenosis trials are compromised by incomplete ascertainment of their angiographic end point. Patients referred for repeat angiography are preferentially selected on the basis of recurrent symptoms and this selection bias leads to an overestimation of the restenosis rate following angioplasty. Restenosis trials with angiographic follow-up for less than 90% of the limbs suffer from this selection bias (3, 206).

2.4. PTA RESULTS

2.4.1. Infrainguinal PTA

The technical success rate of infrainguinal PTA is high, varying from 84% to 91% (209-212). The technical success has been shown to be higher for treated stenoses than occlusions, the corresponding percentages being 86% to 95% versus 74% to 85% (210, 211, 213-215). The long term patency rates of infrainguinal PTA vary in different studies. The early studies are retrospective and there is also a lack of uniformity in reporting. At 1 year, primary patency
rates of 47% to 86% and at three years rates of 42% to 62% are reported in the literature (209, 211, 214-217). Comparison of the results is further complicated by the fact that the proportion of stenoses versus occlusions and the length of the lesions as well as the number of claudicant versus patients with critical limb ischemia vary between individual studies (Table 2).

There are many predictive factors for long-term outcome of femoropopliteal angioplasty. Although type of the treated lesion (stenosis versus occlusion) revealed a significant difference in the primary technical success rate, the type of the treated lesion did not influence the long-term patency (209-211, 214, 221). There are also controversial results, however. In one study with femoropopliteal PTA, stenoses had a better long-term success than occlusions (215). In a meta-analysis including 19 studies, combined 3-year patency rates after balloon dilation in the claudicant group was 61% for stenoses and 48% for occlusions (222). Lesion length has been observed by many authors to be an important determinant for long-term patency (210, 211, 214, 217, 221). Shorter lesions (< 2 cm and 2-5 cm) tend to fare better than lesions greater than 10 cm (214). Another author reported that lesions more than 10 cm in length have a 2.8 fold relative risk of occlusion compared to those lesions under 10 cm (221). The total length of the treated lesions greater than 15 cm had also poorer long term outcome (211). Poor peripheral runoff is associated with a poorer long-term result in many studies. Long-term patency rates of 30% in limbs with poor runoff versus 52% with better runoff were reported by Johnston et.al (215). Poor runoff was claimed to be the strongest determinant for lower long-term patency rates (221). The importance of good runoff for better long-term outcome has
been stressed by several authors (209, 211) but there are also some controversial results (210).

Other procedure related factors have been reported to have a predictive value on long-term patency by several authors. Concentric morphology, regular surface of stenoses, absence of residual stenosis after angioplasty and limbs with a single site of angioplasty favoured a better long-term result (209, 211, 214, 221). More extensive atherosclerotic disease in the treated limb was also noted to predict a poorer long-term result (211).

According to some investigators diabetics have poorer long-term patency (210, 214, 221). However, Johnston et al noticed no statistically significant differences in long-term results between diabetics or nondiabetics (215). If lesion related parameters, e.g. lesion lengths, are similar, there was no difference between the long-term results in diabetics and nondiabetics in another study (223). The deleterious effect of renal failure was noticed in an univariate analysis in one study (221). The clinical stage of the patient before angioplasty may also be predictive, patients with claudication showing better long-term patency than those with critical ischemia (215). In a meta-analysis, the combined 3-year patency rates for stenoses and critical ischemia (43%) and for occlusions and critical ischemia (30%) were lower than for claudicant patients (corresponding values 61% and 48%) (222).
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/limbs (n)</th>
<th>Claudication / critical ischemia % / %</th>
<th>Femoropopliteal artery, %</th>
<th>Mean lesion length, (range)</th>
<th>Stenosis / Occlusion</th>
<th>Primary Success</th>
<th>Long-term success (SEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krepel, -85 (209)</td>
<td>129/164</td>
<td>90/10</td>
<td>100</td>
<td>NA</td>
<td>127/37= 77%/23%</td>
<td>138/164=84%</td>
<td>1y: 81% 2y: 77% 3y: 70%</td>
</tr>
<tr>
<td>Hewes, -86 (210)</td>
<td>118/137</td>
<td>70/30</td>
<td>93</td>
<td>NA</td>
<td>78/59= 57%/43%</td>
<td>67/68=86%*</td>
<td>1y, 2y: 81%* 3y: 61%* 1y: 82%† 2y: 77%† 3y: 68%†</td>
</tr>
<tr>
<td>Murray, -87 (213)</td>
<td>162/193</td>
<td>66/34</td>
<td>100</td>
<td>NA</td>
<td>116/77= 60%/40%</td>
<td>157/193=81%</td>
<td>1y: 72%* 1y: 86%†</td>
</tr>
<tr>
<td>Capek, -91 (214)</td>
<td>152/217</td>
<td>74/26</td>
<td>100</td>
<td>0-2cm: 45% 2-5cm: 29% &gt;5cm: 26%</td>
<td>109/51= 68%/32%</td>
<td>93%*</td>
<td>1y: 71% 2y: 51% 3y: 48%</td>
</tr>
<tr>
<td>Johnston, 92 (215)</td>
<td>236/254</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>89% at 1 m</td>
<td>1y: 70%(3) 2y: 59%(4) 3y: 57%(4)</td>
</tr>
<tr>
<td>Hunink, -93 (216)</td>
<td>106/131</td>
<td>58/42</td>
<td>85</td>
<td>NA</td>
<td>118/13= 90%/10%</td>
<td>95%</td>
<td>1y: 60% 2y: 50% 3y: 45%</td>
</tr>
<tr>
<td>Matsi, -94 (211)</td>
<td>106/140</td>
<td>100</td>
<td>100</td>
<td>8.0cm, (1-31)</td>
<td>71/69= 51%/49%</td>
<td>125/40=89%</td>
<td>1y: 47%(4) 2y,3y:42%(5)</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Size</td>
<td>Lesion Size</td>
<td>Lesion Count</td>
<td>Length</td>
<td>Grade</td>
<td>Diameter</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Vroegindeweij, 95 (18)</td>
<td>62/62</td>
<td>99/1</td>
<td>100</td>
<td>4.7 cm, (0.5-15)</td>
<td>0/62=0%</td>
<td>51/62=82%</td>
<td>1y: 63% (6)</td>
</tr>
<tr>
<td>Murray, -95 (217)</td>
<td>42/44</td>
<td>89/11</td>
<td>100</td>
<td>24.3 cm, (10-40)</td>
<td>18/26=41%</td>
<td>41/44=93%</td>
<td>1y: 86% (5)</td>
</tr>
<tr>
<td>Stanley, -96 (218)</td>
<td>176/200</td>
<td>74/26</td>
<td>100</td>
<td>NA</td>
<td>119/81=59%</td>
<td>146/200=73%</td>
<td>1y: 58% (4)</td>
</tr>
<tr>
<td>Martin, -99 (219)</td>
<td>88/88</td>
<td>74/26</td>
<td>100</td>
<td>NA</td>
<td>83/5=94%</td>
<td>NA</td>
<td>1y: 62% (5)</td>
</tr>
<tr>
<td>Golladde, -99 (212)</td>
<td>74/74</td>
<td>58/42</td>
<td>100</td>
<td>1 cm, (0.1-10)</td>
<td>55/19=74%</td>
<td>67/74=91%</td>
<td>1y success</td>
</tr>
<tr>
<td>Karc, -00 (220)</td>
<td>85/112 (lesions)</td>
<td>59/36, (5% graft prophylaxia)</td>
<td>100</td>
<td>&lt;2 cm: 72% *</td>
<td>2-5 cm: 20% *</td>
<td>5-10 cm: 8% *</td>
<td>104/8=93%</td>
</tr>
<tr>
<td>Clark, -01 (221)</td>
<td>205/219</td>
<td>58/37, (5% *)</td>
<td>83</td>
<td>3.8 cm *</td>
<td>4.7 cm †</td>
<td>172/24=79%</td>
<td>11 technical failures</td>
</tr>
</tbody>
</table>

