# Surveillance of infrainguinal autologous vein bypasses

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PROEFSCHRIFT

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*Aan: mijn ouders*
*Shantie en Danisha*

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*Chapter* **1**

# Preface

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# Aims of the study

## PREFACE

Femorodistal bypass operations are performed increasingly for the treatment of lower limb ischemia. Introduction of fine suture materials and instrumentation, methods that preserve better the intimal layer of venous grafts, and the use of the in situ technique have contributed to the application of surgical lower limb revascularization in many patients with extensive occlusive disease. Despite an acceptable success rate, 20% to 30% of these grafts develop stenotic lesions in the first postoperative year. It is now generally accepted that these stenoses, because of intimal hyperplasia, are the predominant cause of graft failure.

In 1987 color-flow duplex scanning was introduced in the Surgical Department of the Catharina Hospital Eindhoven as a method to visualize peripheral arteries. In earlier studies using gray-scale duplex it was demonstrated that identification of vein graft stenosis was possible and detection and correction of these lesions was successful in preventing graft failure. Color-duplex scanning had not been used for this application before, when in 1989 the results of a pilot study about surveillance using color-flow duplex for the detection of stenosis in femorodistal grafts were published by the Catharina Vascular Surgical group[1]. Color-duplex appeared to offer several advantages over gray-scale duplex scanning, including improved expediency in performing the examination. The results of a larger retrospective study which started after publication of this first study is presented in chapter three (retrospective part). Although this was a retrospective study the preoperative work-up, the operative procedures, the postoperative duplex examinations (follow-up schedule, technique of color-flow Doppler imaging, sample volume placement and Doppler-angle), the use of the different parameters and patient record keeping were strictly standardized and constant during the study period. Specific questions concerning vein graft surveillance, which still existed following the retrospective part were investigated and described in the prospective part of this thesis.

The prospective part of this study was supported by a Grant from the Commission of Investigative Medicine of the Dutch National Health Insurance Council. This study was performed in three vascular centers with experience in infrainguinal vein graft surveillance (Academic Hospital Maastricht, Catharina Ziekenhuis Eindhoven and St. Antonius Ziekenhuis Nieuwegein). The results of this prospective study are presented in chapters four to seven. Chapter two reviews the literature on various aspects of vein graft surveillance as were known in the literature at the time prior to the final analysis of this study.

**Aims of the study**

At the start of the prospective study in 1993 several subjects for further investigation were defined, on the basis of the retrospective work that had been performed before that time. The questions, that were addressed, in the prospective part of this thesis include:

1. What is the role of clinical and graft factors on the development of vein graft stenosis, and their significance for clinical management?
2. How is the diagnostic accuracy of several surveillance parameters in comparison with angiography?
3. Can non-invasive duplex surveillance parameters be used as revision criteria and so substitute the commonly used angiographic revision criterium?
4. Is the first postoperative duplex examination a reliable criterium to categorize grafts into high and low-risk groups for the development of a vein graft stenosis during follow-up?
5. Is there a pattern in the time of onset of graft stenosis during follow-up that allows adoption of an optimal duplex surveillance program?

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*Chapter* **2**

# Postoperative infrainguinal bypass graft surveillance

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## Introduction

Autologous vein bypass grafting is considered the best infrainguinal reconstruction for alleviating symptoms of lower limb ischemia. However, there is a high incidence of graft occlusions resulting in patency rates of 30% to 75% at five years.[1-4] While approximately 10% of grafts fail within the first months, most commonly because of operative technical errors, it has long been assumed that most failures were due to progression of atherosclerosis within the inflow and run-off vessels, and that little could be done to influence this natural course. In the recent years, however, it has become apparent that loss of a bypass because of progression of atherosclerosis tends to occur several years after the procedure and that atherosclerosis can not be considered the most frequent cause of graft occlusion. After the early postoperative period stenotic lesions in the graft and the anastomotic areas are the main cause of graft failure in the first five years after the operation, with 65% to 75% occurring within the first postoperative year.[5] Stenotic lesions are most frequently caused by myointimal hyperplasia, a phenomenon of which the correlation with vein graft occlusion was recognized already in 1973 by Szilagyi.[6] Nevertheless, it was only at the end of the 1980s that the clinical significance of stenosis development in vein grafts and anastomotic areas were confirmed, because of a more general use of postoperative examination by non-invasive techniques.[7,8] The pathogenesis of myointimal hyperplasia in vein grafts is essentially unknown, although several factors have been associated with its occurrence, such as smoking, a high fibrinogen concentration, the presence of anticardiolipin antibodies, preexisting fibrosis in the vein graft, and vein graft flow conditions.[9-12] In addition intraluminal instrumentation may promote myointimal hyperplasia because of endothelial desquamation, subsequent platelet deposition and release of platelet-derived growth factor.[13]

## The rationale for vein graft surveillance

Reconstitution of patency in vein grafts after complete occlusion by thrombectomy or thrombolysis results in a disappointing long-term patency of 20% to 28%. It is generally accepted that the follow-up of patients with infrainguinal vein grafts should be directed towards the identification of failing grafts.[14,15] At this stage relatively minor procedures can often avert impending graft failure. It has been shown that secondary patency of electively revised grafts is comparable with the primary patency in bypasses without stenoses.[8] Only 1/3 of hemodynamically significant graft stenoses can be diagnosed by the return of ischemic symptoms or decreased pulses at physical examination.[16,17] In contrast it has been shown that periodic surveillance using intravenous digital subtraction angiography (iv DSA) or non-invasive methods, such as ankle brachial pressure index (ABI) measurements or duplex scanning, are effective in

identifying graft stenoses. Using these methods stenotic lesions have been found in 25% to 30% of vein grafts with the majority identified in the first year.[6,7,16,18-20]

Which bypasses should be systematically followed? There is no significant difference between the incidence of myointimal hyperplasia or valve site fibrosis in in-situ, non-reversed translocated, reversed and arm-vein grafts.[21-23] Although intima hyperplasia in prosthetic bypasses is frequently observed, especially at the site of distal anastomoses, regular non-invasive examination has not been demonstrated successful in recognizing failing grafts. Occlusions without identifiable stenosis are far more frequent with this type of conduit. Moreover, prosthetic graft attrition is an ongoing process, continuing after the first two years. Several reports now have observed this distinction between vein and prosthetic grafts and have concluded that the application of serial non-invasive examination is far less useful in the latter category.[24,25] The fact that in the United States the Health Care Administration has been reluctant to reimburse for ongoing surveillance of synthetic grafts, whereas it will reimburse for vein graft surveillance, tends to support this conclusion.[26]

Repair of vein graft stenoses has been performed successfully for more than two decades.[27,28] Patch plasty, excision with direct repair, and implantation of jump grafts at the anastomotic sides are the most common operative methods for revision. The results of PTA seem less durable than those of surgical revision, as combined recurrence and failure rates of 33% to 50% were seen.[29-33] Especially when lesions are longer than 1 cm poor results can be expected. It should be considered that myointimal hyperplasia occasionally causes a very diffusely diseased graft, which may be impossible to salvage by a revision.

Correction of high-grade stenotic lesions may improve long-term graft patency rates by approximately 15%.[16,19] Moreover, it was demonstrated that the probability of graft occlusion in patients followed by an intensive surveillance program using serial duplex examinations was less than one-third of that in patients with conventional follow-up.[34] For these reasons in recent years surveillance programs of femorodistal vein grafts using non-invasive methods have been started in many institutions.

**Which surveillance method is best?**

Ankle brachial index (ABI) measurement has been extensively used as an indicator of significant stenosis in grafts and adjacent inflow and run-off arteries.[18,35,36] An interval drop of the resting ABI for identifying impending graft failure has been investigated at different threshold values. Respective decreases of 0.20, 0.15, and 0.10 were evaluated.[17,37-42] However, irrespective the criterion used, the narrow diagnostic range of the ABI appeared a severe limitation for the identification of graft stenoses. For example, values less than 0.15 are within the biologic and measurement variations, while values greater than 0.20 are more often associated with an occluded graft than

with a failing bypass. Moreover, several investigators have found that in 50% to 80% of cases significant stenoses were missed by serial determination of ABI, and one may conclude that ABI measurements do not provide an accurate indicator.[37,38] Some studies have suggested that ABI combined with ankle pressure measurements postexercise and at reactive hyperemia following cuff occlusion might be able to improve the diagnostic sensitivity.[43] A draw-back of these stress tests is a low sensitivity and the fact that they can not be applied in all patients.[37]

Despite its limited diagnostic value in detecting stenotic lesions ankle blood pressure measurements will probably remain part of the follow-up examination. Several investigators use ABI to supplement a duplex surveillance protocol; grafts with evidence of stenoses are being followed at short intervals until a drop in ABI develops.[41,42,44] It has been suggested that frequent serial ABI determinations might result a better yield of stenosis detection than the figures noted above.[25,45]

The usefulness of duplex scanning for methodical follow-up of infrainguinal vein grafts has been recognized and several comparative studies demonstrated that duplex scanning is superior to standard follow-up methods to detect graft stenosis.[7,17,19,40,46] More over, moderate graft stenosis may also be diagnosed and its progression followed to allow timely intervention. The introduction of color-flow duplex systems implied a significant reduction in examination time, compared to the use of conventional gray-scale duplex equipment. The entire graft can be traced quickly and stenotic segments can readily be identified by locally increased peak velocities, and poststenotic turbulence characterized by a color-coded random flow pattern. Quantitative pulsed Doppler velocity measurements can be performed as in conventional duplex scanning.

Preliminary results of echo-enhanced Doppler and duplex imaging with ultrasound contrast agents and power-Doppler in native lower limb artery disease have shown that these may improve the quality of the ultrasound scans.[47-50] The value of these modalities with duplex scanning of infrainguinal vein grafts has to be investigated in greater detail before their ultimate role can be defined.

Non-duplex based surveillance methods, such as impedance measurements have been used for graft surveillance.[51] These methods do not seem to offer a significant advantage over color-flow duplex scanning. Magnetic resonance angiography in its present form is extremely reliable in depicting vascular detail. This method may well replace angiography as a confirmative study in the diagnosis of graft lesions, however, the involved costs makes this method less appropriate for serial use.

**Which duplex criteria should be used and which grafts should be repaired?**

For the identification of failing grafts or stenotic lesions low-velocity and high-velocity duplex criteria can be discriminated. The former criterion only requires measurement of the peak systolic velocity (PSV) at a fixed point at mid-graft level (PSV-graft). This

parameter was particularly easy to determine with gray-scale duplex scanning and most commonly a value of 45 cm/s and lower is considered to indicate the graft at risk. It has been observed however, that this criterion had a low sensitivity for focal lesions and that low PSV-graft values frequently were caused by run-off or inflow disease.[52-54] In contrast the specificity of the PSV-graft was found to be high. If low velocity criteria are used this is usually in combination with high velocity criteria in order to enhance the diagnostic accuracy of the tests.[55,56] At present the most common method of color-flow duplex includes tracing of the entire graft, the identification of sites with flow disturbance and measurement of the PSV at the stenosis. Absolute PSV-values as well as the ratio of the PSV at the stenosis and a normal adjacent arterial segment (PSV-ratio) are used. Threshold values for the PSV-ratio vary in the literature from 1.5 to 3.0.[7,19,22,23,42,53] Another indicator of stenosis is increase of the end-diastolic-velocity (EDV) to greater than 20 cm/s. At present it is not certain which duplex-derived parameter and which value is most accurate to identify grafts at risk for occlusion. Reports about the criterion for graft revision varies. Some authors revise a graft-stenosis when it exceeds 50% DR, while others intervene in stenosis with a DR greater than 70%.[25,57-60]

Not all stenotic lesions require revision. The incidence of bypass occlusions in patients with stenoses ranges from 13% to 100%, depending on the degree of stenosis and the length of follow-up.[34,42] It has been observed that stenoses detected early after the operation tended to progress to occlusions more frequently than stenoses detected after 3 months.[42,61] Stenoses that are identified after 3 months represent more slowly progressing lesions and stenoses identified after 1 year imposed the smallest risk of occlusion.[42,60,62,63]

**Current issues**

The accuracy of duplex scanning is of prime importance in reporting results of surveillance. Many publications lack a detailed account of the sensitivity and specificity of the used parameters in comparison with angiographic bypass studies. It is likely that there are significant differences in the measurements of velocities between different observers as well as between different duplex scanners.[64]

When a high-grade stenosis is detected it still is common practice to perform a confirmary angiography before intervention. Avoiding confirmary angiograms during follow-up is advantageous because it precludes delay of the revisional procedure and it reduce the overall cost of graft surveillance. The criteria to be used have to be defined and its effectiveness have to be analyzed.

When should a duplex surveillance program start, how long should it be continued, and at what frequency should examinations be performed? It is likely that the development of stenoses in all cases begins at the time of surgery and that stenoses

reaching the threshold of diagnosis within the early postoperative period are associated with the highest failure rate. It has been suggested that the first duplex scanning can best be performed at the completion of the operation or before discharge as these examinations prompted early revision in approximately 15% of patients and unrepaired duplex abnormalities required later correction in 32% to 52%.[22,65] On the other hand Passman *et al.*[59] found a poor correlation between the initial duplex scan findings and the subsequent development of a graft stenosis during follow-up.

The vast majority of graft lesions develops within the first twelve months and most authors therefore agree that postdischarge surveillance tests are best performed at 6 weeks and then at the 3rd, 6th, 9th and 12th month.[66] Mohan and Corson propose vigorous surveillance for 6 months, while some other investigators prefer indefinite continuation of the assessments at 6 monthly intervals.[67-69]

Is the use of resources for graft surveillance justified from the sake of limb salvage? Recently this issue was addressed in a review of the literature by Golledge *et al.*, who compared the outcomes in surveillance and non-surveillance vein graft groups.[70] These authors concluded that despite a higher graft patency, surveillance failed to improve the limb salvage rate. One could argue that this study, which was not a formal meta-analysis and considered together claudicants and critical limb ischemia patients, with as a consequence low rates of amputation (12% to 13%), did not allow a proper assessment of the influence of graft surveillance on limb salvage. Moreover, the costs of limb loss for the community are quite high and it has been suggested that if limb loss could be prevented in only 2% of patients a duplex surveillance program would already be cost-effective.[66] A better cost-effectiveness from surveillance may also be considered if the quality of life is compared of patients with relief of claudication because of patent bypass grafts and of patients with intermittent claudication from occluded grafts. Claudication is associated with a considerably impaired quality of life and the expenses to prevent recurrence of this disability may well be justified.[71,72] Nevertheless, formal cost-effectiveness comparisons of surveillance studies will have to be performed.

In 1992 the ad hoc committee on clinical research recommended a randomized trial comparing the results in patients with intensive surveillance combined with intervention for lesions and patients without interventions.[73] At this time such a randomized trial would probably be considered unethical on the basis of the currently existing knowledge regarding the benefits of graft surveillance. The only published randomized study had started in 1988 and was published in 1995.[25] Although, this was a rather small study there was a significantly better patency rate in vein grafts in the intensive surveillance group compared to patients with a conventional follow-up schedule.

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*Chapter* **3**

# Impact of a color-flow duplex surveillance program on infrainguinal vein graft patency. A five-year experience

*Idu MM, Blankensteijn JD, de Gier P, Truyen E, Buth J. Impact of a color-flow duplex surveillance program on infrainguinal vein graft patency. A five-year experience. J Vasc Surg 1993;17:42-53.*

## INTRODUCTION

One reason for follow-up of patients with infrainguinal bypass procedures is to identify failing vein grafts because stenotic lesions develop relatively frequently in these grafts and their anastomotic areas.[1,2] Because the long-term patency rates of grafts after thrombectomy and thrombolysis ranges from 19 to 28%, treatment of a failing graft by use of a relatively minor revision is considered advantageous.[3,4] Because most stenotic graft lesions consist of myointimal hyperplasia and because most are frequently diagnosed within the first 12 to 18 months, a practical surveillance program should concentrate on this initial period. Progression of atherosclerosis in inflow or outflow segments may be the cause of graft failure after longer follow-up periods.[5] The ability of duplex scanning and more recently color-flow duplex scanning compared with conventional clinical follow-up examination, including ankle pressure measurements, to identify developing preocclusive lesions has lead several investigators to recommend serial duplex or color-flow duplex examinations as the surveillance method of choice.[3,6-12] However, several questions with respect to the application of these advanced screening techniques have remained unanswered. The natural course of stenotic lesions has not been completely clarified in that the proportion of untreated stenoses that become occluded is unknown.[13] Do all stenoses require revision or is a selective repair more advisable? Are revision procedures more frequently performed when advanced surveillance techniques are used? Finally, do the patency rates of vein grafts that undergo a comprehensive surveillance program that may result in timely revision improve significantly compared with the patency rates of vein grafts that undergo conventional follow-up?