Note: SEE = standard error of the estimate; NA = not available; y = year(s); * = stenosis; † = occlusion; m = month(s); ° = not specified
The use of stents in iliac arteries have resulted in better initial success and long-term-results (224, 225). In the femoropopliteal region, highly variable 1-year primary patency rates between 22% and 81% with various stents have been reported (99, 101, 102, 226, 227). In three randomised studies, although the primary success rate of stent placement was higher than that after balloon angioplasty alone, the long-term patency was not improved by using stents (228-230). A recently published meta-analysis revealed similar patency rates after balloon dilation and stent implantation (222). The authors of the largest randomised study with 154 treated limbs summarised that the beneficial effect of stents is to rescue PTA failures (229).

The clinical experience of stent-grafts in atherosclerotic femoral artery disease is still very limited. In earlier studies a high incidence of complications, perivascular inflammatory reactions and early thrombosis, were major problems (231, 232). Five of the 14 (36%) successfully treated femoropopliteal arteries with PTFE covered stent-graft occluded within the first month. Collapse of the unsupported section of the graft was seen in one patient and graft kinking in another. The twelve month primary patency rate was 29% and the secondary patency rate 64% (124). A recent study with 80 treated femoral arteries, using PTFE covered stent-graft, reported promising results with primary patency rates of 90% and 79% at 6 and 12 months (125). On the other hand, in a study with a smaller patient population (18 patients), the primary patency rate at 6 months was only 49% (122). The non-supported stent grafts are also used to re-line the affected segments. The feasibility of this method has been shown but the major
draw-back is the absence of support along the graft with a high risk of kinking and thrombosis (233-236).

2.4.2. Infrapopliteal PTA in chronic critical limb ischemia

Experience about infrapopliteal PTA is still very limited. Since the complications of tibial angioplasty can have potentially dire consequences, the use of tibial angioplasty has been reserved mainly for limb salvage situations (237-239). Only a minority of studies have advocated distal PTA for use in patients with moderate to severe claudication to increase the effectiveness and durability of femoropopliteal PTA (240-242).

The quality and sophistication of the equipment, especially the introduction of small-vessel catheters and hydrophilic guide wires, have improved the technical results also in this arterial field (237, 241, 243, 244). Technical developments, such as DSA with road mapping also have improved the efficacy of infrapopliteal PTA.

In many reports of infrapopliteal PTA claudicants and failing or failed bypass grafts are included, although these remain a minority in the outcome analysis (238-240, 243, 245-250). The arterial disease in patients with chronic critical limb ischemia is usually diffuse and multilevel (251, 252). In many studies also lesions above the knee have been included (241, 243, 253-255) and patients referred to the endovascular intervention are often poor surgical candidates (243). These facts complicate the comparison of the results between various studies as well as the comparison of PTA results with those of surgical bypasses.
Technical success rates up to 97%, primary clinical success 51% to 95%, and limb salvage rates up to 87% for infrapopliteal PTA in limb salvage indications, with low complication rates, have been reported in literature (242-244, 246, 247, 253, 255-260). Only a few studies define the primary clinical patency rates with objective criteria and these are very variable, ranging from 46% to 81% (244, 250, 255, 261).

Most of the studies about infrapopliteal PTA in chronic critical limb ischemia patients are feasibility studies and the effect of different risk factors on outcome has not been properly determined. The importance of establishing straight-line flow to the foot was emphasised in one study, with 97% (28/29) of patients experiencing a prompt clinical improvement if angioplasty restored the straight-line flow to the foot, in contrast to 36% (4/11) if this was not achieved. Angioplasty yielded a response only in about one third of limbs in the presence of obstruction distal to the dilation site. Restoring straight-line flow via any of the infrapopliteal arteries appeared sufficient to achieve a clinical response (243). The importance of single-vessel continuous runoff to the foot was also noted by one author, in the analysis of infrapopliteal study including also bypass procedures (42% [23/55]) (248). In a retrospective analysis, PTA of isolated crural limb artery stenoses was proposed to be an efficient therapeutic modality for limb salvage (258). The type of lesion has some impact. Recanalization of occlusions appeared to be less successful than dilation of stenoses (237, 242). The importance of clinical symptoms and type of the treated lesion was emphasised in one study with 37 treated limbs: for patients with isolated stenoses and rest pain the primary patency at 1 year was 82%, in contrast to
66% for pre-occlusive lesions and gangrene or ischemic ulcer (244). On the other hand, in another study the presence of diabetes, type of the lesion or the number of patent crural arteries after successful PTA did not adversely affect the clinical results (255).
3. AIMS OF THE PRESENT STUDY

1. To evaluate the angiographic patterns of restenosis after infrainguinal PTA.

2. To determine the effectiveness of prolonged balloon inflation for improving the unsatisfactory primary result of femoropopliteal PTA.