In this report we detail our experience with the use of color-flow duplex in the follow-up of infrainguinal vein grafts obtained during a 5 year period. Development of stenotic lesions, progression to occlusion (whether or not a secondary intervention has been performed), and the rates of restenosis were the subject of this study. In addition, the contribution of color-flow duplex surveillance to graft patency relative to other factors was evaluated with use of a multivariate analysis.

## PATIENTS AND METHODS

Two hundred one autologous vein bypass grafts of the infrainguinal arteries were studied; 13 instances of graft occlusion at 30 days after the operation, were not considered for analysis. The operations were performed between September 1986 and May 1991, although the follow-up of this study ended at December 1991. The procedures were carried out in 187 patients, of which 129 (69%) were men and 58 (31%) were women. Diabetes mellitus was present in 48 (26%) of all patients. Limb-

threatening ischemia was the indication for the bypass procedure in 128 (64%) cases: 53 procedures were performed for tissue necrosis and 75 for rest pain. Incapacitating claudication was the preoperative symptom in 68 patients (34%) and popliteal aneurysm in five (2%). Forty procedures were repeat operations in which a previous revascularization to the popliteal or crural arteries in the same limb had been performed.

Follow-up of 160 grafts included color-flow duplex scanning every 3 months during the first postoperative year and every 6 months during the second year. Postoperative review in 41 grafts comprised only conventional clinical follow-up (i.e. the recording of symptoms, peripheral pulse assessment and the determination of the ankle blood pressure index [ABI]). These patients visited the outpatient clinic at similar intervals; color-flow duplex was not used at any time during follow-up. The first category of graft recipients was the "color-flow surveillance group" and the second the "clinical follow-up group". Follow-up examinations were performed either by a senior vascular surgeon or by a vascular surgical fellow under supervision by the senior surgeon. The follow-up protocols in these two patient categories were uneven because some members of the vascular surgical group adhered to an established follow-up scheme and relied on clinical parameters during the first period of this study. The vascular surgical group was organized so that the same vascular surgeon performed the initial examination and postoperative follow-up examinations on the same patient. However, the operation was performed by the surgeon who was on duty according to the patient's number on the waiting list. Thus the structure of the vascular practice accounted for sufficient randomization of operating surgeons between the two follow-up categories to preclude any bias from different operators. Therefore a comparison of the color-flow surveillance group with the clinical follow-up group seemed acceptable.

After the second year all patients were seen on a yearly basis in the outpatient clinic to record the patency status of the bypass graft with use of clinical assessment and ABI reading so that the necessity of additional intervention could be determined.

**Bypass procedures**

A variety of techniques were used to perform the bypass procedures. In situ saphenous vein grafts were used when the ipsilateral saphenous vein was available and suitable for use. Ectopic veins were either reversed or non-reversed depending on the vein taper and the optimal size match between vein grafts and inflow and recipient arteries. Small distal or fibrotic segments were replaced by extension or interposition with a segment of arm-vein or greater or smaller saphenous vein. Sites of origin for the bypasses comprised the common femoral in 127 (63%), the superficial femoral artery in 40 (20%), the deep femoral artery in 8 (4%) and the popliteal arteries in 26 (13%) patients. The distal recipient arteries included the proximal popliteal in 17 patients

(8.5%), the distal popliteal in 75 (37%) and one of the crural arteries in 102 (54%). Although scientific proof of efficacy is lacking, postoperative anticoagulation by coumarin derivates was begun in all patients, in accord with traditional treatment in the Netherlands, and was continued until contra-indications occurred. Treatment was usually discontinued because of patient refusal to take this medication and not because of adverse effects or graft occlusion.

**Color-flow duplex examination**

Our technique of color-flow duplex examination has been described previously, and only a few points will be summarized.[12] For this study a Philips-Quantum I color-flow duplex scanner (Philips Medical Systems, Inc., Shelton, Conn.) was used. Moving red cells in the vessels generate Doppler shift frequencies. Direction and velocity dependent color-coded flow is displayed, with red for flow in one direction and blue for the reverse. The higher the Doppler shift frequency, the whiter the color is depicted. Stationary tissues are indicated in gray-scale, which provides a sharp delineation of the vessel wall when the color-flow image is superimposed. The graft was examined from the groin down the entire length to below the distal anastomosis and the first centimeters of the recipient artery. Color images were examined for the presence of biphasic flow, wall irregularities, stenotic decrease of color saturation and poststenotic turbulence (i.e., color bruits). After the graft was imaged, midstream pulsed Doppler velocity spectral signals were recorded from diseased and normal vessel segments. The following parameters were evaluated: (1) the percent diameter reduction (DR) measured by color-flow image at the stenosis and at a nearby normal graft segment, (2) the peak systolic velocity (PSV) at a normal mid-thigh graft segment, (3) the PSV-index (i.e., the ratio of the PSV at the normal mid-thigh graft and the maximum PSV at a stenotic lesion or, in normal grafts, at the narrowest point of the below-knee graft), and (4) the end-diastolic velocity (EDV). Values of the PSV-index in normal grafts approximate 1.00; lower values indicate a stenosis. In an earlier study from our institution it was demonstrated that a threshold value of 0.65 was a good discriminator of normal and stenotic bypass grafts.[12] The presence of a stenotic lesion is determined on the basis of these parameters, whereas its severity was estimated. Because the diagnostic value of these parameters was reported earlier[11] only PSV-index data will be analyzed in the present study.

**Angiography**

In a graft, in which a stenosis of 30% or greater or an occlusion was suspected on the basis of findings with color-flow duplex examination or on the basis of clinical criteria, intraarterial digital subtraction angiography (DSA) was requested. Accurate assessment of the diameter ratio of stenotic and normal graft sites was facilitated by multiple projections as well as magnified views. A run-off resistance score was

determined for all grafts in accord with the Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery.[14] Preoperative and intraoperative angiograms as well as postoperative DSA studies were reviewed for this purpose. The films that showed most detail of run-off and foot artery anatomy were used to assess the run-off resistance score.

**Data analysis**

Cumulative primary graft patency as defined by the Ad Hoc Committee on Reporting Standards was determined by the life table method.[14] In addition the assisted primary graft patency, in which the revision of a stenotic but open graft is not considered an endpoint of patency, was determined.[15] Group comparisons for statistical differences in graft patency were performed with use of the logrank test. The Fisher exact test was used for paired comparisons of discrete data in different groups. Comparison of continuous variables in groups was performed with the Mann-Whitney test. Univariate comparison of patency rates in groups with color-flow surveillance and clinical follow-up was performed for multiple risk factors and bypass characteristics. Twelve variables were selected because of significant group differences at univariate comparison or clinical relevance, and they were subjected to a multiple regression analysis with a Cox proportional hazard model to examine independent associations.[16] In this analysis the relative risk indicates the probability of graft occlusion; values greater than 1.0 indicate an increased risk and values between 0 and 1.0 indicate a decreased risk. Only when *p*-values are less than 0.05 did the relative risk have statistical significance.

## RESULTS

**Variables**

The median duration of follow-up until death, graft occlusion or the last visit to the outpatient clinic was 21 months (range 1 to 63 months). There were no marked differences between the patient groups that underwent color-flow surveillance and clinical follow-up with respect to sex, risk factors, ABI, run-off resistance score and graft characteristics (Table I). In patients who underwent color-flow surveillance the median age was 68 years (range 34 to 92), and in patients who underwent clinical follow-up the median age was 70 years (range 54 to 86).

**Table I.** Sex, risk factors and graft characteristics in groups with color-flow duplex surveillance and clinical follow-up.

| *Variable* | *No. with color-flow surveillance (%)* | *No.with clinical follow-up (%)* |
|---|---|---|
| Sex | | |
| Male | 102 (68) | 27 (73) |
| Female | 48 (32) | 10 (27) |
| Presenting symptoms | | |
| Tissue loss G or U | 44 (27) | 9 (22) |
| Rest pain | 59 (37) | 16 (39) |
| Claudication | 54 (34) | 14 (34) |
| Aneurysm | 3 (2) | 1 (2) |
| Associated diseases and risk factors | | |
| Diabetes mellitus | 42 (26) | 8 (19) |
| Hypertension | 46 (29) | 16 (39) |
| Smoking | 106 (68) | 30 (75) |
| Hypercholesterolemia | 43 (29) | 8 (22) |
| History of other vascular disease | 102 (63) | 28 (68) |
| Preoperative ABI <0.50 | 99 (64) | 20 (51) |
| SVS/ISCVS run-off score >2.0 | 119 (74) | 26 (63) |
| Graft | | |
| Previous ipsilateral infrainguinal recon. | 35 (22) | 5 (12) |
| Other than in situ vein graft | 61 (38) | 18 (44) |
| Popliteal proximal anastomosis | 10 ( 6) | 3 ( 7) |
| Crural distal anastomosis | 90 (56) | 19 (46) |
| Venovenous anastomosis | 26 (16) | 6 (15) |
| Size of graft <3.5 mm | 70 (44) | 8 (29) |

Percentage of sex relate to number of patients. Other percentages relate to number of grafts. G is gangrene; U is ulceration; SVS/ISCVS is Society for Vascular Surgery / International Society for Cardiovascular Surgery.

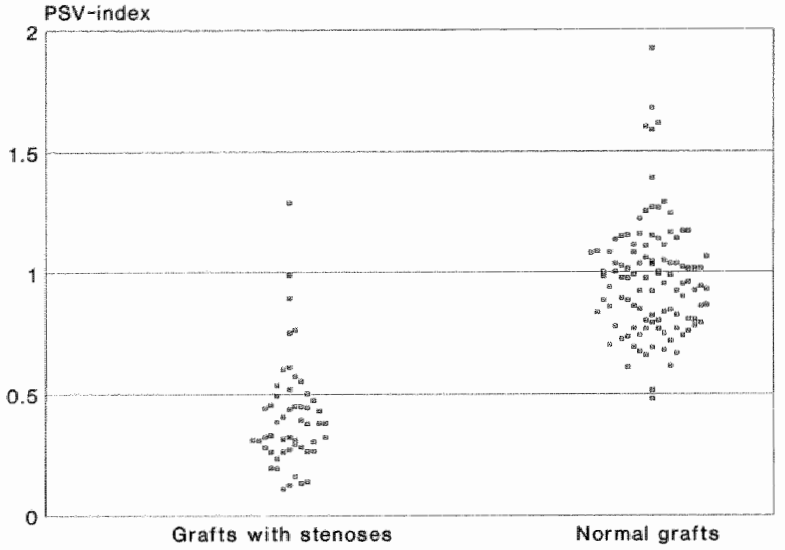
**Identification of stenoses**

During follow-up examination stenoses were identified in 58 (29%) vein grafts. Simultaneous stenoses of lesser severity remote from the principal stenosis were found in 14 grafts. For the purpose of this report only the principal stenosis was considered. Thirty-four of these stenoses were focal (stenosis length ≤2 cm), 15 were intermediate (stenosis length 2 to 4 cm) and 9 reflected a more diffuse diseased vein graft (stenosis length >4 cm). The location of the stenosis was in the inflow artery in 8 grafts, at the proximal anastomosis in 14, in the body of the graft above-knee in 18, and below-knee in 12, at the distal anastomosis in 4, and within the first centimeters of the run-off vessels in 2 grafts. The time of first occurrence was within the first 3 months in 12 grafts, between 3 and 6 months in 16, from 6 to 12 months in 21, between 12 and 18 in 2, and after 18 months in 7 grafts. The latest occurrence was 34 months after the bypass procedure.

The incidence of graft stenoses in the color-flow surveillance group was 32% (52 grafts), which was higher than the incidence of graft stenoses in the clinical follow-up group. In this latter group stenotic lesions were diagnosed in three grafts (7%) before occlusion ($p$ <0.001). In three additional grafts in the group that underwent clinical follow-up, a stenosis was identified after thrombolysis.

Return of clinical symptoms, decrease of ABI, and the level of the PSV-index were correlated with the presence of graft stenoses. Clinical symptoms identified only 19 (33%) of the grafts with stenotic lesions. In 17 grafts (8%) reliable ankle pressure measurements were not possible due to incompressible crural vessels. No adequate ankle pressure data at different points of follow-up were available in 8 other patients. The ABI was a poor indicator of stenoses. A significant drop (>0.15) in ABI between early postoperative measurements and values at the time of stenosis identification or at the last follow-up was observed in only 19 (38%) grafts with a stenotic lesion, whereas normal grafts were associated with a change in ABI of less than 0.16 in 110 (87%). The PSV-index provided a good discrimination between stenotic and normal bypasses (Figure 1). Values lower than 0.65 were associated with stenotic lesions in 47 (90%), whereas higher values indicated a normal graft in 104 (96%). We conclude that symptoms and a change in ABI are poor indicators of stenoses, whereas the PSV-index is a highly accurate discriminator.

**Figure 1.** Correlation of PSV-index in vein grafts with and without graft stenosis. Mean PSV-index is 0.41 ± 0.22 (SD) for stenotic grafts and 0.97 ± 0.24 (SD) for normal grafts, $p$ <0.001.




**Treatment of stenoses**

Forty of the 58 grafts with stenoses underwent repeat intervention. Vein patch angioplasty was used in 22 grafts, balloon dilatation was used in 11, segmental graft replacement was used in 6, and a Simpson atherotome (Devices for Vascular Intervention, Inc., Redwood City, Calif.) was used to remove a thickened valve cusp in 1 graft. The reason that reintervention was not performed in 18 grafts was the patients refusal of additional procedures in 3 cases, graft occlusion when waiting for admission in 4, and doctor choice in 11 cases. In this latter category eight stenoses had less than 50% DR. In grafts that underwent color-flow surveillance 34 (21%) repeat interventions were performed compared with three (7%) revisions on a patent graft in the group with clinical follow-up ($p$ = 0.03). In this latter category three additional grafts were treated by thrombolytic therapy followed by a revisional procedure.

The incidence of permanent graft occlusions relative to the diameter reduction as classified by intraarterial DSA and relative to whether or not a repeat graft intervention had been performed is represented in Table II. No repeat procedures were performed in grafts with 30% to 49% DR, and no graft failures were observed in this group. Grafts with stenoses of 50% to 69% occluded more often if no revision was performed. For grafts with greater than 69% stenosis the difference in occlusion rate between revised and non-revised lesions is highly significant. There were no differences between grafts

with different degrees of stenosis when a repeat procedure had been performed. In the non-revised bypasses the occlusion rate was higher in lesions of 50% or greater DR compared with 30% to 49% DR.

A third intervention for graft stenoses was required in 10 (25%) bypass grafts; eight grafts were for recurrent stenoses, and two were for new lesions at sites in remote from the earlier lesion. More than two revisions were performed in three bypass grafts, with a maximum of five repeat reinterventions in one graft. There was no correlation between the incidence of recurrent stenoses and a specific type of revision of the initial lesion.

**Table II.** Stenotic grafts and incidence of graft occlusions relative to diameter reduction and graft revision.

| *Stenoses group* | *No. of revised occlusions/grafts (%)* | *No. of not revised occlusions/grafts (%)* | *Fisher exact test p-value* |
|---|---|---|---|
| group 1 (30% to 49% DR) | -/- (-) | -/8 (-) | *NS* |
| group 2 (50% to 69% DR) | 1/11 (9) | 4/7 (57) | 0.047 |
| group 3 (70% to 99% DR) | 3/29 (10) | 3/3 (100) | 0.004 |

In revised grafts there were no significant group differences in the frequency of occlusions. In grafts not revised the difference was significant between groups 1 and 3 (Fisher exact $p = 0.006$) and between groups 1 and 2 (Fisher exact $p = 0.02$), but not between groups 2 and 3. *NS*, Not significant.

**Long term results**

Primary and assisted primary patency rates relative to the type of follow-up, (i.e. for grafts that underwent color-flow surveillance and grafts that underwent clinical follow-up) are shown in life table format in Figures 2 and 3 and Table III. Color-flow surveillance is associated with a primary patency that is not different from that in grafts that underwent clinical follow-up. In contrast, in grafts that underwent color-flow surveillance the assisted primary patency is significantly higher than in grafts that underwent clinical follow-up (91% and 72% at 3 years, respectively).

The limb salvage rate was assessed for both follow-up groups. At 5 years the cumulative limb salvage rate was 99% in the color-flow surveillance group compared with 92% in grafts in the clinical follow-up group. This difference was significant at a $p$-value of 0.004. The high overall salvage rate of 97% can be explained by the fact that first month graft failures were not taken into account.

To account for any simultaneous effects of variables reported to influence late patency in the total series after vein grafting, 12 selected variables were subjected to assisted primary patency analysis, logrank analysis, and risk estimate from Cox analysis. Improved assisted primary patency was strongly related to color-flow surveillance as an independent variable (Table IV). The relative risk was 0.27, which means that the risk of occlusion for a graft monitored with color-flow duplex scanning is estimated less than one-third of that for grafts that undergo clinical follow-up. There were no interactions between the other covariates in the model. No other factors had a significant influence on the risk of graft failure. We conclude that the yield of stenosis detection with serial color-flow duplex screening resulted in an optimal use of repeat interventions, whereas use of clinical parameters ultimately resulted in a higher percentage of graft thrombosis because stenotic lesions are missed.