3. To determine the influence of prolonged balloon inflation on the long-term results of femoropopliteal PTA.

4. To determine the utility of infrapopliteal PTA on chronic limb ischemia.

5. To examine the relationship of angiographic restenosis and the clinical manifestation of lower limb ischemia after infrapopliteal PTA.
4. MATERIALS AND METHODS

4.1. Patient population

The study population consists of three prospective trials conducted between October 1989 and December 1999 in Kuopio University Hospital. Altogether 425 patients with 510 limbs treated with infrainguinal PTA were included. Two hundred and fifty seven of the 425 patients (60%) were claudicants and 168 (40%) suffered from chronic critical limb ischemia. Demographic data of the study population and the locations and types of the treated infrainguinal lesions are given in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Patients and PTAs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic parameters of the patients, n=425</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>- men</td>
</tr>
<tr>
<td>- women</td>
</tr>
<tr>
<td>Associated diseases</td>
</tr>
<tr>
<td>- coronary artery disease</td>
</tr>
<tr>
<td>- hypertension</td>
</tr>
<tr>
<td>- cerebrovascular diseases</td>
</tr>
<tr>
<td>- diabetes</td>
</tr>
<tr>
<td>Smoking history</td>
</tr>
<tr>
<td>- current or ex-smoker</td>
</tr>
<tr>
<td>- never smoked</td>
</tr>
</tbody>
</table>

Lesions, n=934

Note: Numbers in parentheses are percentages.
The first of these three studies was performed during 1989-1992. Because of clinically suspected recurrent disease, a control angiography was performed on 52 patients (61 limbs) out of the 263 patients (Study I). Unless mentioned, all data in the following sections refer to the two subsequent trials. During the period May 1995 to December 1997 ninety-seven patients with femoropopliteal artery PTA was performed on 112 limbs (femoropopliteal study, Studies II and III). Ninety-three of these patients suffered from intermittent claudication, and four had chronic critical limb ischemia. From April 1996 to April 1997, infrapopliteal PTA was performed for 65 consecutive patients, suffering from chronic critical limb ischemia (infrapopliteal study, Study IV). Five of the infrapopliteal PTA procedures, performed during evening or weekends because of chronic critical limb ischemia were excluded because the angiographic and/or clinical documentation did not fulfill the criteria of the infrapopliteal study. Thus the final study material documented procedures on 72 limbs of 60 patients. Complementary femoropoplital PTA was performed on 32 patients.

All claudicant patients had undergone an exercise program for at least 6 months, before the decision to undergo invasive treatment. The treatment decision for the patients was made in a meeting of vascular surgeons and interventional radiologists. The main principle for patient selection for femoropopliteal PTA was that angioplasty was used as a primary invasive treatment for lesions shorter than 10 cm. Longer femoropopliteal lesions were treated surgically unless there were co-morbidities that contraindicated surgical treatment. Infrapopliteal PTA for patients with chronic critical limb ischemia was used as the primary treatment modality in all situations in which the
interventional radiologist considered that it was possible to reconstruct at least one artery to the level of the distal third of the calf. None of these patients had undergone prior PTA or surgical operations of lower limb arteries. An earlier study from our institution was used as a reference study for study III (211).

4.2. Patient investigations before PTA

The initial evaluation of the patients included medical history and physical examination performed by a vascular surgeon. The ankle brachial index was also measured during exercise (a treadmill exercise test with ankle pressure measurements) from claudicant patients. Ankle brachial indexes at rest were not routinely measured in patients with chronic critical limb ischemia. Prior outpatient-tailored intra-arterial DSA of the aorta and run-off vessels was always performed. The following clinical chemical parameters were routinely registered before PTA: plasma hemoglobin, hematocrit, platelet count, partial thromboplastin time, prothrombin time and serum creatinine. Other clinical chemical parameters such as plasma fibrinogen, serum antithrombin-III, serum cholesterol, serum high-density lipoprotein cholesterol and serum triglycerides were not routinely registered in patients with chronic critical limb ischemia. Basic clotting parameters and serum creatinine were always available before the PTA procedure. Just before the angioplasty, duplex ultrasound (US) evaluation was performed proximal and distal to the femoropopliteal stenosis or occlusion. Peak velocity values were registered and the velocity waveform was assessed. If the planned procedure was solely infrapopliteal, duplex US evaluation was not routinely performed.
4.3. Target arteries and follow-up angiographies

The target arteries and PTA-procedures of 184 infrainguinal PTAs (Studies II, III and IV) are shown in Table 4. Mean age of patients with femoropopliteal PTA was 70 years (range, 45-88 years) and those with infrapopliteal PTA had an average age of 72 years (range, 38-92).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Femoropopliteal study</th>
<th>Infrapopliteal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of treated limbs</td>
<td>112</td>
<td>72</td>
</tr>
<tr>
<td>Type of the treated femoropopliteal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- stenosis</td>
<td>74</td>
<td>22</td>
</tr>
<tr>
<td>- occlusion</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Type of the treated infrapopliteal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- stenosis</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>- occlusion</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Mean total length of the treated segments</td>
<td>7.2 cm (range 0.5-31)</td>
<td>7.7 cm (range 1-40)</td>
</tr>
<tr>
<td>Angiographic success (technical success) on limb basis</td>
<td>82/112=73.2 %</td>
<td>32/72=44 %</td>
</tr>
<tr>
<td>Peripheral runoff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no patent calf vessel</td>
<td>Pre PTA 36</td>
<td>Post PTA 17</td>
</tr>
<tr>
<td>- one patent calf vessel</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>- (2-3) patent calf vessels</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Duration of balloon inflation</td>
<td>Pre PTA 36</td>
<td>Post PTA 17</td>
</tr>
<tr>
<td>- standard (1 to 3 minutes)</td>
<td>19</td>
<td>72</td>
</tr>
<tr>
<td>- prolonged (&gt; 3 minutes)</td>
<td>93</td>
<td>0</td>
</tr>
</tbody>
</table>
In study I, follow-up angiographies of the 61 limbs of clinically suspected restenosis revealed 75 recurrent lesions in 57 limbs. Four limbs showed development of a new lesion despite no restenosis at the angioplasty site. In seven limbs with recurrent disease, the atherosclerotic changes had also progressed outside the treatment area. The mean time from the primary procedure to control angiography was 14 months (range 1-60 months).

During the follow-up period of the infrapopliteal study (Study IV), after infrapopliteal angioplasty for chronic critical limb ischemia, the follow-up angiography was performed on 61% of treated limbs with 118 treated lesions. Eight patients (with nine limbs) refused follow-up DSA, only three of these patients were clinical failures with unhealed ulcers. The follow-up angiography was not possible for 12 limbs, because of major amputation performed early as a result of lack of primary clinical success and for seven limbs because of the death of the patient. Mean time from the primary infrapopliteal PTA to follow-up angiography was 10 months (range 1-18 months).

4.4. PTA procedure

The angiographic laboratory was equipped with digital fluoroscopy, and “road mapping” was available (Multistar; Siemens, Erlangen, Germany). Selective angiography was performed using an antegrade approach through the ipsilateral common femoral artery. Comparison with the prior diagnostic angiography was performed to check for possible changes. The introducer sheaths ranged from 5 to 7 French (F). A 5-F introducer sheath was used in 16 of the 72 infrapopliteal procedures (=22%). In the case of stent placement a 7-F
introducer sheath was utilised. The balloon catheter was chosen to match the diameter of the nondiseased artery adjacent to the lesion and the balloon length was chosen to match the length of the lesion.

In the femoropopliteal procedures, the size of the balloon catheter and the assessment of the initial result were determined by IVUS with a 3.5-F, 30-MHz catheter (Sonos Intravascular; Hewlett Packard, Andover, MA / Sonicath CV, Mansfield / Boston Scientific, Watertown, MA) whenever possible. Balloon dilation was performed by increasing gradually the atmospheric pressure by one unit every 15-30 seconds up to 8 atmosphere (ATM), or higher, until no indentation was visible on the balloon (Opta; Cordis Europe, Oosteinde, Netherlands). A three-step dilation protocol was performed. First, a standard 1-3 minutes dilation was performed, if the primary result was considered inadequate (residual diameter stenosis exceeded 30% or if a dissection causing compromise of blood flow was detected in the angiography or by IVUS), the procedure was continued with a prolonged, up to 30 minutes dilation with the use of the initial conventional balloon catheter. The third step, if the result still remained unsatisfactory, was a longer additional dilation performed with a specially designed perfusion balloon catheter (Smash; Schneider Europe, Bulach, Switzerland) of the same diameter as the initial balloon catheter. In the perfusion balloon catheter proximal to the balloon, the shaft of the catheter contains six side holes, with a diameter of 0.035 inch, opening into an eccentrically situated guide wire channel. The side holes provide blood flow through the guide wire channel during inflation while the guide wire is removed. The catheter was tested in an experimental circulation model designed to
simulate peripheral angioplasty (262). During balloon inflation, a continuous slow drip of heparinized saline (1000 units of heparin in 500mL of saline) was infused into the proximal guide wire channel. Pressure was maintained at 4-6 ATM during the inflations. For inflations lasting longer than 1 hour, the patient was returned to his / her own bed. The severity of the lesion, stenosis or occlusion, was taken into account while considering the length of dilation: longer dilations were performed in total occlusions. Especially, long inflations were performed for extensive, long dissections. Also the ability of a patient to lie on the angiography table for longer times was taken into account.

Balloon inflation procedures of 1-3 minutes’ duration and 8-18 ATM pressure were performed in infrapopliteal PTA. The basic goal of infrapopliteal PTA was to reconstitute the patency of all three infrapopliteal arteries as long as possible whenever some angiographic filling of the peripheral portions of the particular artery was seen in selective contrast media injections.

Aftercare of the patients took place in the department of vascular surgery, and the patients were routinely discharged on the day after the PTA procedure.

4.5. Patient medication

Patients routinely received 250 mg acetylsalicylic acid on the day of the procedure and continued to take the same daily dose. A prophylactic dose of nifedipine (10 mg) by mouth was given 5-10 minutes before angioplasty. At the beginning, 5000 units of heparin was given intra-arterially and additional doses of 2500 units, if the procedure was lengthy, were administered to maintain activated clotting time (ACT) (Hemocron; International Technidyne, Edison, NJ)
over 220 seconds during the intervention (total dose did not exceed 10 000 units in any patient). Thrombolytic therapy was not routinely used in the treatment of arterial occlusions. Boluses of intra-arterial nitroglycerin (250 µg) were administered especially when infra-popliteal lesions were treated. After the procedure, low molecular weight heparin injections (dalteparin, 200 units / body weight / day) or 24 hour heparin infusions were used because of multisegemental or long-segment procedures, especially if the PTA result was unsatisfactory (major flow limiting dissection). Ticlopidine medication was initiated on the day of the procedure when infrainguinal lesions were treated by using a stent and the drug treatment was continued for up to one month (250 mg twice a day for one week and then 250 mg daily). Long-term anticoagulant therapy was not routinely used.

4.6. Patient follow-up

For the patients in the femoropopliteal study (Studies II and III), the duplex US examination was repeated at discharge proximal and distal to the femoral angioplasty site and comparisons between pre and post PTA peak velocity values and waveforms were made to evaluate the immediate hemodynamic success. The groin was checked for possible hematomas and pseudoaneurysms with US imaging. Patients were followed-up at 1, 3 and 6 months, and yearly thereafter. The treadmill exercise test with ankle pressure measurements was performed on every visit for the patients with femoropopliteal PTA. Follow-up angiography was performed because of symptomatic, clinically suspected recurrent disease.
The patients of the infrapopliteal study (Study IV) were scheduled for visit to a vascular surgeon twelve months after the angioplasty for evaluation of the clinical condition of the treated leg according to Rutherford-Becker classification (263). During follow-up, these patients and their primary care physicians were advised to contact a vascular surgeon if critical ischemia reappeared. Follow-up angiography was also scheduled for this visit unless it had not been performed earlier because of a clinical recurrence of critical ischemia. The patients with chronic critical limb ischemia with infrapopliteal PTA performed were followed up for 12-24 months.

4.7. Analysis of the films

For all of the angiographies, type of the lesion (stenosis or occlusion), morphology of stenoses (eccentric, concentric or mixed) and calcification of the lesion (heavily calcified, moderately calcified or noncalcified) were registered. Stenosis quantitation (percent diameter stenosis) was performed with a digital micrometer on a conventional viewbox from pre-and post-PTA angiographies as well as from follow-up angiographies. Lesion length was measured with the use of an external x-ray positive ruler. The number of arteries that were stenosed less than 50% and reached the malleolar level were calculated in each treated limb (peripheral runoff range, 0-3) (264).

In the analysis of films of patients with recurrent disease after infrainguinal PTA, the localisation of the lesions (in the proximal, middle, or distal portion of the superficial femoral artery, popliteal artery, and infrapopliteal arteries) was based on anatomic landmarks and external radiopaque ruler (Study I). Analysis
of the angiographic data of these patients was performed on a “per lesion” basis.

Quantification of geometric diameter stenosis before femoropopliteal PTA, after a standard dilation, and after a prolonged dilation was also performed with use of DSA software supplied by the manufacturer (Siemens, Erlangen, Germany) when the impact of dilation time was studied (Studies II and III).

Analysis of the angiographies before and after infrapopliteal angioplasty as well as side by side comparison with the follow-up angiography at one year were performed (Study IV). Status of the pedal vessels (dorsal pedal and common plantar) was classified on a three-point scale: direct filling, filling through collaterals, and no filling (265). The improvement in the angiographic filling of arteries (no filling versus direct antegrade or collateral filling) at the anatomic site of the most severe ischemia was assessed from post angioplasty angiography. If rest ischemia was the manifestation of the ischemia, the improvement in the filling of pedal arteries was regarded as fulfilling the criterion.
4.7.1. Repeatability of film reading

A sample of 30 randomly selected postinterventional films were independently analysed by two experienced interventional radiologists on a conventional viewbox without knowledge of the clinical result of the intervention. The interreader agreement for the angiographic result assessed by Kappa coefficient was good (Kappa = 0.72 ). The final analysis of all angiographies (pre-PTA, post-PTA, and follow-up) was performed by one reader blinded to the clinical result of the intervention.