**Figure 2.** Cumulative primary patency rates in grafts that undergo color-flow (CF) surveillance and in grafts that undergo clinical (CL) follow-up.

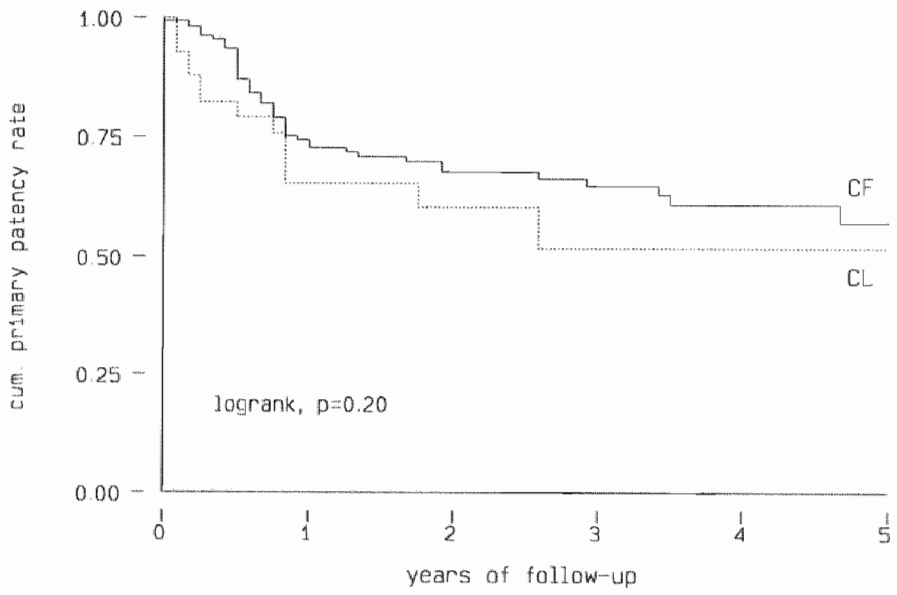
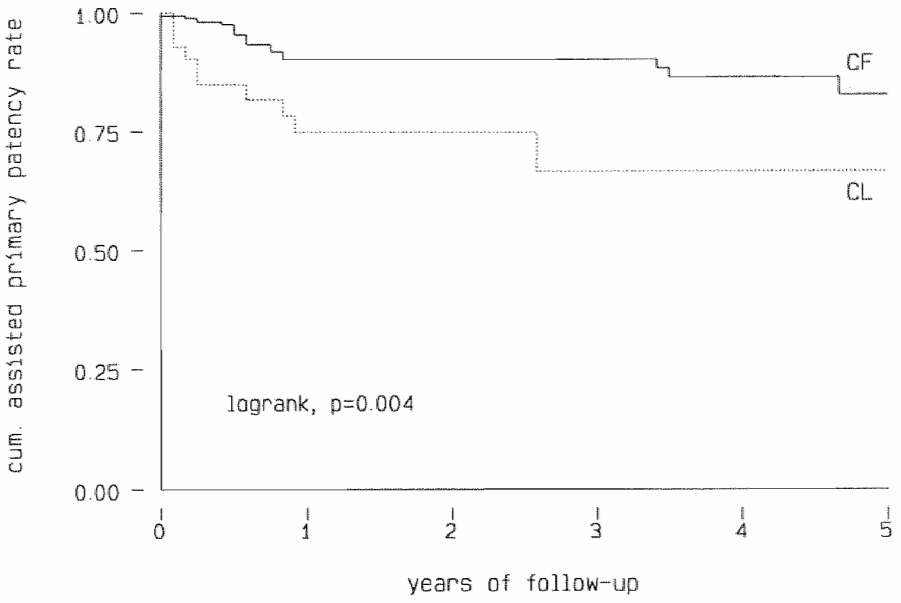


**Figure 3.** Cumulative assisted primary patency rates in grafts that undergo color-flow (CF) surveillance and in grafts that undergo clinical (CL) follow-up.




## DISCUSSION

The concept of investigating and repairing of preocclusive vein graft lesions is not new. Since the 1960s a number of investigators have advocated the salvage of functionally failed grafts by the revision of stenoses before graft thrombosis occurs.[17,18] Symptoms do not always correlate with patency. In 1979, in a study of 597 grafts, Szilagyi *et al.*[19] reported a lack of symptomatic improvement in 6.1% of patent grafts. When Doppler-recorded blood pressure measurements, frequently complemented by pulse volume recordings, had come into general use, patent but hemodynamically failed bypass grafts were identified. The importance of early correction of the anatomic abnormalities was emphasized in these studies.[2,6,20] The development of duplex scanning techniques and more recently color-flow duplex scanning enabled the detection of anatomic imperfections in vein grafts not associated with either the presence of symptoms or the deterioration of ankle pressures.[9-11,21,22] In the present study, symptoms were present in only 33% of stenoses, and an interval drop in ABI was seen in 38%; in comparison, the PSV-index demonstrated 90% of lesions with a DR greater than 30% as confirmed with intraarterial DSA.

**Table III.** Life table primary and assisted primary graft patency analysis for vein grafts that underwent color-flow surveillance and clinical follow-up.

| *Follow-up Protocol* | *Interval (mo)* | *No. at risk* | *Failed grafts* | *No. withdrawn* | *Interval patency rate(%)* | *Cumulative patency rate(%)* | *SE* |
|---|---|---|---|---|---|---|---|
| *Color-flow duplex surveillance* | | | | | | | |
| Primary patency | 0-6 | 160 | 10 | 17 | 94 | 100 | 0.0 |
| | 6-12 | 133 | 26 | 16 | 80 | 94 | 2.0 |
| | 12-24 | 91 | 7 | 26 | 92 | 78 | 3.9 |
| | 24-36 | 58 | 2 | 15 | 97 | 72 | 5.0 |
| | 36-48 | 41 | 2 | 18 | 95 | 69 | 6.0 |
| | 48-60 | 21 | 1 | 9 | 95 | 66 | 8.4 |
| Assisted primary patency | 0-6 | 160 | 4 | 17 | 98 | 100 | 0.0 |
| | 6-12 | 139 | 10 | 19 | 93 | 98 | 1.3 |
| | 12-24 | 110 | 0 | 32 | 100 | 91 | 2.6 |
| | 24-36 | 78 | 0 | 21 | 100 | 91 | 3.1 |
| | 36-48 | 57 | 2 | 25 | 96 | 91 | 3.9 |
| | 48-60 | 30 | 1 | 12 | 97 | 88 | 5.6 |
| *Clinical follow-up* | | | | | | | |
| Primary patency | 0-6 | 41 | 7 | 8 | 83 | 100 | 0.0 |
| | 6-12 | 26 | 5 | 3 | 81 | 83 | 6.7 |
| | 12-24 | 18 | 1 | 6 | 94 | 71 | 9.0 |
| | 24-36 | 11 | 1 | 4 | 91 | 67 | 11.6 |
| | 36-48 | 6 | 0 | 3 | 100 | 61 | 15.5 |
| | 48-60 | 3 | 0 | 2 | 100 | 61 | 22.0 |
| Assisted primary patency | 0-6 | 41 | 6 | 8 | 85 | 100 | 0.0 |
| | 6-12 | 27 | 3 | 4 | 89 | 85 | 6.3 |
| | 12-24 | 20 | 0 | 6 | 100 | 78 | 8.2 |
| | 24-36 | 14 | 1 | 5 | 93 | 78 | 9.8 |
| | 36-48 | 8 | 0 | 4 | 100 | 72 | 13.4 |
| | 48-60 | 4 | 0 | 2 | 100 | 72 | 19.0 |

**Table IV.** Determinants of outcome of assisted primary patency in 201 infrainguinal vein grafts by Cox proportional hazard analysis.

| *Variable present* | *Estimated coefficient* | *SD* | *T-ratio* | *p-value* | *Relative risk* |
|---|---|---|---|---|---|
| Diabetes mellitus | 0.60 | 0.49 | 1.22 | 0.22 | 1.83 |
| Preoperative ABI <0.51 | -0.16 | 0.95 | -0.17 | 0.87 | 0.71 |
| Critical ischemia | 0.85 | 0.68 | 1.25 | 0.21 | 2.33 |
| Hypertension | 0.71 | 0.48 | 1.50 | 0.13 | 2.04 |
| History of smoking | 0.86 | 0.55 | 1.59 | 0.11 | 2.37 |
| History of other vascular disease | -0.28 | 0.49 | -0.57 | 0.57 | 0.76 |
| SVS/ISCVS run-off score >2.0 | -0.04 | 0.09 | -0.46 | 0.64 | 0.69 |
| Previous ipsilateral reconstruction | 0.87 | 0.57 | 1.52 | 0.13 | 2.38 |
| In situ vein graft | 0.14 | 0.52 | 0.27 | 0.78 | 1.15 |
| Venovenous anastomosis | 0.54 | 0.54 | 1.00 | 0.32 | 1.72 |
| Crural distal anastomosis | 0.45 | 0.56 | 0.80 | 0.42 | 1.57 |
| Color-flow duplex surveillance | -1.32 | 0.50 | -2.67 | 0.01 | 0.27 |

The diagnostic yield of color-flow duplex scanning can be improved by combining high-velocity and low-velocity criteria. In a recent article Taylor *et al.*[23] found a sensitivity of 100% and a specificity of 98% by the combined use of the ratio of the PSV within a stenosis and at a normal graft segment. However, the concept of whether the revision of anatomic lesions that are asymptomatic and do not cause an interval drop in ABI really improves long-term patency has been challenged by some authors.[24] We have attempted in this study to answer this and other questions that are pertinent to the rationale and outcome of vein graft surveillance.

The incidence of stenotic lesions in vein grafts differs between series, depending on the severity of stenosis that is included and the screening techniques used. In patients monitored clinically and with ankle pressure measurements, the incidence ranges from 5% to 21%,[2,3,25] whereas color-flow duplex scanning detected 20% to 34% of graft lesions.[10,11] We found stenoses in 7% of grafts that underwent clinical follow-up compared with 32% in the color-flow surveillance group. This emphasizes that clinical examination and conventional non-invasive testing fail to recognize many graft stenoses, as other researchers have shown.[8,26-28] Similarly, the rate of repeat interventions varies between series. Our revision rate was 21%, which is comparable to 28% in the series of 250 vein grafts reported recently by Bandyk *et al.*[7] In contrast, in our clinical follow up series only 7% of failing but patent graft underwent revision.

Five-year patencies as low as 28% to 47% have been documented after revisions performed in grafts that had already thrombosed, as opposed to 82% to 93% late patency rates after elective repair of screen-detected stenoses in patent bypasses.[3,29] In addition, once a screen-detected stenosis has been successfully revised, patency rates of greater than 80% at 5 years can be achieved, a result similar to that with non-stenosed bypass grafts.[7] However, we do not know how many stenoses would have progressed to occlusion without revision.

Our analysis differs from earlier studies in that we compared 3-year patency rates in two groups of vein grafts constructed during the same period by the same group of surgeons. The first group of patients took part in a comprehensive color-flow duplex surveillance program, and the second smaller group differed only in that the follow-up was clinically based during the first 2 years. There was no difference in the primary patency rates in the two groups. However, the assisted primary patency was much higher in the color-flow surveillance group, where the intervention rate was greater.

Comparison of patency rates between a group that underwent graft surveillance and a group of historic controls that did not undergo surveillance was reported by Moody *et al.*[30] These investigators achieved an improvement in 1-year patency rates of 15% in patients that who were prospectively screened by duplex scanning. Our observation of a 13% difference in patency rates after 1 year and 19% after 3 years compares well with these findings. The independent correlation of color-flow surveillance and improved patency rates was confirmed by a proportional hazard model, which showed that the probability of graft occlusion was less than one-third of that with clinical follow-up. No other factors were independently related to an increased risk of failure.

The observed rates of stenosis in the two groups leads to the reasonable assumption that two-thirds of stenotic lesions that undergo clinical follow-up remain occult and may cause graft thrombosis. However, there are few data on the natural history of stenotic lesions in bypass grafts and anastomoses. Grigg *et al.*[31] and Moody *et al.*[13] found a 21% to 23% incidence of thrombosis in stenotic bypass grafts in which a conservative policy was followed. In the present study of stenotic grafts with and without revision, respectively, 10% and 39% failed (Table II), signifying that a graft stenosis is not an innocuous problem. The treatment of graft lesions in our series depended on several factors, such as a waiting list for vascular procedures, patient compliance with therapy, and surgeons diverging attitudes on how aggressive the treatment of these lesions should be. We could therefore correlate the fate of stenoses with active or conservative treatment.

The severity of stenosis was a significant risk factor. No occlusions were seen when stenoses of less than 50% DR were treated conservatively. In lesions 50% to 69% and 70% to 99% DR, respectively, 57% and 100% occluded. These findings currently dictate our policy for repeat revision. A revisional procedure is not

considered in the category with 30% to 49% DR. When a lesion of this degree is identified, color-flow duplex scanning is performed at 6 weeks, and thereafter the surveillance schedule is at routine intervals. In the 50% to 69% DR category a selective approach is used, and additional factors are considered. For example, lesions longer than 1.5 cm with an absolute residual diameter greater than 2 mm, as estimated with color flow imaging, are initially observed. Our threshold for performing a balloon angioplasty of a short lesion is rather low. Satisfactory results of balloon angioplasty in lesions with a length of 1 to 1.5 cm have been reported, whereas surgical correction is the best treatment in longer lesions.[32,33] Szilagyi *et al.*[1] observed on serial arteriographic examinations that most occlusions occurred in short graft stenoses, whereas grafts with more diffuse intimal thickening tended to remain patent. In a lesion of more than 1.5 cm length and of intermediate severity we favor a conservative policy and use color-flow duplex scanning with reduced intervals to check on progression. As was previously reported by our group, stenoses exceeding 69% DR are reliably identified by an increase of the EDV to greater than 20 cm/s at the site of the stenosis.[12] Intervention without delay is indicated in all lesions of this severity. A recurrent stenosis after a repeat procedure was encountered in this study in 25% of cases. This is comparable to the incidence of 17% to 23% found in other series.[27,32] We have separated the true recurrent stenoses from lesions that develop remote from the initial revision site, and it appeared that most tertiary lesions (80%) were in fact recurrences. Because of variation in techniques we could not show a correlation with the initial type of revision. However, Bandyk *et al.*[27] found that especially for longer lesions a segmental graft replacement is associated with a lower rate of recurrence than is a vein patch angioplasty. A more liberal use of segmental graft replacement or sequential bypass for lesions longer than 2 cm may reduce the rate of recurrent stenosis.

The enhancement of duplex with color-flow imaging considerably simplifies the examination of vein grafts.[10,11] One of the drawbacks of gray-scale duplex is the time involved to search for high-velocity areas. In contrast, color-flow imaging readily identifies stenotic areas, and an improved display of the vessel lumen helps to differentiate stenoses from caliber changes related to the natural tapering of vein grafts. These advantages add to the reliability of the examinations. Although color-flow duplex imaging is currently the best method for graft screening, this examination remains laborious, is expensive, and does not show the run-off vessels well. Simpler tests for repetitive examinations during the first 12 to 18 months have been sought. Graft volume flow measurements do not require longitudinal tracking of the entire bypass graft, and the ratio of the reactive hyperemia and resting flow had been investigated by Chang *et al.*[34] They found that this ratio had a limited predictive value for stenotic lesions and a positive test always needed confirmation by a complete duplex examination. Wyatt *et al.*[35] reported on non-invasive impedance analysis to identify vein grafts at risk. They observed a good agreement with arteriographically

diagnosed graft or run-off lesions. The results with this new method will have to be confirmed by others. Inflow and particularly outflow obstructions, may benefit from the development of these new methods. These lesions can cause graft failure as do lesions in the graft itself.

Although many new screening techniques will effectively detect the graft at risk, few will localize the lesion. Most graft stenoses can be well visualized by use of color-flow duplex scanning, and when no multiple lesions are present and the stenosis is focal, revision without confirmatory angiography may be possible.[36] Furthermore, criteria for quantification of stenoses have been established that enable color-flow duplex scanning to be used reliably as a planning tool.[12]

In conclusion, in our experience a color-flow duplex surveillance program seems to have a significant beneficial effect on infrainguinal vein graft patency. Stenosis detection was improved by more and better revisional procedures. However, prospective validation of these findings is required, and further trials should be directed to the development of a simpler screening method with comparable reliability. When a stenosis is detected by such a non-invasive method, a color-flow duplex examination may be an adequate substitute for pretreatment angiography in some cases.