4.8. Criteria for classifying procedure outcome

Angioplasty was regarded as angiographically successful (technical success) if the measured residual diameter stenosis of the treated lesion was less than 30% of the reference vessel diameter at angiography after balloon angioplasty. Prolonged balloon inflation was classified as definitely useful if the diameter stenosis improved by at least 20%, compared with that after the standard balloon inflation (Study II). For infrapopliteal angioplasty in patients with chronic critical limb ischemia, the angiographic outcome was also classified as successful on a “limb basis” if at least one continuous crural artery with less than 30% residual stenosis reached the malleolar level after PTA. The angiographic patency was defined on the basis of the lesion (Study IV).

Major complications were defined as those that prolonged the hospital stay, affected treatment substantially and adversely, or necessitated surgical intervention. Amputation below or above the knee was defined as a major amputation, and a toe amputation was defined as a minor amputation.
Determination of the primary hemodynamic success of femoropopliteal PTA was based on duplex US on the day after PTA. Doppler velocity waveforms were classified into three categories: normal (diastolic backflow present), no diastolic backflow, no flow (264). Hemodynamic success was defined as an improvement in the category of the Doppler velocity waveform or at least doubling of the peak velocity in the popliteal artery distal to the site of angioplasty (211, 266). The overall death rate during the follow-up period and 30-day mortality were registered.

Primary patency (final result of the original angioplasty) and secondary patency (including repeated PTAs) were determined by means of the original criteria of Rutherford and Becker (263) using the ankle-brachial index (i.e., the treated artery segment was patent if the ankle-brachial index at rest increased by more than 0.10 initially and did not deteriorate by more than 0.15 from the maximum early postprocedural level). The patency rates were also calculated by using updated criteria of Rutherford (267) (i.e. the ankle-brachial index is not more than 0.10 below the highest postprocedural index). When the follow-up angiography was performed, the patency was based on it. The treated artery segment was classified as angiographically patent if the visually estimated percent diameter stenosis was less than 50%.

The clinical response in patients with chronic critical limb ischemic was defined as successful (i.e., primary clinical success was achieved) if the Rutherford-Becker category of the limb improved by at least one grade (264). After infrapopliteal PTA in patients with chronic critical limb ischemia, primary clinical patency (result of the original angioplasty) and secondary clinical
patency (taking into account repeat PTA) were determined by the duration of
the achieved clinical response. Limb salvage was defined as avoidance of
major amputation.

4.9. Statistical analysis

The differences between pre- and postinterventional continuous variables were
tested with Student’s t-test for paired observations. Univariate logistic
regression analyses for continuous variables and the Pearson chi-square test
for discrete variables were employed to analyze the determinants of primary
angiographic success, primary hemodynamic success, patency at follow-up
angiography and the primary clinical success of the intervention. The Kaplan-
Meier method was used to calculate the cumulative patency rate, cumulative
clinical patency rate and the cumulative limb salvage rate versus time of follow-
up for individual variables and subgroups, and the statistical difference between
survival curves was determined by means of the log rank test (Mantel-Cox).
Variables that reached statistical significance (p<0.05) were used as covariates
in the stepwise Cox proportional hazards model (Cox multiple regression
analysis) or multiple logistic regression analysis. The level of significance for
inclusion in multiple regression analyses was less than 0.10, and the level of
significance for removal from the model was greater than 0.15.
4.10. Approval of the Ethics Committee

The study was approved by the Ethics Committee of Kuopio University Hospital (March 1995).
5. RESULTS

5.1. Angiographic patterns of restenosis (Study I)

An angiographically confirmed recurrent disease after symptomatic recurrence of infrainguinal PTA was more frequently a stenosis when the original target lesion was a stenosis (92%, 44 / 48) than when the original lesion was a total occlusion (59%, 16 / 27) (p<0.001). When the original target lesion was a stenosis, the total length of the recurrent lesion was longer than that of the original lesion [3.9 ± 3.9 cm (mean ± standard deviation) vs 2.8 ± 2.7cm; p=0.03]. Half of the restenoses (22 / 44) extended beyond one or both ends of the original stenosis i.e., extended to the previously angiographically disease-free arterial segment. The stenoses that developed in recurrent stenotic disease were significantly shorter than the stenoses that were encountered after total occlusions (2.5 ± 2.4 cm vs 6.5 ± 2.6 cm; p=0.05). When the original target lesion was an occlusion, the length of the recurrent lesion was shorter than that of the original occlusion (7.1 ± 5.0 cm vs 9.9 ± 6.9 cm; p=0.02). This difference was especially notable in the group of lesions that developed recurrent stenotic disease (p=0.006), while the reocclusions were practically the same length as the original occlusion (p=0.81) (Figure 1). The recurrent stenoses (6 / 16) seemed to be slightly clustered at the lower part of the originally occluded segment.
5.2. Results of femoropopliteal PTA (Studies II and III)

5.2.1. Primary hemodynamic success

On the day after angioplasty, 92.9% (104 / 112) of the interventions were hemodynamically successful. In stepwise multiple logistic regression analysis, only the type of lesion proved to be an independent determinant of primary hemodynamic success. When the lesion was a stenosis, the primary hemodynamic success was better than when it was an occlusion (p=0.01, odds ratio 16.47 [95% confidence interval [CI] 1.93-139.2]).
5.2.2. Long-term patency

The cumulative primary and secondary patency rates versus time of follow-up calculated with the Kaplan-Meier method for all the 112 treated limbs are shown in Figure 2. The primary patency rate was 42% ± 5%, (± standard error of the estimate, SEE) at 1 year, 39% ± 5% at 2 years and 39% ± 5% at 3 years. The secondary patency rate was 51% ± 5% (SEE) at 1 year and 47% ± 5% at 2 and 3 years. The only independent predictor in stepwise Cox multiple regression analysis for poorer long-term patency was if lesions in the infrapopliteal or iliac artery of the limb were also treated (Table 5).

![Graph showing cumulative primary and secondary patency rates versus time](image)

**Figure 2.**
Results of Kaplan-Meier analysis for the primary and secondary patency rates for 112 femoropopliteal PTAs. Standard error of the estimate at all time points < 0.05. Numbers indicate number of cases remaining as a function of time since angioplasty. Initial failures are included.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Additional treated lesions</th>
<th>Kaplan-Meier, Primary patency rate (%)</th>
<th>Cox multiple regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoropopliteal</td>
<td>- yes</td>
<td>28% (0.07)</td>
<td>23% (0.08)</td>
</tr>
<tr>
<td></td>
<td>- no</td>
<td>55% (0.06)</td>
<td>54% (0.06)</td>
</tr>
<tr>
<td>Infrapopliteal</td>
<td>Serum creatinine</td>
<td>&lt;=130 μmol/L</td>
<td>55% (0.07)</td>
</tr>
<tr>
<td></td>
<td>- &gt;130 μmol/L</td>
<td>24% (0.10)</td>
<td>24% (0.10)</td>
</tr>
<tr>
<td></td>
<td>Angiographic improvement of the ischemic area</td>
<td>- yes</td>
<td>62% (0.07)</td>
</tr>
<tr>
<td></td>
<td>- no</td>
<td>8% (0.07)</td>
<td></td>
</tr>
</tbody>
</table>

Note: * Numbers in parentheses are standard errors of the estimate. ** Numbers in brackets are 95% confidence intervals.
5.2.3. Impact of prolonged dilation

Among the 112 femoropopliteal interventions, standard dilation (1 to 3 minutes) was utilised in 19 procedures with a mean inflation time of 1.8 minutes (range 1 to 3 minutes) and prolonged dilation in 93 procedures with the mean inflation time of 31 minutes (4 to 180 minutes). Among the 93 procedures, the perfusion balloon catheter was utilised in 35 procedures with the mean inflation time of 75 minutes (range 30-180 minutes). The proportion of total occlusions was larger in the prolonged dilation group than in the standard dilation group (41% vs 14%, p=0.03). Angiographic analysis of 39 lesions with unsatisfactory result after standard dilation showed definitive improvement in 37 (95%) of the lesions after prolonged dilation. The mean residual diameter stenosis at DSA decreased from 49% to 27%. The only target-related factor that proved to be of some importance on primary angiographic result was calcification of the lesion; the response of noncalcified lesions to prolonged inflations was slightly poorer (p=0.08).

A subgroup analysis of the 59 interventions composed of only femoropopliteal balloon angioplasty was performed. In this subgroup the primary hemodynamic success was 98% (58 / 59). The dilation time did not correlate with the primary hemodynamic success. Long term patency, calculated by the Kaplan-Meier method, was tested with different cut off points according to the dilation time: 3 minutes, 5 minutes, 10 minutes and 15 minutes. No statistically significant differences were found between the groups. The primary patency rate was 58% ± 10% (SEE) in the subgroup of procedures with less than ten minutes dilation time (n=28) and 56% ± 9% in the subgroup with
longer than ten minutes dilation (n=31) (p=0.98) at 1, 2 and 3 years. These subgroups did not differ statistically significantly in terms of the tested demographic variables (gender, diabetes, coronary disease), peripheral run-off, the primary angiographic result, lesion morphology, the number of diseased vessels in the treated limb, or the mean length of the treated lesion.

5.3. Infraopliteal PTA (Study IV)

5.3.1. Primary angiographic and clinical success

The primary angiographic success rate for PTA of stenoses was 84% (102 / 121) and that of occlusions 61% (41 / 67). The angiographic filling (either direct or through collaterals) in the arteries at the anatomic site of the most severe ischemia was improved in 78% (56 / 72) of the treated limbs. The only factor that correlated statistically significantly with primary angiographic success was the type of treated lesion; the primary result of PTA was better when the treated lesion was a stenosis (p<0.001).

A primary clinical success rate of 63% (45 / 72) was achieved in these treated limbs. Fifty percent (36 / 72) of the limbs recovered to be asymptomatic or the patient suffered only from claudication after the primary PTA procedure. In stepwise multiple logistic regression analysis, renal insufficiency (serum creatinine >130 µmol/L) (p=0.002, odds ratio 10.3, 95% CI 2.11-44.5) and lack of improvement in the angiographic filling at the most ischemic area (p=0.0009, odds ratio 14.1, 95% CI 2.97-66.7) proved to be independent predictors of poorer primary clinical success.
5.3.2. Angiographic patency and long-term clinical success

The overall angiographic patency (primary failures included) was 47% (56 / 118). Excluding the primary failures, the angiographic restenosis rate was 32% (20 / 63) for stenoses and 52% (14 / 27) for total occlusions, yielding an overall restenosis rate of 38% (34 / 90). Eight de novo infrapopliteal and two femoral artery stenoses (>50%) were registered at follow-up angiography. The length of the successfully treated segment correlated negatively with the angiographic patency (p=0.004).

The primary clinical patency rate was 48% ± 6% (SEE) at 12 and at 18 months. The secondary clinical patency rate was 56% ± 6% (SEE) at 12 and at 18 months. By excluding the primary clinical failures, the primary and secondary clinical patency rates at 18 months were 76% ± 7% (SEE) and 90% ± 5%, respectively. Elevated serum creatinine (>130 μmol/L) and lack of angiographic improvement in the arterial filling at the most ischemic area at DSA immediately after PTA proved to be significant determinants for poorer clinical patency in Cox multiple regression analysis (Table 5). The cumulative limb salvage rate at 12 and 21 months assessed by the Kaplan-Meier method for the treated limbs was 80% ± 5% (SEE). Elevated serum creatinine (>130 μmol/L) and lack of angiographic improvement in the filling at the most ischemic area proved to be independent determinants for poorer limb salvage rate in Cox multiple regression analysis (corresponding odds ratios 2.95 [95% CI 0.91-9.54] and 7.37 [95% CI 2.17-25.0]).
Of the 53 patients still living 1 year after the primary PTA, there were 46 ambulatory persons living in their own homes, the other seven patients were bedridden. At the same time, 32 of the 60 treated patients (=53%) had not undergone major amputation, and either had no symptoms or only suffered claudication of the treated limb.

5.3.3. Angiographic restenosis versus clinical manifestation of chronic lower limb ischemia

The clinical result for limbs in which the infrapopliteal status at the follow-up angiography was unchanged from the immediate postinterventional status (no restenotic lesions exceeding 50%) did not differ statistically significantly from that for limbs with a worsened status (p=0.10). As can be seen in Figure 3, a

![Figure 3](image)

Figure 3. Preservation of achieved clinical patency after infrapopliteal PTA according to the presence of angiographic restenosis. Group 1: no restenosis at follow-up angiography. Group 2: restenosis at follow-up angiography. Note: primary clinical success rate = 80% (35/44).
continued clinical patency was registered at the time of the follow-up angiography in two thirds of the limbs with a primary clinical success even though there was evidence of angiographic restenosis.

5.4. Clinical events during follow-up

The clinical events during the follow-up for femoropopliteal and infrapopliteal PTAs are shown in Table 6. Two adjunctive surgical procedures were performed: one endarterectomy of the common femoral artery to improve inflow, and one femoro-femoral cross-over bypass operation because of an occluded iliac stent. One patient died because of septicemia 5 days after infrapopliteal PTA.