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*Chapter* **4**

# Factors influencing the development of vein graft stenoses and their significance for clinical management

*Idu MM, Buth J, Hop WCJ, Cuypers Ph, van de Pavoordt EDWM, Tordoir JMH. Factors influencing the development of vein graft stenoses and their significance for clinical management. (Submitted)*

## INTRODUCTION

Femorodistal bypass operations are performed increasingly often for the treatment of lower limb ischemia. Autologous vein has been the preferred graft material for infrainguinal arterial reconstruction since the use of reversed saphenous vein was first described in 1949 by Kunlin.[1] Unfortunately, 20% to 30 % of vein grafts develop stenoses in the first postoperative year, due to myointimal hyperplasia.[2-6] The majority of graft stenoses are asymptomatic until they result in a graft occlusion.[7] Regular non-invasive examinations followed by elective revision of failing but non-occluded grafts have become a valued strategy, which is believed to salvage conduits as well as limbs.[8-12] Of all non-invasive screening tests frequent duplex ultrasound scanning is, despite the fact that it is time consuming and elaborate, currently the most commonly used method, which has the best correlation with angiography.[3,4,7,13-17]A surveillance program is generally considered to be indicated for all infrainguinal vein grafts at least for a the first postoperative period.[18,19] From the view of responsible use of resources it may be advantageous to tailor duplex surveillance programs in such a way that only patients with grafts at higher risk of stenosis are followed by intensive surveillance. Therefore, factors which carry a high or a low-risk for the occurrence of vein graft stenoses need to be defined.

Because a high-grade stenosis is a serious threat to graft patency, a revision to resolve the lesion is indicated without delay. Correction of patent-stenotic grafts has resulted in a superior secondary patency rate compared to revision of occluded-stenotic grafts.[9] In this report the results are presented of a prospective cohort study of patients with infrainguinal venous bypasses, which were enrolled into a fixed protocol of serial non-invasive testing for the identification of severe lesions in the graft or its adjacent arterial segments. Surgical or catheter interventions were performed when high-grade lesions were confirmed by angiography. In this multicenter study standardized inclusion criteria, uniform surveillance techniques in the participating centers and digital subtraction angiography (DSA) were used in all patients for validation of lesions. Objectives of this analysis were: to assess the influence of a number of clinical and graft factors on the development of stenotic lesions, and to investigate options of modification of grafting techniques or duplex surveillance programs according to proven clinical and graft risk factors.

## PATIENTS AND METHODS

Patients of three institutions following the same surveillance protocol were included in a prospective cohort surveillance study. 300 Patients with autologous vein bypass grafts of the infrainguinal arteries were studied. Patients entered the study if they had

an open bypass prior to discharge from the hospital. There was only one graft per patient included in this study. This study was a combined effort of three vascular surgical departments: the University Hospital Maastricht (61 grafts), Sint Antonius Hospital Nieuwegein (62 grafts), and Catharina Hospital Eindhoven (177 grafts). All centers had a well-equipped and staffed clinical vascular laboratory. 46 Patients with vein grafts operated in the same period were not considered for analysis because of death of the patient (11), irreversible graft occlusion (17), amputation with open bypass within 30 days after the operation (8), or no return for surveillance visits (10). The operations were performed between June 1993 and September 1995 and the follow-up of this study ended in September 1996. Of the 300 patients 179 (60%) were men, and 121 (40%) were women. The mean age was 70 years (range 33 to 93). Diabetes mellitus (type 1 or 2) was present in 117 (39%) patients. Critical ischemia was the indication for the bypass procedure in 216 (72%). 83 (28%) Procedures were redo operations, i.e. new grafts, as a previous attempt of revascularization of the popliteal or crural arteries in the same limb had been performed. The distal anastomosis was in 150 (50%) at the level of the popliteal artery or tibioperoneal trunk and in 150 (50%) at a crural artery. The run-off score as determined on the basis of preoperative angiograms[20] indicated an impaired run-off (score >2.0) in 178 (59%) of the patients. Two hundred thirty seven (79%) of grafts consisted of a single greater saphenous vein segment, while composite grafts of multiple saphenous or arm-vein segments were used in 63 (21%). Of those 13 (4%) had only arm-vein segments used. Other preoperative risk factors and graft characteristics are summarized in Table I.

Preoperative angiography was performed in all cases to identify the optimal site of the proximal and the distal anastomosis. Duplex assessment of the greater saphenous vein was performed if there was doubt about its suitability. A variety of techniques was used to perform the bypass procedures. In situ saphenous vein grafts were used when the ipsilateral saphenous vein was available and suitable for use. Ectopic veins were either reversed or non-reversed, depending on the vein taper and the optimal size match between vein grafts and inflow and recipient arteries. Small distal or fibrotic segments were replaced by a segment of arm-vein or greater saphenous vein. All operations were performed by vascular surgeons, vascular fellows, or by residents in their last term of surgical training supervised by a vascular surgeon. All operations were done on either general or epidural anesthesia. Postoperative anticoagulation with coumarins (dicoumarol or acenocoumarol) was instituted postoperatively in all patients that had no contraindications to use. In the three participating institutions the same graft surveillance protocol was used. The adherence to the protocol was accomplished by frequent visits of a data manager and a study nurse, who performed the data collection. Vascular laboratory meetings were organized regularly to ascertain an uniform duplex scanning and measurement

technique, and recording of parameters. All examinations were performed by qualified technologists.

**Table I.** Risk factors and graft characteristics in 300 infrainguinal vein grafts.

| *Variables* | *Number of grafts (%)* | |
|---|---|---|
| Presenting symptoms | | |
| Tissue loss from G or U | 109 | (36) |
| Rest pain | 107 | (36) |
| Claudication | 78 | (26) |
| Aneurysm | 6 | (2) |
| Associated disease and risk factors | | |
| Female gender | 121 | (40) |
| Diabetes mellitus | 117 | (39) |
| Hypertension | 94 | (31) |
| History of smoking | 210 | (70) |
| History of other vascular disease | 152 | (51) |
| Preoperative data | | |
| ABI <0.60 | 223 | (78) [2] |
| SVS/ISCVS[1] run-off score >2.0 | 178 | (59) |
| Graft | | |
| Previous ipsilateral infrainguinal reconstruction | 83 | (28) |
| Other than in situ graft | 172 | (57) |
| Proximal anastomosis below common femoral artery | 111 | (37) |
| Crural distal anastomosis | 150 | (50) |
| Venovenous anastomosis | 54 | (18) |

ABI is ankle brachial blood pressure index; G is gangrene; U is ulceration; 1: SVS/ISCVS is Society for Vascular Surgery / International Society for Cardiovascular Surgery; 2: incompressible vessels in 15 patients.

**Surveillance protocol**

Before discharge from the hospital graft patency was confirmed by a graft velocity measurement at mid-thigh level of the bypass. Entire graft intraoperative or predischarge duplex scanning was infrequently performed during this study, therefore these data were not included in the analysis. For the study, however, only the outcomes of entire bypass duplex scannings during follow-up were used in addition with ankle pressure measurements at rest and during reactive hyperemia (RH). Surveillance visits were routinely performed at 6 weeks, 3 months, 6 months, 9 months and 12 months. In grafts without abnormalities subsequent follow-up examinations consisted of ankle blood pressure measurements at rest and during RH at 18, 24 and 30 months after the operation. The rationale for restricting duplex examinations to the first postoperative year has been well-documented in the literature[3]. An intraarterial DSA (Catharina Hospital and Sint Antonius Hospital) or an intravenous DSA (University Hospital Maastricht) was performed if one of the following criteria for a failing graft were present: recurrent claudication or rest pain, interval decrease of the ABI >0.15, a peak systolic velocity ratio (PSV-ratio) >2.0, a peak systolic velocity at the mid-thigh graft (PSV-graft) <45 cm/s, and an end-diastolic velocity (EDV) >20 cm/s. If the intravenous study had insufficient resolution a subsequent intraarterial DSA was performed. Accurate assessment of the angiographic diameter ratio of stenotic and normal graft sites was facilitated by multiple projections as well as by magnified views. If at DSA examination a stenosis of 70% diameter reduction (DR) or greater was observed either in the graft, the anastomoses or in the adjacent artery segments a revisional procedure, either a PTA or an open surgical procedure, was planned. In fact, this angiographic criterium was the sole determinant for the decision for intervention. After lesion repair surveillance was continued until one year after the revision. In case of a stenosis with a DR of 50% to 70% no intervention was undertaken, but subsequent surveillance duplex examinations were performed at reduced intervals. If there was no further increase of the PSV-ratio a conservative approach was adopted and the surveillance schedule resumed at routine intervals. Bypasses with less than 50% DR were considered normal grafts. Patients without evidence of graft stenosis at surveillance examination underwent a DSA after their consent was obtained. These control DSA studies were made either 6 months or 1 year after the operation, a choice that was determined by randomization.

**Surveillance examination**

Systolic ankle blood pressure (ABP) measurements were performed with the patient supine using a 15 cm wide blood pressure cuff, and the average of two measurements was recorded. The highest of the right and left systolic brachial blood pressure was used to determine the ankle brachial blood pressure index (ABI). Ankle blood pressure during reactive hyperemia was measured following suprasystolic thigh cuff inflation during a 3-minute period. The color-flow duplex equipment that was used consisted of a Acuson 128 XP/10 in the Catharina Hospital, a Hewlett Packard Sonos 1000 in the University Hospital Maastricht and a Hewlett Packard Sonos 2000 in the Sint Antonius Hospital. In the three centers a 7.5 MHz transducer was applied, unless the vein graft was deep, when a 5.0 MHz transducer was used. The examination technique, such as the use of similar angles of insonation of the pulsed Doppler with respect to the vessel axis, sites of velocity measurements, ankle blood pressure measurements and reactive hyperemia induction was uniform in the participating vascular laboratories. The vein graft was examined from the groin down the entire length to below the distal anastomosis on to the first centimeters of the recipient run-off artery. Color coded images were studied for stenotic flow patterns and a percent diameter reduction (DR) was measured by use of color-image at the stenosis and at a nearby normal graft segment. After the graft was imaged midstream pulsed Doppler velocity spectral signals were recorded from diseased and normal vessel segments.

**The clinical and graft factors**

The recorded preoperative clinical factors recorded included: (1) indication for revascularization, (2) preoperative ankle brachial blood pressure index, (3) presence of diabetes mellitus, (4) smoking habits, (5) hypertension, (6) angina pectoris or (7) previous history of myocardial infarction, (8) of myocardial revascularization, (9) of central vascular reconstruction or (10) of peripheral vascular reconstructions. These factors were diagnosed and graded according to the Suggested Standards for Reports Dealing with Lower Limb Ischemia.[22] In addition the following graft characteristics were recorded: (1) grafting technique, (2) anastomotic sites, (3) site of any venovenous anastomoses, (4) external diameters of the vein graft, and (5) total length of the graft prior to wound closure. In addition the intraoperation quality control method was recorded, which either was angioscopy, angiography or duplex examination. Peroperative graft factors were recorded on a standardized form filled in by the operating surgeon immediately after the procedure.

To assess the occurrence of graft stenoses, regularly measured PSV-ratios were used as an indicator of *significant graft stenosis*, which was defined as a PSV-ratio >2.5. *Event causing stenosis* was defined if a stenosis required a revision. All revised lesions had a diameter reduction greater than 70% on confirmatory angiography. In

addition, stenoses that had caused a graft occlusion before a revision was undertaken, were also defined: *event causing stenoses*.

**Data analysis**

The occurrence of *significant graft stenosis* and *event causing graft stenosis* were the end-points of patency and were correlated with the different factors. The time interval between the operation and the occurrence of the stenosis was recorded. Univariate comparison between the stenotic and non-stenotic grafts was performed for all defined patient and bypass characteristics using logrank testing. To examine independent associations variables with significant group differences at univariate comparison were combined with some factors of particular clinical relevance and were subjected to a multiple regression analysis using a Cox proportional hazard model.[21] For these analyses SPSS 7.0 for Windows statistical software was used.

## RESULTS

**Vein graft stenoses**

17 Preoperative risk factors and graft characteristics were correlated with the occurrence of two different end-points, i.e. the development of *significant graft stenosis* and *event causing graft stenosis* during follow-up. The univariate correlation of all variables with the two endpoints during follow-up is indicated in Table II. The only factor for which a statistically significant correlation with the development of *significant graft stenosis* could be demonstrated was the minimal graft diameter. The other factors did not have statistical correlation with the development of *significant graft stenosis*. Factors that had a significant correlation with the development of *event causing graft stenosis* were the minimal graft diameter, use of venovenous anastomosis and the length of the graft (Table II).

These 3 factors were selected for a multivariate analysis with a Cox proportional hazard model[23] with *event causing graft stenosis* as endpoint (Table III). Some additional clinically relevant risk factors were selected for this analysis as well. These factors were: (1) site of distal (crural) anastomosis, (2) grafting technique (non in situ technique), (3) previous peripheral revascularization and (4) indication for the operation (rest pain or gangrene). The minimal intraoperatively measured graft diameter showed to be the single independent factor, that significantly correlated with the development of *event causing graft stenoses* during subsequent follow-up overtoning the other variables.

**Table II.** Univariate correlation of preoperative clinical and graft parameters and the occurrence of *significant* or *event causing vein graft stenosis*.

| *Parameter* | | *No. of patients* | ***Significant graft stenosis*** *1-year free-of-stenosis rate (%)* | *logrank p-vaue* | ***Event causing graft stenosis*** *1-year free-of-stenosis rate (%)* | *logrank p-value* |
|---|---|---|---|---|---|---|
| Critical limb ischemia | No | 84 | 66 | | 78 | |
| | Yes | 216 | 60 | 0.51 | 70 | 0.051 |
| Diabetes mellitus | No | 183 | 66 | | 72 | |
| | Yes | 117 | 54 | 0.16 | 72 | 0.74 |
| Smoking | No | 168 | 58 | | 69 | |
| | Yes | 132 | 66 | 0.32 | 75 | 0.63 |
| Hypertension | No | 206 | 63 | | 75 | |
| | Yes | 94 | 58 | 0.24 | 66 | 0.21 |
| Angina Pectoris | No | 250 | 61 | | 70 | |
| | Yes | 50 | 64 | 0.40 | 80 | 0.36 |
| Myocardial Infarction | No | 203 | 60 | | 70 | |
| | Yes | 97 | 66 | 0.24 | 77 | 0.32 |
| PTCA / CABG[1] | No | 259 | 63 | | 73 | |
| | Yes | 41 | 53 | 0.35 | 63 | 0.17 |
| Previous central recon. | No | 271 | 63 | | 71 | |
| | Yes | 29 | 53 | 0.50 | 78 | 0.77 |
| Previous peripheral recon. | No | 217 | 61 | | 71 | |
| | Yes | 83 | 64 | 0.8 | 74 | 0.74 |
| Preoperative ABI[2] | <0.60 | 223 | 62 | | 73 | |
| | ≥0.60 | 62 | 62 | 0.83 | 70 | 0.66 |
| SVS/ISCVS[3] run-off score | ≤2.0 | 122 | 65 | | 76 | |
| | >2.0 | 178 | 59 | 0.33 | 70 | 0.15 |

**Table II - continued.** Univariate correlation of preoperative clinical and graft parameters and the occurrence of *significant* or *event causing vein graft stenosis*.

| *Parameter* | | *No. of patients* | ***Significant graft stenosis*** *1-year free-of-stenosis rate (%)* | *logrank p-value* | ***Event causing graft stenosis*** *1-year free-of-stenosis rate (%)* | *logrank p-value* |
|---|---|---|---|---|---|---|
| Grafting technique | in situ | 128 | 58 | | 72 | |
| | non in situ | 172 | 64 | 0.42 | 71 | 0.82 |
| Proximal anast. | CFA[4] | 189 | 59 | | 68 | |
| | Prox. SFA[5] | 52 | 58 | | 79 | |
| | Dist. SFA/Popl.[6] | 59 | 71 | 0.39 | 80 | 0.21 |
| Crural anastomosis | No | 150 | 64 | | 75 | |
| | Yes | 150 | 60 | 0.49 | 68 | 0.11 |
| Minimal graft diam. | <3.5 mm | 38 | 41 | | 48 | |
| | ≥3.5 mm | 262 | 65 | 0.002 | 75 | 0.001 |
| Venovenous anast. | No | 246 | 64 | | 75 | |
| | Yes | 54 | 51 | 0.09 | 58 | 0.005 |
| Length of graft | ≤40 cm | 100 | 66 | | 77 | |
| | 40-60 cm | 140 | 61 | | 73 | |
| | >60 cm | 60 | 54 | 0.46 | 61 | 0.025 |

1. PTCA/CABG is percutaneous transluminal coronary angioplasty / coronary aorta bypass graft; 2. ABI is ankle brachial pressure index, incompressible vessels in 15 patients; 3. SVS/ISCVS is Society for Vascular Surgery / International Society for Cardiovascular Surgery; 4. CFA is common femoral artery; 5. Prox. SFA is proximal superficial femoral artery; 6. Dist. SFA/ Popl. is distal superficial femoral artery / popliteal artery.