**Table 6. Clinical events during follow-up after infrainguinal PTA.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Femoropopliteal study</th>
<th>Infrapopliteal study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs, n</td>
<td>112</td>
<td>72</td>
</tr>
<tr>
<td>Mean follow-up time, months</td>
<td>22 (range 1-47)</td>
<td>10 (range 5-24)</td>
</tr>
<tr>
<td>Re-PTAs, n</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>- mean time from primary PTA, months</td>
<td>18 (range 3-39)</td>
<td>4 (range 1-6)</td>
</tr>
<tr>
<td>Surgical bypass operations, n</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>- femoropopliteal</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>- femorodistal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Amputations, n</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>- major</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>- minor</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>30-day mortality, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death rate during follow-up, %</td>
<td>16</td>
<td>25</td>
</tr>
</tbody>
</table>
5.5. Complications

During the 214 endovascular interventions (repeated PTAs included) on the 184 limbs, there were five major specific local vascular complications that required treatment. One infrapopliteal embolization, without tissue loss, after balloon angioplasty of a femoropopliteal stenosis required intra-arterial thrombolytic therapy (Urokinase 500 000 units). One growing hematoma of the groin required surgical operation immediately after angioplasty. One access site pseudoaneurysm required surgical treatment and two access site pseudoaneurysms were successfully treated with US-guided compression. The rate of major specific local vascular complications was 2.3% (5 / 214). Four minor specific local vascular complications occurred: four puncture site hematomas that did not require any treatment. Hence, the overall complication rate was 4.2% (9 / 214).
6. DISCUSSION

6.1. Recurrent disease after infrainguinal PTA

The finding of the present study confirms previous reports that symptomatic recurrence is mainly due to the restenotic process at the angioplasty site, in only 6.6% of the limbs a new lesion was responsible for the recurrence of symptoms (19, 20, 268). In a study of femoropopliteal artery angioplasty, the symptomatic recurrence was mainly caused by the restenotic process as the influence of new lesions in other areas is only minimal (20). Similar observations were also reported by other investigators, who found the rate of recurrent disease after femoropopliteal angioplasty to be approximately 2.5 times the rate of new lesions (19). Further, in the present study the type of primary target lesion predicted the type of recurrent disease. Also, an analysis based on duplex scanning stressed the importance of the type of the original lesion; occluded lesions were more likely to restenose after lower limb artery PTA (269).

A clear tendency for stenosis recurrence in the distal half of the treated segment rather than in the proximal part was noted after treatment of femoropopliteal occlusions (20). This tendency was not so evident in the present study. Also in another analysis of mainly femoropopliteal stenoses only a few of the recurrent lesions were peripheral from the initial lesion; the lesions were mainly located in the centre (87). A similar result was reported in a study of lower limb balloon angioplasty for chronic critical limb ischemia (270). In the present study half of the restenoses extended to the previously disease-free arterial segment, beyond one or both ends of the original lesion. After coronary
angioplasty, the restenotic lesions also tended to be longer than the original stenoses (271). One possible explanation is that there is endothelial injury at these “shoulder” areas, induced by balloon inflation, since in areas outside the original lesions, angiographic progression was detected in only 18% of the limbs. One could also argue that occlusive lesions at the shoulder areas are mainly caused by progression of atherosclerosis. Due to adaptive remodelling, there may be remarkable atherosclerotic plaques that are angiographically occult already at the time of the primary intervention. Thus, after the compensatory capacity is fully utilised, the angiographic progression of the disease can be rapid.

6.2. Role of prolonged balloon dilation

Postprocedural residual stenosis has been found to be predictive of restenosis in coronary angioplasty studies (6, 272, 273). Also after femoropopliteal angioplasty, the presence of residual stenosis worsened the prognosis (214). In the present study prolonged balloon dilation improved the unsatisfactory primary result of femoropopliteal artery angioplasty; the same initial improvement was demonstrated in an earlier published coronary angioplasty study (198). The primary hemodynamic success in the present study was also high, nearly 100%. Contrary to expectations this dilation strategy did not result in superior long-term results. However, the long-term results of the present study, primary patency of 42% at one year and 39% at 2 and 3 years, are very similar to those of the reference study that utilised standard dilation strategy on femoropopliteal angioplasty. In the reference study, primary patency
rates of 47% at 1 year and 42% at 2 and 3 years were achieved (211). Studies on coronary angioplasty also implied that although prolonged dilation resulted in a high procedural success, the restenosis rate is similar to that reported in large studies of patients treated with standard angioplasty (202, 203).

The reason for the unfavourable long-term result may be elastic recoil, that occurs after the completion of angiography, even though the initial result is acceptable (24). Placement of a stent has been shown to induce more severe vascular wall damage than balloon angioplasty and as a consequence myointimal hyperplasia is more pronounced (274). Hence, another possible explanation is that prolonged balloon inflation causes more severe vessel wall damage than standard dilation, and stimulates the restenotic process.

The present study does not give an answer to what is the optimal balloon inflation strategy. Since prolonged dilation improves effectively the acute angiographic finding in cases of unacceptable result after 1-3 minutes dilation, an additional dilation with the conventional balloon up to 30 minutes seems warranted, especially in lesions that are poor candidates for stent placement. The usefulness of longer dilations with the perfusion balloon catheter seems questionable because of practical reasons, it is fatiguing for patients to lie still for long times and this strategy requires excessive time in busy daily practice.
6.3. Determinants of long-term patency

The long-term clinical success and limb salvage rate (80% at one year) observed in the present study in patients with chronic critical limb ischemia are comparable with those reported by others (244, 246, 250, 255, 257, 258, 261). Furthermore, in surgical series, the reported limb salvage rates are also comparable with the present study varying from 81% to 87% (275-277). In a multicenter trial consisting of over 500 femorodistal bypass operations, 46% of the patients were alive, had not undergone major amputation, and had no symptoms or only claudication 12 months after the procedure (278), the corresponding figure in the present study being 53%. It is to be noted that, although, in the present study the patients with chronic critical limb ischemia had a very extensive infrapopliteal disease, the primary clinical success was almost the same as that reported after bypass operations (278). Furthermore, it is to be emphasised that no surgical bypass operations were performed on any of the limbs after PTA. Partly, the patients were regarded as poor surgical candidates because of their advanced age and poor general condition, partly because of the poor condition of their peripheral arteries. On the other hand, percutaneous procedures do not appear to compromise surgical revascularization (279-281).

Renal insufficiency proved to be an independent risk factor for poor clinical result of the infrapopliteal PTA. Clinical success was achieved in fewer than one in every four of the patients with elevated serum creatinine. The importance of uraemia has been discussed also by some other investigators (282, 283). End stage renal disease (ESRD) was found to be the most important predictor of
repeat target lesion revascularization after coronary angioplasty comparing patients with and without ESRD. Target lesion revascularization was twice as frequent in the ESRD group compared with the control group during the 9-month follow-up period (35% vs 16%, p<0.05) (284). The outcome of dialysis patients is very poor after infrainguinal bypass grafting (285). Renal failure was also observed to be a statistically significant risk factor for loss of patency after femoropopliteal angioplasty in an univariate analysis (221). The reason for the degrading effect of uraemia remains largely obscure, but these patients may have inherent difficulties with healing and an increased rate of infection as a result of impaired host resistance.