**Table III.** Cox proportional hazard model relating several factors and occurrence of *event causing vein graft stenosis*.

| *Factor* | *β* | *SE* | *Wald* | *Sign.* |
|---|---|---|---|---|
| Minimal graft diameter | -0.70 | 0.27 | 6.8 | 0.009 |
| Venovenous anastomosis | 0.47 | 0.26 | 3.17 | 0.08 |
| Length of graft | 0.19 | 0.17 | 1.14 | 0.29 |
| Crural anastomosis | -0.05 | 0.26 | 0.03 | 0.85 |
| Grafting technique | -0.01 | 0.23 | 0.002 | 0.96 |
| Previous peripheral recon. | -0.11 | 0.25 | 0.20 | 0.65 |
| Critical ischemia | 0.33 | 0.28 | 1.40 | 0.24 |

The factors were categorized into subgroups the same way as described in Table II.

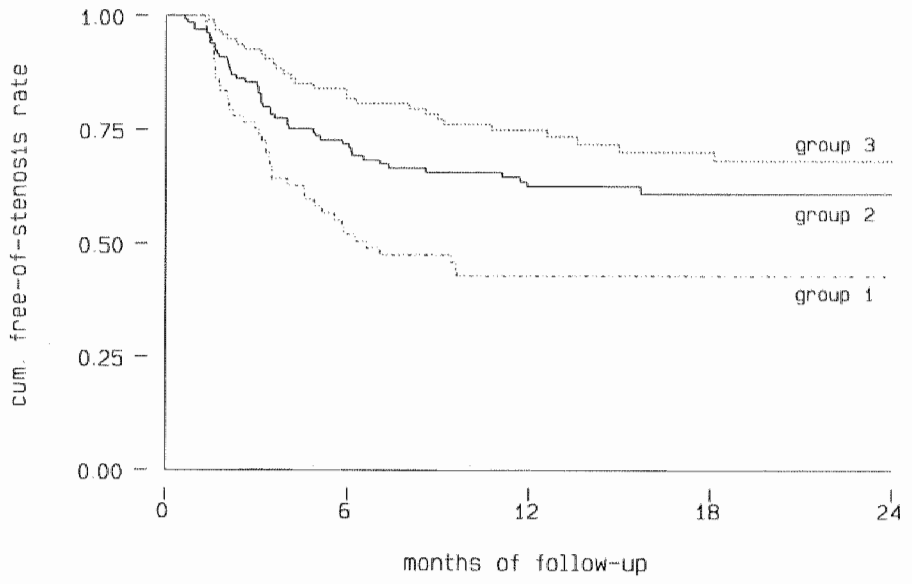
Kaplan-Meier curves indicating a *free-of-stenosis* state were constructed with the occurrence of significant stenosis as the event (Figure 1). Groups with a intraoperatively measured minimal graft diameter <3.5 mm (group 1), between 3.5 and 4.5 mm (group 2), and >4.5 mm (group 3) were compared. At one year group 1, 2, and 3 had *free-of-stenosis* rates of 40%, 58%, and 75% respectively. Group 1 differed from groups 2 and 3 ($p$, respectively 0.02, <0.001), and group 2 differed from group 3 ($p$ = 0.03).

**Grafting techniques**

To investigate the role of the grafting technique the results in grafts with a minimal diameter of <3.5 mm measured intraoperatively, and the results in grafts modified by the use of multiple composite vein segments or arm-veins to obtain a wider conduit, were compared. Thus, two groups were defined: group A consisting of 25 single segment greater saphenous vein grafts, all with a minimal graft diameter of <3.5 mm, and group B consisting of 11 arm-vein grafts and 41 composite vein grafts, all with a minimal diameter of ≥3.5 mm. Life table analysis demonstrated no difference in *free-of-stenosis* rate with the occurrence of *significant graft stenosis* as the event between group A and B, with 12 month patencies of 38% and 55% respectively ($p$ = 0.1). However, the secondary patency at one year was 76% and 94% respectively, which represented a significant difference ($p$ = 0.03). The 1-year secondary patency in group B was comparable with the patency of grafts which consisted of a single segment greater saphenous vein with a minimal diameter of ≥3.5 mm, 94% and 93% respectively. If only femorocrural grafts were considered the 1-year secondary patency

in group A (20 femorocrural grafts) and group B (24 femorocrural grafts) were 75%, and 91% respectively, which difference was not significant.

**Figure 1.** Rate of maintenance of *free-of-stenosis* state, defined as a focal PSV-ratio ≥2.5, represented by Kaplan-Meier curves in patient groups according to the intraoperatively measured minimal graft diameter: group 1 (diam. <3.5 mm), group 2 (diam. 3.5 to 4.5 mm) and group 3 (diam. >4.5 mm (group 3). (group 1 vs group 2: $p = 0.02$, group 1 vs group 3: $p < 0.001$, group 2 vs group 3: $p = 0.03$).




## DISCUSSION

After discharge the majority of graft failures occur within the first two years and progressive graft stenosis is the most frequent cause. These lesions are caused by myointimal hyperplasia which usually is a focal process. It may occur throughout the graft as well as in the areas of the anastomoses.[22] Color-flow duplex surveillance programs are effective in detecting these lesions prior to graft occlusion, allowing interventions with good expectation on success.[8,10-13] Other non-invasive tests, such as ankle blood pressure measurements have not nearly been as accurate in identifying stenotic graft lesions.[14-17] An optimal surveillance program implies all infrainguinal

venous grafts to be screened. However, a comprehensive follow-up of this nature is extremely time consuming and associated with high costs.

A number of studies have been focussed to unravel the origin of vein graft stenoses.[2-4,22] Assessment of influence of several preoperative patient and intraoperatively determined graft characteristics on stenosis formation was the subject of the present analysis. Of all factors investigated in our study the minimal graft diameter appeared the single variable that significantly correlated with the occurrence of graft stenosis. Markers of advanced atherosclerosis, such as diabetes mellitus, the presence of critical limb ischemia, a high run-off score, and the presence of tissue necrosis, were not correlated with a higher rate of vein graft stenosis. Operative technical factors, such as site of the distal anastomosis (crural arteries) and the graft technique (i.e. non in-situ technique) failed to show any significant correlation with the occurrence of vein graft stenosis either. Although the minimal graft diameter is an important risk factor for vein graft stenosis development, it is difficult to stratify patients into a group in which surveillance is particularly indicated and a group that does not require regular duplex testing at follow-up. Patients with a graft diameter ≥3.5 mm still develop stenoses considered a 1-year *free-of-stenosis* rate of 58% and 75% of grafts with a minimal graft diameter between 3.5 to 4.5 mm and >4.5 mm respectively. These incidences are, in our opinion, not acceptable to justify denying patients in these categories a duplex surveillance program. Our findings are in agreement with other studies, that also documented an unfavorable effect on durable patency of small caliber grafts.[23-25] Grafts bearing segments with a less than 3.5 mm diameter are at increased risk of failure for several reasons. It has been suggested that small caliber vein grafts are more vulnerable to intraoperative damage during harvesting than larger vein grafts. This was particularly true during valve lysis associated with the in situ technique. Injury of this nature may initiate local myointimal hyperplastic response, which may in small caliber veins result in high-grade stenoses. Moreover, small vein grafts may result from previous episodes of phlebosclerosis or have other pre-existing saphenous vein pathology. The presence of pre-existing saphenous vein pathology renders the overall quality of the conduit.[26,27] In their study Bandyk *et al.* demonstrated that peroperatively diagnosed graft lesions were significant promoters of the development of vein graft stenoses.[28] Also the observation that none of the factors, generally assumed to reflect a poorer general vascular status of the patient, did show a correlation with the development of vein graft stenosis tended to support the hypothesis that vein graft stenosis is caused by local graft-related factors, such as pre-existing vein pathology and operative injuries to the conduit. To assess the role of discrete peroperatively diagnosed abnormalities of the vein graft in subsequent development of vein graft stenosis we now perform a predischarge duplex examination including scanning of the entire vein graft and its adjacent arterial segments. This analysis will be the subject of a future study.

At the present time we hesitate to use small caliber segments of a vein graft, because of a high incidence of failure. Alternative sources of autologous vein segments, such as the contralateral saphenous vein or arm-veins, are preferred instead. Earlier studies demonstrated satisfactory results with the use of arm-veins and spliced grafts.[29-32] In our series composite vein grafts and arm-vein grafts both with a minimal diameter of ≥3.5 mm had a one year *free-of-stenosis* rate of 55% compared with 38% in the group with single greater saphenous grafts with a minimal diameter <3.5 mm. This difference just failed to reach statistically significance, perhaps due to small group sizes. However, the secondary patency rate was significantly better in the combined group with composite vein and arm-vein grafts compared to small caliber single greater saphenous vein grafts. This pattern indicates that grafts of arm vein or composite vein grafts have a tendency to develop less frequently stenotic lesions, while in addition treatment of these lesions is more often successful. An additional alternative therapeutic option when just a short vein segment is available, due to a small or fibrosed segment, may be the use of an open superficial femoral artery segment or popliteal artery as the site of the proximal anastomosis.[33,34] The number of short vein grafts in the present study was too small for a useful analysis.

The results reported in the literature about prosthetic grafts varied, but in particular if femorocrural grafts are considered low patencies were observed.[35-38] The secondary patency rates were between 5% and 55%. In contrast, in our series the 1-year secondary patency rate of femorocrural grafts with composite vein and arm-vein grafts was 91%. These results are in concordance with those of Harward *et al.*, and of Chalmers *et al.*, who reported 1-year secondary patencies of 85-91%.[39,40] It may be concluded from our own observations as well as those of others that the use of arm-vein or composite vein grafts for femorocrural bypass grafting is the preferable option if the saphenous vein is less than 3.5 mm in width.

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*Chapter* **5**

# Diagnostic accuracy of several surveillance parameters to detect vein graft stenoses

*Part of this chapter has been published as:*
*Idu MM, Buth J, Hop WCJ, Cuypers Ph, van de Pavoordt EDWM, Tordoir JMH. Vein graft surveillance: Is graft revision without arteriography justified and what criteria should be used? J Vasc Surg 1998;27:399-413.*

## INTRODUCTION

Autogenous vein grafts provide the best conduit for bypass treatment of femoropopliteal and femorocrural occlusive disease. However, bypass longevity is threatened by the development of stenoses, either from intimal hyperplasia or from fibrous stricture development in 20% to 30%.[1-3] Frequent non-invasive examinations followed by elective revision of failing, but non-occluded grafts has become a valued strategy, which is believed to salvage conduits as well as limbs.[4-7] Arteriography allows the demonstration of significant vein graft stenoses and in fact this method was used in the first comprehensive study reporting on the phenomenon of graft stenosis by Szilagyi *et al.* in 1973.[1] The presence of a significant arteriographic stenosis is a reliable predictor of graft failure unless the lesion is repaired.[8-10] There is no consensus about which of the non-invasive methods or parameters as applied during follow-up have the best correlation with angiographically critical graft stenoses. Replacing angiographic evaluation of vein graft stenosis by duplex scanning would be advantageous.[11] Graft occlusions may occur within the interval between the surveillance visit and the confirmative angiography.[9] Avoiding angiograms during follow-up would not only result in less delay of the revisional procedure, it also would reduce the overall cost of graft surveillance programs. In this report the results are presented of a prospective cohort study with strictly standardized surveillance techniques, digital subtraction angiography (DSA) in a series of patients with infrainguinal venous bypasses. The objective of this study was to assess the accuracy of different surveillance parameters in comparison with angiography as a gold standard. For this analysis there will be a comparison on the basis of digital subtraction angiograms (DSA) performed in this series.

## PATIENTS AND METHODS

Patients of three institutions following the same surveillance protocol were included in a prospective cohort surveillance study from June 1993 to September 1995. The study protocol, patient characteristics and the surveillance protocol are described in chapter 4 of this thesis.

### Surveillance parameters

The following surveillance parameters were evaluated: (1) the peak systolic velocity at a normal mid-thigh graft segment (PSV-graft, cm/s), (2) the PSV at the severest stenotic site (PSV-max, cm/s), (3) the ratio of the PSV-max and the PSV at a nearby normal segment, proximally (or distally in case the graft stenosis was near the proximal anastomosis) of the stenosis (PSV-ratio), (4) the end-diastolic velocity at the

site of the stenosis or in normal grafts at the narrowest segment of the bypass below the knee (EDV, cm/s), (5) diameter reduction of the stenosis on the color image (DR %), (6) the duplex measured flow in resting conditions at the mid-thigh graft (flow rest, ml/min), (7) flow at the mid-thigh graft during reactive hyperemia (flow RH, ml/min), (8) ankle blood pressure at rest (ABP, mmHg), (9) ankle brachial blood pressure index (ABI), and (10) ankle brachial blood pressure index at reactive hyperemia (ABI-RH).

**Study endpoints, data analysis**

All data were prospectively recorded and entered into a computerized database. The 10 surveillance parameters were correlated in a univariate analysis with angiographic outcomes. This study is based on the DSA studies performed in the corresponding time. The criterion of an angiographic DR of 70% was selected as in previous studies this degree of lesion has been associated with a high risk of graft failure.[8-10,12] Angiograms were dichotomized into groups with a DR of 0 to 70% and a DR ≥ 70%. An univariate comparison of both outcomes was performed with the use of the Mann-Whitney test. All non-invasive factors that demonstrated a significant difference ($p < 0.05$) for the arteriographic categories in the univariate comparison were subjected to a multivariate analysis using logistic regression models.[13] Variables with an independent correlation with the angiographic severity of stenoses were identified by backward elimination of the factors that contributed the least to the model. Receiver operating characteristic (ROC) curves were used to determine threshold values that provided the best separation in lesion categories.[14]

## RESULTS

**Angiograms and graft revisions**

In the 300 patients 351 DSA studies were performed during follow-up. 182 DSA studies were performed for a change in surveillance parameters, most commonly a PSV-ratio >2.0, while 169 normal control DSA studies were performed in vein grafts without focal increase of PSV. Table I represents the indications and results of the 351 DSA studies performed. Excluded from the study were 22 angiograms: 8 patients had an angiogram but failed to appear for non-invasive examinations, 5 patients had a graft occlusion without identified stenosis and 9 patients had a complete occlusion of the run-off artery immediately distal of their bypass. All graft occlusions were accurately diagnosed by color imaging and absence of flow signals allowing determination of clinical management. For correlation of angiographic findings and listed surveillance parameters 329 DSA studies were available.

**Table I.** The indications and results of the 351 digital subtraction angiograms performed.

| *Results* | *N.* | *Indications* | *n.* |
|---|---|---|---|
| DR <70% | 197 | :control | 161 |
| | | :stenosis on duplex | 33 |
| | | :low PSV-graft | 3 |
| DR 70% to 99% | 132 | :stenosis on duplex | 123 |
| | | :low PSV-graft | 7 |
| | | :control DSA | 1 |
| | | :clinical symptoms | 1 |
| Total graft occlusion | 2 | :detected on duplex | 2 |
| Partial graft occlusion | 3 | :detected on duplex | 3 |
| Run-off artery occlusion | 9 | :detected on duplex | 2 |
| | | :low PSV-graft | 3 |
| | | :clinical symptoms | 3 |
| | | :control DSA | 1 |
| Miscellaneous | 8 | :no duplex to correlate | 8 |

**Graft surveillance parameters**

All duplex and ABP derived parameters were correlated for groups with DSA confirmed lesions <70% and ≥70% DR (Table II). Differences were observed for all parameters except for graft flow-RH and the significance was borderline for the resting graft flow. Despite statistical differences there was a considerable overlap of parameter outcomes in the DSA study groups. The best discrimination between grafts with and without significant stenoses was observed in PSV-max and PSV-ratio, which parameters are by definition strongly related with each other. There were no differences in the correlation of the PSV-ratio and the angiographic degree of stenosis between the three participating centers. The correlation of the PSV-ratio with the angiographic diameter reduction for the whole group is represented in Figure 1. Eight variables that demonstrated a significant difference in the univariate analysis, were subjected to a multivariate analysis by logistic regression. This resulted in a model containing two variables (PSV-ratio and ABP) with an independent association with the presence of a high-grade stenosis (Table III).

**Table II.** Univariate correlation of duplex and ankle blood pressure derived parameters and DSA category with a DR <70% and a DR ≥70% stenosis.

| *Parameter* | *DSA <70% mean (± SD)* | | *DSA ≥70% mean (± SD)* | | *Sign. 2-tailed* |
|---|---|---|---|---|---|
| PSV-graft | 60 | (24) | 47 | (23) | < 0.001 |
| PSV-max | 147 | (77) | 270 | (108) | < 0.001 |
| PSV-ratio | 1.9 | (1) | 5.4 | (2.6) | < 0.001 |
| EDV | 6 | (16) | 34 | (49) | < 0.001 |
| DR % | 24 | (23) | 54 | (19) | < 0.001 |
| Flow rest | 190 | (203) | 164 | (170) | 0.019 |
| Flow RH | 268 | (285) | 258 | (295) | 0.164 |
| ABP | 148 | (40) | 120 | (39) | < 0.001 |
| ABI | 1.0 | (0.3) | 0.8 | (0.3) | < 0.001 |
| ABI-RH | 0.9 | (0.2) | 0.7 | (0.3) | < 0.001 |

For abbreviations see text.

**Table III.** Logistic regression model relating two variables to the probability of stenosis with ≥70% DR.

| *Variable* | *β* | *SE* | *Wald test*[1] | *p-value* |
|---|---|---|---|---|
| PSV-ratio | 1.14 | 0.13 | 78.43 | <0.001 |
| ABP (mmHg) | -0.01 | 0.005 | 8.28 | 0.004 |
| Constant | -2.17 | 0.77 | - | - |

1. degrees of freedom = 1.

As a next step ROC-curves were used to evaluate the sensitivity and specificity of the PSV-ratio alone and combined with the ABP to identify graft stenoses ≥70% DR. Of PSV-ratio alone a value of 3.0 provided the best outcome and was associated with a sensitivity of 80% and a specificity of 84%. The sensitivity and specificity of the other PSV-ratios are presented in Table IV. Use of the combined parameter "PSV-ratio and ABP" provided little improvement in sensitivity and specificity as compared with the PSV-ratio alone (Figure 2). Therefore it was concluded that to distinguish angiographic

lesions of ≥70% from less severely stenosed grafts use of the PSV-ratio only is sufficient. In an additional multivariate analysis in graft subgroups it was demonstrated that of the 8 surveillance parameters the PSV-ratio had the best correlation with the presence of high-grade lesions in in-situ or ectopic non-reversed grafts, in reversed grafts, in femoropopliteal grafts, and in infrapopliteal grafts.

**Figure 1.** The correlation of the PSV-ratio with the angiographic diameter reduction.

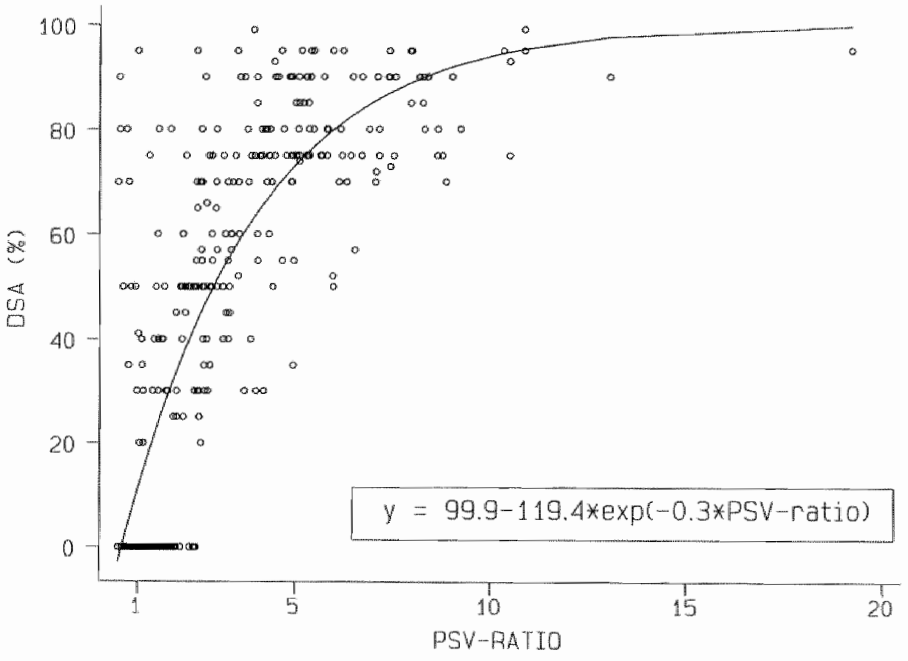
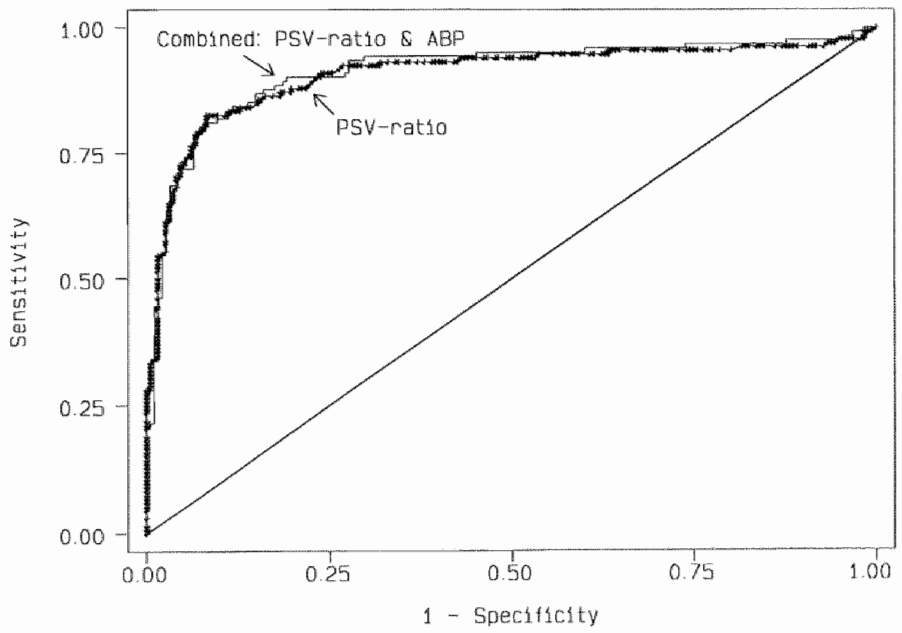


**Table IV.** The sensitivity and specificity of the PSV-ratio in identifying vein graft stenosis with an angiographic diameter reduction ≥70%.

| *PSV-ratio* | *Sensitivity* | *Specificity* |
|---|---|---|
| ≥2.00 | 88% | 61% |
| ≥2.50 | 86% | 74% |
| ≥2.75 | 82% | 81% |
| ≥3.00 | 80% | 84% |
| ≥3.25 | 78% | 88% |
| ≥3.50 | 75% | 92% |
| ≥4.00 | 70% | 94% |

**Figure 2.** Receiver operating characteristic (ROC) curves of the peak systolic velocity (PSV)-ratio and of the combined parameter PSV-ratio and ankle blood pressure (ABP).



## DISCUSSION

It is generally accepted that the follow-up of patients with infrainguinal vein grafts should be directed toward the identification of failing grafts. At this stage relatively minor procedures can often avert impending graft failure.[15,16] For the identification of grafts with stenotic lesions ankle blood pressure measurements and more recently duplex and color-flow duplex examinations have been used.[4,17-20] With duplex examinations low-velocity and high-velocity criteria can be distinguished. The former criterion requires only measurements of the peak systolic velocity (PSV) at a fixed point at mid-graft level (PSV-graft). It has been observed, however, that this criterion had a low sensitivity for focal lesions and that low PSV-graft values (low flow state grafts) were frequently caused by run-off or inflow disease.[12,21,22] At present the most commonly used color-flow duplex examination includes tracing of the entire graft, identification of sites with flow disturbance, and measurement of the PSV at the stenosis. Absolute PSV values as well as the ratio of the PSV at the stenosis and a normal adjacent arterial segment are used. Threshold values for the PSV-ratio vary in the literature from 1.5 to 3.5.[4,10,19,21,23,24] In the present study the correlation of a set of 10 duplex and ankle blood pressure (ABP) derived parameters, all reported in the literature were determined. In addition to the parameters described above reactive hyperemia tests combined with ABI and duplex derived volume flow measurements were included.[25,26] End-diastolic velocities were recorded as well. This variable has been indicated as a correlant with high-grade graft lesions, a relationship of which the hemodynamic background was recently described by Papanicolaou *et al.*[27] Correlation of all parameters and the degree of stenosis as measured on the angiograms was performed. All angiographic diameter reductions and surveillance variables were obtained in a strictly uniform fashion in the three institutions that participated in this carefully monitored prospective study. The surveillance parameters were determined by different duplex apparatus by a group of 9 vascular laboratory technicians. Nevertheless, correlation of key surveillance and angiographic variables resulted in comparable outcomes in the institutions. Using multivariate analysis the PSV-ratio and the ABP appeared the most important independent predictor of a significant stenosis, overtoning all other parameters. The combination of these two variables however provided hardly a better sensitivity and specificity to identify graft stenosis $\geq 70\%$ than the PSV-ratio alone. A PSV-ratio >3.0 was a reasonable indicator of the presence of a stenosis $\geq 70\%$ DR, with a sensitivity of 80% an a specificity of 84%. In conclusion, of many surveillance parameters the PSV-ratio has the best correlation with the angiographic degree of stenosis.

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*Chapter* **6**

# Vein graft surveillance: Is graft revision without arteriography justified and what criteria should be used?

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## INTRODUCTION

Autogenous vein grafts provide the best conduit for bypass treatment of femoropopliteal and femorocrural occlusive disease. However, successful patency is threatened by the development of stenosis in 20% to 30%.[1-3] Frequent non-invasive examinations followed by elective revision of failing, but non-occluded grafts has become common practice, which is believed to salvage conduits as well as limbs.[4-7] The presence of a significant arteriographic stenosis is a reliable predictor of graft failure unless the lesion is repaired.[8-10] Replacing angiographic evaluation of vein graft stenosis by duplex scanning would be advantageous.[11] Graft occlusions may occur within the interval between the surveillance visit and the confirmative angiography.[9] Avoiding angiograms during follow-up would not only result in less delay of the revisional procedure, it also would reduce the overall cost of graft surveillance programs. This approach assumes that surveillance examinations have a high positive predictive value (PPV) and negative predictive value (NPV) to avoid unnecessary interventions and in order not to miss a large proportion of patients with failing grafts. There is no agreement on what outcomes of surveillance measurements are reliable indicators of expected graft failure or obvious need for intervention. In this report the results are presented of a prospective cohort study with strictly standardized surveillance techniques and digital subtraction angiography (DSA) in a series of patients with infrainguinal venous bypasses and a fixed protocol with regard to interventions for documented severe lesions in the graft or the adjacent arterial segments. The objective of this study was to examine correlations of parameters with the fate of the graft during follow-up. In addition the threshold level for the angiographic degree of stenosis to distinguish grafts with a high and a low risk of failure was validated.

## PATIENTS AND METHODS

The study protocol, patient characteristics and the surveillance protocol has been described in chapter 4 of this thesis.

### Study endpoints, data analysis

The occurrence of primary events in relation with the presence of a time-dependent risk factor, such as a PSV-ratio above a predefined level, can be determined by a cumulative hazard analysis and transient state method with Kaplan-Meier curves.[13,14] With this method the cumulative primary patency rate is assessed in two groups of observations. Group A involves all patients as long as a surveillance measurement remains within specified limits, for example a PSV-ratio <3.0 (Figure 2). In this group

the observation time starts at the time of the procedure (T = 0). If the PSV-ratio exceeds 3.0 a patient ceases to be part of group A and is further represented in group B. Patients are part of group B from the moment their surveillance parameters have exceeded the threshold value (T = 0). In both groups any patient reaching an endpoint of primary patency (primary event, i.e. a graft revision or occlusion) is represented as a drop in patency. Basically, this method, which was described by Mantel and Byar in 1974, allows a comparison of patency rates between patients with and without a time-dependent risk factor.[13,15] A perfect predictive value of a risk factor regarding the occurrence of events is represented by a 100% patency in group A and a zero patency in group B. As our previous study (chapter 5) has shown that the PSV-ratio is the best non-invasive parameter to grade vein graft stenosis, the PSV-ratio is used to define the groups.

## RESULTS

### Graft revisions and patencies

The median follow-up period was 20 months (range 1 to 40). Localization of revised stenoses, types of revision and numbers of graft occlusions are summarized in Table I. Interventions were performed in 84 (28%) of the grafts and the total number of revisions including multiple stenoses and recurrences was 144. Primary graft occlusions were diagnosed in 31 cases. In 16 the occlusion occurred without obvious cause, but in 15 patients the presence of a high-grade lesion was known. In the latter cases there usually was a delay to revise the graft and sometimes refusal or inability of the patient to return for the procedure. The 2-year primary patency determined by standard Kaplan-Meier life table analysis was 52% (SE 3%), and the secondary patency was 79% (SE 3%) for the total study group (Appendix A, see also notes to the Table I).

**Table I.** Graft stenoses, revisions and occlusions in 300 patients during follow-up.

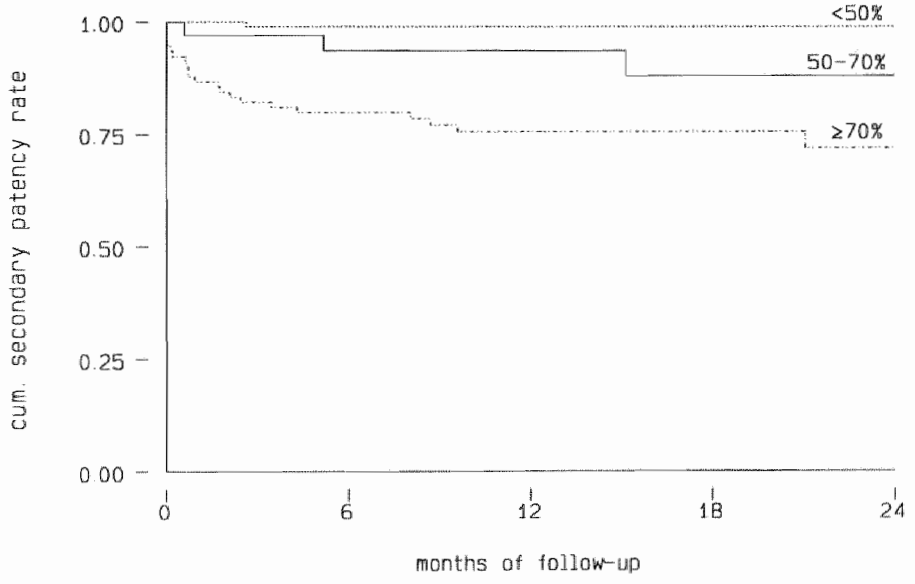
| | *Number* |
|---|---|
| Localization of revised stenoses (DSA) (n = 144 stenoses)* | |
| Inflow artery | 1 |
| Proximal anastomosis | 30 |
| Graft above the knee | 27 |
| Graft at the knee | 18 |
| Graft below the knee | 17 |
| Distal anastomosis | 39 |
| Run-off artery | 12 |
| Type of first time revision (n = 84 revisions)** | |
| PTA (atherectomy, stent) | 35 |
| Patchplasty | 17 |
| Interposition graft | 14 |
| Jump graft | 18 |
| Simultaneous revision of multiple stenoses (no. of revisions) | 13 |
| Subsequent revisions (no. of patients) | |
| 2 revisions | 31 |
| 3 revisions | 8 |
| Graft occlusions as primary event (n = 31 occlusions)** | |
| Occlusion without obvious cause | 16 |
| Occlusion with known high-grade stenosis | 15 |

* The total number of 144 revised stenoses involved the first time revisions (n = 84), simultaneous revisions of multiple stenoses (n = 13), and subsequent 2nd and 3rd revisions (n = 47); ** The total of 31 occlusions, together with 84 first time revisions constituted the patients with a primary event (n = 115) in the regular life table primary graft patency analysis for 300 patients (Appendix A). In 12 patients the occlusion was later than 6 months after the last surveillance examinations rendering any relation uncertain. Therefore these were not considered as a primary event in the transient state life table leaving 103 primary event patients for analysis (Appendix B, C and D).

**70% Angiographic diameter reduction as a risk factor of occlusion**

A validation was performed whether graft stenoses of 70% angiographic diameter reduction or greater imposed the greatest risk for occlusion. Therefore the secondary patency rate was compared for grafts with different degrees of stenosis, using the transient state method. In this analysis the onset of the observation periods coincided with the time of the arteriogram determining the classification. In the Kaplan-Meier curve using the transient state method the secondary cumulative patency is represented of grafts with a stenosis of <50%, 50% to 70%, ≥70% DR (Figure 1). The 18-month secondary patency rate in patients with <50% DR angiographic stenoses was 99%, in stenoses of 50% to 70% DR the patency was 87%, and in stenoses ≥70% it was 78% (Appendix B). It should be noted that as per protocol patients with a degree of stenosis less than 70% were not revised in this study, whereas all patients with a 70% lesion or greater had a graft revision planned. The validity of a 70% DR threshold value as discriminator between grafts with a high risk of failure or otherwise was clearly supported by this observation.