The importance of good peripheral runoff on the long-term success of femoropopliteal artery PTA has been stressed by many investigators (211, 215, 221). However, in the present study the peripheral runoff proved not to be a statistically significant determinant. The restoration of straight-line flow to the foot in patients with critical limb ischemia has also been found to be important for clinical improvement (243) and limbs with at least one patent calf vessel had a better salvage rate than those where there was no patent vessel reaching the ankle (286). The importance for a good clinical result by reconstituting vascular circulation in patients with chronic critical limb ischemia is also confirmed by the finding of the present study that improved angiographic filling (either direct antegrade or through the collaterals) in the arteries at the site of the most severe ischemia (e.g., an ulcer) predicted better primary and long-term success. Actually, improving arterial filling at the most ischemic area, even through collaterals, seems to be adequate.
Treatment of additional infrapopliteal sites to improve outflow after femoropopliteal artery PTA of claudicants did not predict a better long-term result. In fact those cases were associated with a poorer result that probably reflects the more diffuse and extensive nature of atherosclerosis on these patients. It is notable, however, that the peripheral runoff improved remarkably owing to the 34 adjunctive infrapopliteal PTAs. Before PTA 32% (36 / 112) of the of the limbs had no patent infrapopliteal vessel, while after PTA this proportion was only in 15% (17 / 112). The use of infrapopliteal PTA in patients with claudication is controversial, some of the studies have recommended this approach (240, 245, 249) while others are negatively inclined or recommend the use of infrapopliteal PTA only in carefully selected cases because of the potential of catastrophic complications (238, 239, 242). Overall, the results of the present study do not support the contention that active treatment of stenotic lesions of the outflow tract in claudicants would be beneficial in terms of the long-term result. The same conclusion was made by the authors of a recently published review article (287).

6.4. Complications

The complication rate was very low (the rate of major complications 2.3%), the complications being mainly at the access site. After infrainguinal PTA, the reported rates of major complications vary from 2.4% to 6.3% (209, 211, 214-217). Two distal embolizations were encountered after femoropopliteal PTA of 140 limbs in our reference study (211) while in the present study only one embolization was encountered in 112 procedures. Thus, prolonged dilation
strategy did not result in an increased number of peripheral embolizations. According to published PTA reports, complications have been encountered more often in patients with critical limb ischemia (215, 288). This tendency was not noted in the present study. Even after infrapopliteal PTA, no peripheral distal embolizations were encountered.

The 30-day mortality was 0.5%. The reported perioperative mortality rates after infrainguinal surgical bypass operations vary greatly; from 0 to 7.4% (276, 280, 289-291). Actually, patients with chronic critical limb ischemia suffer numerous, usually cardiovascular co-morbidities that may contribute to the incidence of perioperative complications (276, 292). Due to the less invasive nature of percutaneous procedures, angioplasty offers an attractive treatment option in this kind of patient population, also, taking into account the clearly shorter hospital stay after the procedure (208).

6.5. Discrepancy of clinical and angiographic restenosis

The angiographic restenosis rate of 38% in the present study after successful infrapopliteal angioplasty is very well comparable with the results obtained by balloon angioplasty of coronary arteries (3, 5). The result compares favourably with a previously published study, consisting of iliac, femoropopliteal and infrapopliteal lesions in patients with chronic critical limb ischemia, where there was an angiographic restenosis rate of 55% (16/29) (270). The aim of the present study was to obtain a follow-up angiography of all patients on whom infrapopliteal PTA was performed because of chronic critical limb ischemia, but
13% of them refused to undergo the procedure and, thus, the angiographic patency may suffer from a selection bias.

The continued clinical patency was registered in two-thirds of the limbs with a primary clinical success and angiographic restenosis in patients with chronic critical limb ischemia treated with infrapopliteal PTA. This phenomenon has also been reported by others. Partial or complete healing obtained in 14 patients with ulceration was maintained at 6 months in 11 patients despite the fact that eight of them had significant restenosis at the angioplasty site (270). Similar results have been obtained after femorodistal bypass operations; 13% of limbs with occluded bypasses showed improvements in clinical symptoms and 35% had avoided amputation at 12 months (278). One possible explanation is that a period of improved blood supply may be sufficient to allow the healing of a trophic lesion which could account for the long-term success despite the occlusion of the graft, or PTA site. Furthermore, balloon angioplasty may provide the time needed for the development of a collateral circulation (293, 294). Overall, it seems that although primary clinical success correlates closely with the state of revascularization achieved by the intervention (improvement in the arterial filling at the site of the most severe ischemia), maintenance of clinical patency is less dependent on the duration of this angiographic result.
7. SUMMARY AND CONCLUSIONS

The purpose of the present study was to clarify the problem of restenosis in symptomatic recurrence after infrainguinal angioplasty, to seek means to diminish the restenosis after femoropopliteal artery PTA, and to assess utility of infrapopliteal PTA as a primary treatment of chronic critical limb ischemia, as well as to determine the primary angiographic patency and to evaluate the importance of angiographic status on the clinical results of infrapopliteal artery PTA.

The present study confirms the finding that restenosis after a symptomatic recurrence is prone to develop at the angioplasty site. This study emphasises the significance of the type of the original lesion on the type of restenotic lesion and, also, indicates that the restenoses after treatment of stenosis extends to the previously disease-free arterial segment. The study highlights the limited role of prolonged balloon dilation strategy as this strategy failed to improve the long-term results, although, the primary result of femoropopliteal artery PTA was improved by this procedure. Finally, the study underlines the use of infrapopliteal angioplasty as a primary invasive treatment option in patients with chronic critical limb ischemia, even those with extensively diseased infrapopliteal arteries. It is important to appreciate that the achieved clinical patency was preserved despite restenosis at the angioplasty site.
On the basis of the present study, the following conclusions can be drawn:

1. The recurrent disease after balloon angioplasty of infrainguinal stenosis extends frequently beyond one or both ends of the original target lesion, and the type of recurrent disease depends on the original lesion type.

2. Prolonged dilation is a feasible and effective method for improving an unsatisfactory primary result of femoropopliteal artery PTA.

3. The routine use of prolonged dilation is not warranted since this strategy does not result in superior long-term patency rates of femoropopliteal artery PTA. In cases if there is an unacceptable result after 1-3 minutes’ dilation, an additional dilation with the conventional balloon up to 30 minutes seems warranted, especially in lesions that are poor candidates for stent placement.

4. Infraopliteal PTA is a feasible primary treatment for chronic critical lower limb ischemia with moderate primary angiographic and clinical success, a low complication rate, and a high cumulative limb salvage rate. On the other hand, active treatment of infrapopliteal arteries of claudicant patients does not seem to be justified, because it does not improve the long-term results of femoropopliteal artery PTA.

5. The angiographic restenosis rate of infrapopliteal arteries is high; 32% for stenoses and 52% for total occlusions, yielding an overall restenosis rate of
38%. Despite the presence of angiographic restenosis after infrapopliteal PTA in patients with chronic critical limb ischemia, the achieved clinical patency is preserved in most cases.
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APPENDIX: ORIGINAL PUBLICATIONS