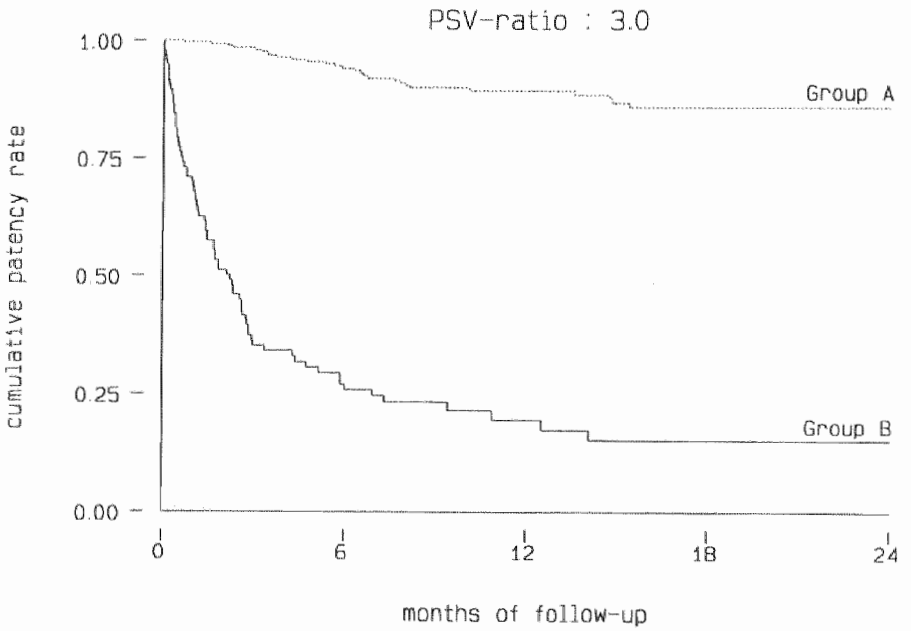
**Figure 1.** Secondary patency rates represented by Kaplan-Meier curves of patients with a angiographic stenosis <50%, 50% to 70% and ≥70%.



**Graft patency relative to surveillance parameters**

During the total follow-up-period 103 of 300 (34%) patients reached a primary patency endpoint (84 revisions and 19 primary occlusions within 6 months of the last surveillance duplex examination). Redo interventions were not included for this analysis. (See for a detailed account of graft revisions and occlusions in life table analysis the notes to Table I). From the investigation described in chapter five of this thesis, it appeared that the PSV-ratio was the best indicator of a high-grade graft stenosis. Therefore a series of cutoff values of this parameter was correlated with the occurrence of primary clinical events by cumulative hazard analysis with transient state method and Kaplan-Meier graphs. It is of note that in this study the only indication for revision of a graft lesion was a stenosis of 70% DR or greater at angiography.

**Figure 2.** Primary patency rates represented by Kaplan-Meier curves of patients with a PSV-ratio <3.0 (group A) and patients with a PSV-ratio ≥3.0 (group B). In group A, T = 0 coincided with the time of operation and in group B, T = 0 coincided with the first time the observed PSV-ratio was ≥3.0. Curve of group A depicts the patency as long as the PSV-ratio has not exceeded 3.0 (transient state method).



The first assessment was for a PSV-ratio of 3.0. Of the 300 patients in the study population 264 initially had a PSV-ratio <3.0 and therefore belonged to group A, while 97 patients, either had a PSV-ratio ≥3.0 at their initial surveillance examination or at a later time during following-up to be part of group B (Figure 2 and Appendix C). The 18-month primary patency of group A was 86% and in group B it was 15%. Alternatively these findings may be expressed as negative predictive value (NPV), represented by the primary patency in group A, and positive predictive value (PPV), which is equal to 100 minus the primary patency in group B. Thus the 18-month NPV of a PSV-ratio 3.0 is 86% and the PPV is 85%. This represents a just moderate agreement with the actual clinical course. Primary events in spite of a PSV-ratio <3.0 occurred in 27 patients and in 21 patients events failed to appear although they had a PSV-ratio ≥3.0. For clinical application an algorithm based on a single surveillance parameter does not appear sufficiently accurate to replace prerevision angiography.

In 23 patients the PSV-ratio progressed from <2.5 to ≥4.0 during the surveillance period. The PPV and NPV of PSV-ratios 2.5, 3.0, and 4.0 are represented together in Figure 3. None of these criteria was entirely correct in indicating whether a primary event would or would not occur, i.e. the PPV and NPV were less than 100% (Table II). A PSV-ratio of 2.5 was associated with a 18-month patency in group A of 89%, whereas a PSV-ratio of 4.0 had a patency in group B of 7%. If the best predictive values were combined by using the PSV-ratios 2.5 and 4.0 in one algorithm a better correlation with the occurrence of primary events was obtained than with one cutoff value (Figure 4 and Appendix D). The accuracy of this criterion was represented by a NPV of 89% and a PPV of 93% (Table II). If used as an algorithm the observation of a PSV-ratio <2.5 may be interpreted as a graft not at risk and graft surveillance should be continued. If a PSV-ratio ≥4.0 is recorded a graft is at high risk for failure and a revision should be scheduled without the need of a pretreatment angiogram. Cases with PSV-ratios between 2.5 and 4.0 represent an intermediate risk group and an angiographic study is indicated to verify whether a stenosis of 70% DR or greater is present.

**Table II.** Prediction of endpoints of primary patency by different PSV-ratios.

| *PSV-ratio threshold value* | *NPV %* | *PPV %* |
|---|---|---|
| 2.5 | 89 | 79 |
| 3.0 | 86 | 85 |
| 4.0 | 80 | 93 |

NPV is negative predictive value; PPV is positive predictive value; indicated NPV and PPV represent 18-month value.

**Figure 3.** Primary patency rates represented by Kaplan-Meier curves of patients with PSV-ratios less (upper curves) or greater (lower curves) than 2.5, 3.0 and 4.0 (transient state method).

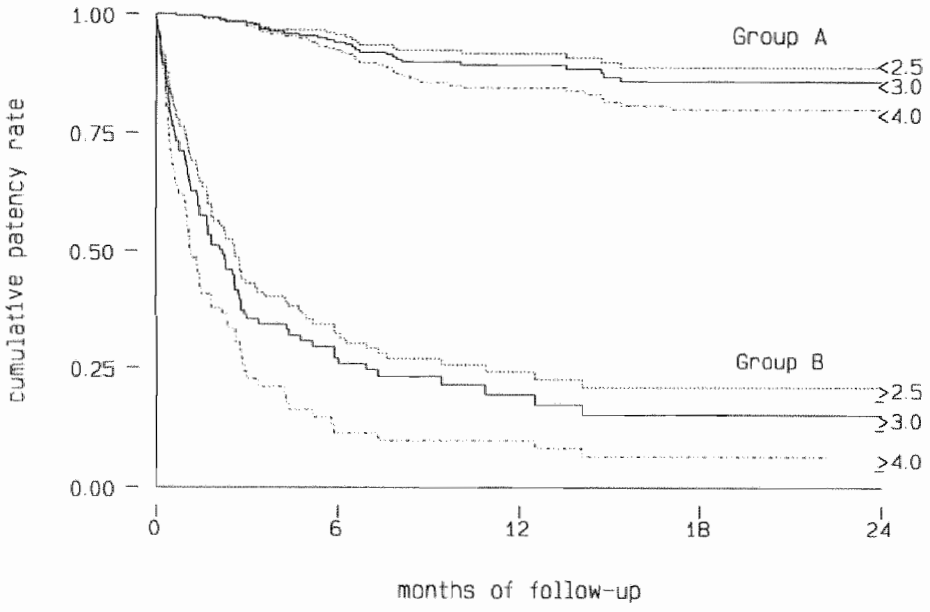
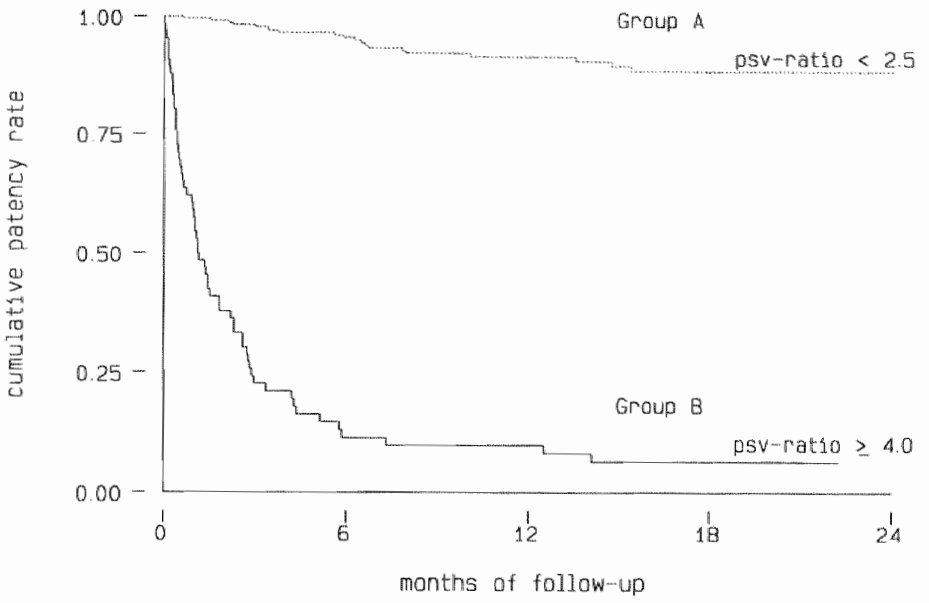


**Figure 4.** Primary patency rates represented by Kaplan-Meier curves of patients with a PSV-ratio <2.5 (group A) and patients with a PSV-ratio ≥4.0 (group B) (transient state method).




In Table III the consequences of the two-parameter algorithm are summarized. If this algorithm had been applied 5 patients with a PSV-ratio ≥4.0 would have undergone an intervention, but had in fact no revision as their angiographic stenoses were less than 70% (false positive observations). The angiographic stenoses in these 5 patients had a DR of 60%, 55%, 55%, 45% and 40%. Had interventions been performed on the basis of duplex findings these may be considered unnecessary treatment. 20 Grafts had a primary event in spite of a PSV-ratio <2.5 (false negative observation). This category included a sudden graft occlusion without obvious cause in 8, and revision of high-grade lesions on the basis of angiograms in 12 patients. These latter patients, although they had no signs of a localized velocity increase, still had lesions in the graft, the inflow or the run-off. Angiograms were requested because of a "low flow state" (PSV-graft <45 cm/s) in 7 patients, return of severe symptoms in 4 patients, and in only one patient the stenosis was detected coincidentally on a protocol-directed control DSA. Moreover, in the two-parameter algorithm 64 DSAs were required in patients with a PSV ratio between 2.5 and 4.0 (Table III), while a graft revision without angiography would have been scheduled in 61 patients (true positive diagnosis, i.e. patients with a

PSV ≥4.0 and terminal event - Appendix D). This implied a 49% reduction in DSAs compared with a policy of requesting an angiogram in any patient with a PSV-ratio of 2.5 or greater. On the basis of these observations it was concluded that a two-parameter algorithm could be practically applied in a surveillance program to limit the use of angiographic studies.

**Table III.** Revisions, conservative approaches and angiograms with two surveillance algorithms.

| *Diagnosis* | *Consequences if algorithm was applied* | *Two-parameter algorithm no. of patients* | *Single-parameter algorithm no. of patients* |
|---|---|---|---|
| False positive | Unnecessary revisions of lesions with DR <70% | 5 | 21 |
| False negative | Acute occlusion or no treatment in spite of lesions with DR ≥70% | 20 | 27 |
| Uncertain | DSAs required | 64 | 0 |

Single-parameter algorithm includes: conservative approach in PSV-ratios <3.0, intervention in PSV-ratios ≥3.0, and no angiograms. Two-parameter algorithm includes: conservative approach in PSV-ratios <2.5, digital subtraction angiogram (DSA) in PSV-ratios 2.5 to 4.0 to determine the degree of stenosis and whether an intervention is indicated, and intervention without angiogram in PSV-ratios ≥4.0.

## DISCUSSION

It is generally accepted that the follow-up of patients with infrainguinal vein grafts should be directed toward the identification of failing grafts. At this stage relatively minor procedures can often avert impending graft failure.[16,17] Most vascular surgeons still consider intraarterial DSA mandatory before performing an intervention on a graft stenosis detected by non-invasive surveillance methods. However, there is some variation in the severity of the stenosis that is considered to represent a considerable risk of graft failure. A DR of 50% has been proposed as the critical level by several authors,[4,18-23] while others believe a lesion with a 70% DR to indicate a failing vein graft.[2,8-10,20,21] It may be assumed that these differences at least in part, account for the variations in the critical PSV-ratios that have been reported in the literature. In the

present study the angiographic DR was measured by radiologists blinded for the findings at duplex examinations. In a validating assessment we found that a 70% threshold correlated significantly with graft failure. Non-revised stenoses of 50% to 70% had a better patency than stenoses of 70% DR or greater, which fell in the patient category with revisions.

Angiography to confirm a suspected asymptomatic graft lesion is cumbersome and it causes delay of effective treatment, which may result in graft failure if the stenosis is high-grade. In the this prospective study 15 vein grafts with known presence of a stenosis failed during the interval between the last surveillance visit and the intervention. In addition, angiographic evaluation adds considerably to the cost of follow-up, making surveillance programs less cost-effective. A surveillance schedule by which angiography is avoided altogether would be ideal.[11] It was examined whether a single-parameter surveillance algorithm based on a PSV-ratio of 3.0 provided such a scheme. However a NPV of 86% (27 patients false negative) and a PPV of 85% (21 patients false positive) was not satisfactory. To compare the positive and negative predictive values of different surveillance parameters an appropriate statistical technique was used.[15] This statistic is very similar to the logrank statistics, except that group membership is not fixed along time. With cumulative hazard analysis and transient state method using Kaplan-Meier life tables PSV-ratios above a threshold value were considered risk factors and their agreement with actual occurrence of primary events was assessed. In this analysis patients with normal PSV-ratios serve as a pseudo-control group.

Although not all grafts with a high-grade stenosis occlude and some without lesions still fail, no surveillance algorithm will be perfect. Requirements for an algorithm in our view should include as a first priority the avoidance of unnecessary interventions, which corresponds with a high PPV. The second priority is to miss as few severe stenoses as possible, corresponding with a high NPV. The final requirement is to avoid angiograms or at least a portion of it. The two-parameter algorithm outlined in this study distinguished three risk classes for graft failure requiring different management strategies. The algorithm implicated a conservative approach in patients with a PSV-ratio <2.5, a revision without preceding angiography with PSV-ratios >4.0, and a DSA in patients with PSV-ratios between 2.5 and 4.0. The non-invasive diagnostic criteria when correlated with the actual angiographic findings had a PPV of 93% and an NPV of 89%. Of the 5 patients with a false positive diagnosis 3 had a stenosis greater than 50% at the time of angiography, which perhaps might have justified a revision. Of the 20 patients with a false negative diagnosis 8 had a graft occlusion without any prior duplex or angiographic evidence of a stenotic lesion. We assume that these grafts could not have been salvaged by a revision. Of the other patients only one had a completely missed stenosis, while the other patients had either "low flow state" grafts or recurrent clinical symptoms. Although these variables are

poor indicators of graft stenoses in statistical models they do have clinical significance and should be considered combined with high velocity criteria.[23,24] Thus one could argue that with a structured non-invasive diagnostic protocol and a reduced use of angiograms in a series of 300 patients only 2 with a false positive diagnosis and 1 with a false negative diagnosis would have received inappropriate treatment, which seems an acceptably low rate.

The two-parameter algorithm needs to be evaluated in a future prospective study. Other aspects than the degree of stenosis that may influence planning of interventions are length and multiplicity of lesions. Both features can be studied adequately by modern color-flow duplex equipment. Lesions of less than one centimeter can be scheduled for percutaneous angioplasty and longer lesions for operative repair either by patch angioplasty or by interposition grafting.[25]

In conclusion, an algorithm using two cutoff levels to delineate patient groups with a low, an intermediate and a high risk of graft failure seems applicable. Clinical management can be based on this decision tree. The number of angiograms during follow-up in patients with a significantly increased PSV-ratio can be reduced considerably as these need to be requested in the intermediate group only.

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**Appendix A.** Life table primary and secondary graft patency analysis for 300 infrainguinal vein grafts.

| *Interval (mo)* | *No. grafts at risk* | *No. grafts with terminal events* | *No. grafts withdrawn* | *Interval patency rate* | *Cum. patency rate* | *SE* |
|---|---|---|---|---|---|---|
| *Primary patency* | | | | | | |
| 0-3 | 300 | 36 | 3 | 0.88 | 0.88 | 0.02 |
| 3-6 | 261 | 35 | 10 | 0.86 | 0.76 | 0.02 |
| 6-9 | 216 | 26 | 10 | 0.88 | 0.67 | 0.03 |
| 9-12 | 180 | 5 | 25 | 0.97 | 0.65 | 0.03 |
| 12-15 | 150 | 7 | 37 | 0.95 | 0.61 | 0.03 |
| 15-18 | 106 | 3 | 10 | 0.97 | 0.59 | 0.03 |
| 18-21 | 93 | 1 | 18 | 0.99 | 0.59 | 0.03 |
| 21-24 | 74 | 1 | 13 | 0.99 | 0.58 | 0.03 |
| 24-27 | 60 | 0 | 13 | 1.00 | 0.58 | 0.03 |
| *Secondary patency* | | | | | | |
| 0-3 | 300 | 2 | 5 | 0.99 | 0.99 | 0.01 |
| 3-6 | 293 | 16 | 11 | 0.94 | 0.94 | 0.01 |
| 6-9 | 266 | 6 | 12 | 0.98 | 0.92 | 0.02 |
| 9-12 | 248 | 2 | 36 | 0.99 | 0.91 | 0.02 |
| 12-15 | 210 | 3 | 44 | 0.99 | 0.89 | 0.02 |
| 15-18 | 163 | 2 | 17 | 1.00 | 0.88 | 0.02 |
| 18-21 | 144 | 0 | 24 | 0.99 | 0.87 | 0.02 |
| 21-24 | 120 | 1 | 22 | 0.99 | 0.86 | 0.02 |
| 24-27 | 97 | 1 | 25 | 0.97 | 0.84 | 0.02 |

**Appendix B.** Life table secondary graft patency analysis for 300 patients with infrainguinal vein grafts relative to the angiographic diameter reduction (transient state method).

| *Interval (mo)* | *No. grafts at risk* | *No. grafts with terminal events* | *No. grafts withdrawn* | *Interval patency rate* | *Cum. patency rate* | *SE* |
|---|---|---|---|---|---|---|
| *Angiographic DR <50%* | | | | | | |
| 0-3 | 117 | 1 | 17 | 0.99 | 0.99 | 0.01 |
| 3-6 | 99 | 0 | 26 | 1.00 | 0.99 | 0.01 |
| 6-9 | 67 | 0 | 6 | 1.00 | 0.99 | 0.01 |
| 9-12 | 67 | 0 | 20 | 1.00 | 0.99 | 0.01 |
| 12-15 | 47 | 0 | 4 | 1.00 | 0.99 | 0.01 |
| 15-18 | 43 | 0 | 16 | 1.00 | 0.99 | 0.01 |
| 18-21 | 27 | 0 | 7 | 1.00 | 0.99 | 0.01 |
| 21-24 | 20 | 0 | 9 | 1.00 | 0.99 | 0.01 |
| *Angiographic DR 50% to 70%* | | | | | | |
| 0-3 | 36 | 1 | 3 | 0.97 | 0.97 | 0.03 |
| 3-6 | 32 | 1 | 4 | 0.97 | 0.94 | 0.04 |
| 6-9 | 27 | 0 | 4 | 1.00 | 0.94 | 0.04 |
| 9-12 | 23 | 0 | 6 | 1.00 | 0.94 | 0.04 |
| 12-15 | 17 | 0 | 0 | 1.00 | 0.94 | 0.04 |
| 15-18 | 17 | 1 | 5 | 0.93 | 0.87 | 0.07 |
| 18-21 | 11 | 0 | 3 | 1.00 | 0.87 | 0.07 |
| 21-24 | 8 | 0 | 3 | 1.00 | 0.87 | 0.07 |
| *Angiographic DR ≥70%* | | | | | | |
| 0-3 | 88 | 13 | 5 | 0.85 | 0.85 | 0.04 |
| 3-6 | 70 | 2 | 2 | 0.97 | 0.82 | 0.04 |
| 6-9 | 66 | 2 | 9 | 0.97 | 0.80 | 0.04 |
| 9-12 | 55 | 1 | 6 | 0.98 | 0.78 | 0.05 |
| 12-15 | 48 | 0 | 11 | 1.00 | 0.78 | 0.05 |
| 15-18 | 37 | 0 | 10 | 1.00 | 0.78 | 0.05 |
| 18-21 | 27 | 0 | 6 | 1.00 | 0.78 | 0.05 |
| 21-24 | 21 | 1 | 3 | 0.95 | 0.74 | 0.06 |

**Appendix C.** Life table primary graft patency analysis for 300 patients with infrainguinal vein grafts relative to observed PSV-ratio <3.0 or ≥3.0 (transient state method).

| *Interval (mo)* | *No. grafts at risk* | *No. grafts with terminal events* | *No. grafts withdrawn* | *Interval patency rate* | *Cum. patency rate* | *SE* |
|---|---|---|---|---|---|---|
| *Group A: PSV <3.0* | | | | | | |
| 0-3 | 264 | 5 | 10 | 0.98 | 0.98 | 0.01 |
| 3-6 | 249 | 9 | 45 | 0.96 | 0.94 | 0.02 |
| 6-9 | 195 | 8 | 21 | 0.96 | 0.90 | 0.02 |
| 9-12 | 166 | 1 | 31 | 0.99 | 0.89 | 0.02 |
| 12-15 | 134 | 3 | 34 | 0.97 | 0.87 | 0.02 |
| 15-18 | 97 | 1 | 11 | 0.99 | 0.86 | 0.03 |
| 18-21 | 85 | 0 | 17 | 1.00 | 0.86 | 0.03 |
| 21-24 | 68 | 0 | 13 | 1.00 | 0.86 | 0.03 |
| *Group B: PSV ≥3.0* | | | | | | |
| 0-3 | 97 | 62 | 2 | 0.35 | 0.35 | 0.05 |
| 3-6 | 33 | 7 | 3 | 0.78 | 0.27 | 0.05 |
| 6-9 | 23 | 3 | 5 | 0.85 | 0.23 | 0.04 |
| 9-12 | 15 | 2 | 4 | 0.85 | 0.20 | 0.04 |
| 12-15 | 9 | 2 | 0 | 0.78 | 0.15 | 0.04 |
| 15-18 | 7 | 0 | 0 | 1.00 | 0.15 | 0.04 |
| 18-21 | 7 | 0 | 3 | 1.00 | 0.15 | 0.04 |
| 21-24 | 4 | 0 | 3 | 1.00 | 0.15 | 0.04 |

**Appendix D.** Life table primary graft patency analysis for 300 patients with infrainguinal vein grafts relative to observed PSV-ratio (transient state method).

| *Interval (mo)* | *No. grafts at risk* | *No. grafts with terminal events* | *No. grafts withdrawn* | *Interval patency rate* | *Cum. patency rate* | *SE* |
|---|---|---|---|---|---|---|
| *PSV-ratio: 2.5* | | | | | | |
| *Group A (PSV-ratio <2.5)* | | | | | | |
| 0-3 | 252 | 5 | 8 | 0.98 | 0.98 | 0.01 |
| 3-6 | 239 | 5 | 46 | 0.98 | 0.96 | 0.01 |
| 6-9 | 188 | 6 | 22 | 0.97 | 0.92 | 0.02 |
| 9-12 | 160 | 1 | 31 | 0.99 | 0.92 | 0.02 |
| 12-15 | 128 | 2 | 36 | 0.98 | 0.90 | 0.02 |
| 15-18 | 90 | 1 | 10 | 0.99 | 0.89 | 0.02 |
| 18-21 | 79 | 0 | 12 | 1.00 | 0.89 | 0.02 |
| 21-24 | 64 | 0 | 12 | 1.00 | 0.89 | 0.02 |
| *Group B (PSV-ratio ≥2.5)* | | | | | | |
| 0-3 | 113 | 63 | 4 | 0.43 | 0.43 | 0.05 |
| 3-6 | 46 | 11 | 3 | 0.75 | 0.33 | 0.05 |
| 6-9 | 32 | 5 | 5 | 0.83 | 0.27 | 0.04 |
| 9-12 | 22 | 2 | 4 | 0.90 | 0.24 | 0.04 |
| 12-15 | 16 | 2 | 2 | 0.87 | 0.21 | 0.04 |
| 15-18 | 12 | 0 | 0 | 1.00 | 0.21 | 0.04 |
| 18-21 | 12 | 0 | 4 | 1.00 | 0.21 | 0.04 |
| 21-24 | 8 | 0 | 6 | 1.00 | 0.21 | 0.04 |

**Appendix D - continued.** Life table primary graft patency analysis for 300 patients with infrainguinal vein grafts relative to observed PSV-ratio (transient state method).

| *Interval (mo)* | *No. grafts at risk* | *No. grafts with terminal events* | *No. grafts withdrawn* | *Interval patency rate* | *Cum. patency rate* | *SE* |
|---|---|---|---|---|---|---|
| *PSV-ratio: 4.0* | | | | | | |
| *Group A (PSV-ratio <4.0)* | | | | | | |
| 0-3 | 273 | 7 | 10 | 0.97 | 0.97 | 0.01 |
| 3-6 | 256 | 12 | 32 | 0.95 | 0.93 | 0.02 |
| 6-9 | 212 | 15 | 17 | 0.93 | 0.86 | 0.02 |
| 9-12 | 180 | 2 | 30 | 0.99 | 0.85 | 0.02 |
| 12-15 | 148 | 4 | 41 | 0.97 | 0.82 | 0.03 |
| 15-18 | 103 | 2 | 11 | 0.98 | 0.80 | 0.03 |
| 18-21 | 90 | 0 | 18 | 1.00 | 0.80 | 0.03 |
| 21-24 | 72 | 0 | 13 | 1.00 | 0.80 | 0.03 |
| *Group B (PSV-ratio ≥4.0)* | | | | | | |
| 0-3 | 66 | 51 | 0 | 0.23 | 0.23 | 0.05 |
| 3-6 | 15 | 7 | 1 | 0.52 | 0.12 | 0.04 |
| 6-9 | 7 | 1 | 0 | 0.86 | 0.10 | 0.04 |
| 9-12 | 6 | 0 | 0 | 1.00 | 0.10 | 0.04 |
| 12-15 | 6 | 2 | 0 | 0.67 | 0.07 | 0.03 |
| 15-18 | 4 | 0 | 1 | 1.00 | 0.07 | 0.03 |
| 18-21 | 3 | 0 | 2 | 1.00 | 0.07 | 0.03 |
| 21-24 | 1 | 0 | 1 | 1.00 | 0.07 | 0.03 |

*Chapter* 7

# Economizing vein graft surveillance programs

*This chapter was modified from:*
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*Eur J Vasc Endovasc Surg 1998 (in press)*

## INTRODUCTION

Intrinsic vein graft stenosis is a major threat to infrainguinal bypasses. In approximately 30% of all vein grafts stenotic lesions will develop, due to intima hyperplasia, remodeling or fibrosis.[1-3] Vein graft surveillance has been shown to be an effective method of identifying stenotic lesions, thus allowing repair of these defects before graft thrombosis occurrs. However, the necessity for repetitive duplex testing during a longer period of time makes considerable demands on patients and vascular laboratories. Better utilisation of resources may be obtained by restricting surveillance testing to patients at high-risk of developing graft stenosis. Several patient factors, operative technical and vein graft related factors have been identified as being associated with an increased risk of stenosis development or graft occlusion.[4,5] Recently it has been suggested that most stenotic lesions are the result of progression of residual vein graft lesions or platelet deposits already present at the time of operation. In this view it might be possible that patients with grafts that have a high risk of developing significant lesions during follow-up can be identified by the first postoperative duplex scanning soon after the bypass procedure.[6-8]

The large majority of graft lesions develop within the first 12 months, and many authors agree therefore, that surveillance may be discontinued at that time.[4,9] Others have stressed that serial examinations can not be dispensed after 1 year and graft surveillance should be continued for longer periods, if not for the duration of the patient's life.[10-13] An alternative way of reducing expenses and workload involved with stenosis detection may be to limit the duration of the surveillance period and thus the number of examinations.

In this study the effectiveness of these two strategies targeted to a reduction of duplex surveillance testing was investigated. The first strategy attempted to reduce the number of patients for continued surveillance by identifying grafts with a higher risk of significant stenosis, indicated by the presence of early duplex abnormalities. In the second strategy the effect of reducing the duration of the surveillance program in the overall patient group, with regard to the number of graft stenoses that would be missed, was examined.

## PATIENTS AND METHODS

The study protocol, patient characteristics and the surveillance protocol has been described in chapter 4 of this thesis.

To assess the optimal duration of graft surveillance, a regularly measured PSV-ratio was used as an indicator of "significant graft stenosis" (PSV-ratio $\geq 2.5$). An "event causing stenosis" was present if a stenosis required a revision. All revised

lesions had a diameter reduction greater than 70% on angiography. Moreover, stenoses that had caused a graft occlusion before a revision was undertaken, were defined "event causing stenoses". A stenosis was classified a "*de novo* stenosis" if the previous PSV-ratio was <2.0, and a "progressive stenosis" if it was ≥2.0 at a previous visit and increased by 1.0 or more.

Intraoperative or predischarge duplex entire graft scanning was infrequently performed during the study. Therefore these data were not included in the analysis. Early duplex scanning was defined as the first complete graft examination, which was after 4 to 6 weeks.

**Definitions and data-analysis**

A primary event was defined as revision of a stenotic but patent graft, or graft occlusion. Primary graft failure was used as the study endpoint for a patient. The efficacy of initial surveillance measurements as predictor for the development of severe graft stenosis was represented by the primary patency. For all patients the occurrence of primary events and the time interval between the event and the initial duplex scanning was recorded. Kaplan-Meier curves were used with grafts categorised according to the PSV-ratio at the first surveillance visit. Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the initial PSV-ratio for predicting primary graft failure in the first year. The analysis was performed using SPSS 7.0 for Windows statistical software.

## RESULTS

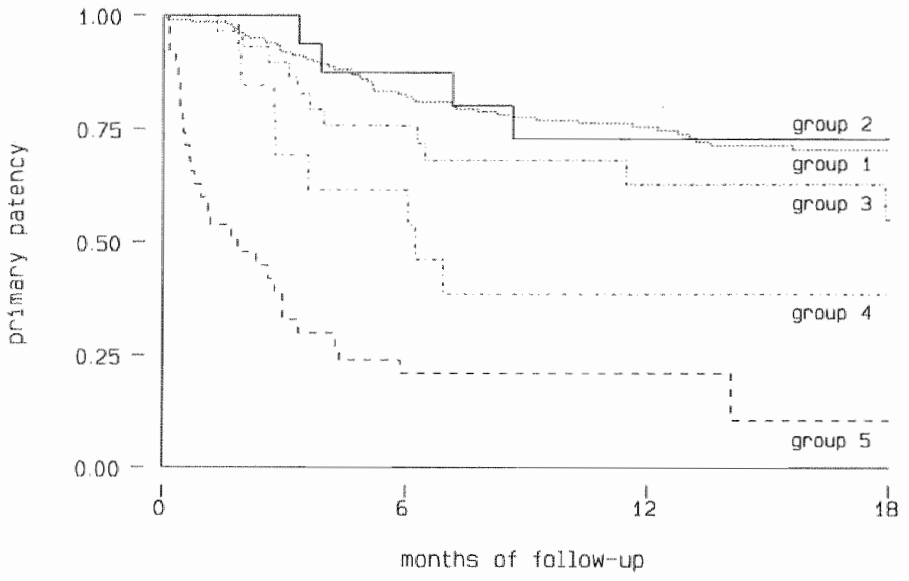
**Initial duplex examination**

Most (74%) of the initial duplex examinations were performed within 6 weeks after the operation, and 94% were performed within three months after graft implantation. Kaplan-Meier curves of the primary patency were constructed for patient groups with an initial PSV-ratio <1.5 (group 1), 1.5 to 2.0 (group 2), 2.0 to 2.5 (group 3), 2.5 to 3.0 (group 4), and ≥3.0 (group 5) (Figure 1). Patients with "early lesions" groups 2 and 3 did not show a different course of their primary patency than patients with "normal grafts" (group 1) (primary patencies at 12 months of 63%, 73%, and 71% respectively). The primary patency of group 4 and 5 at 12 months was 38% and 21% respectively. Group 4 differed from groups 1 to 3 ($p$, respectively, <0.001, 0.07, 0.01), and group 5 differed from groups 1 to 3 ($p$, all <0.001).

The clinical applicability of the initial PSV-ratio to discriminate grafts with a high and a low probability of encountering a primary event during the first year was further assessed by a ROC-analysis, represented in Figure 2. There was no distinct threshold value for this separation, as the best combination of sensitivity and

specificity was still rather low (54% and 75% respectively). The secondary 12-month patency for groups with a PSV-ratio ≥3.0 and <3.0 was 80% and 92% respectively ($p = 0.01$).

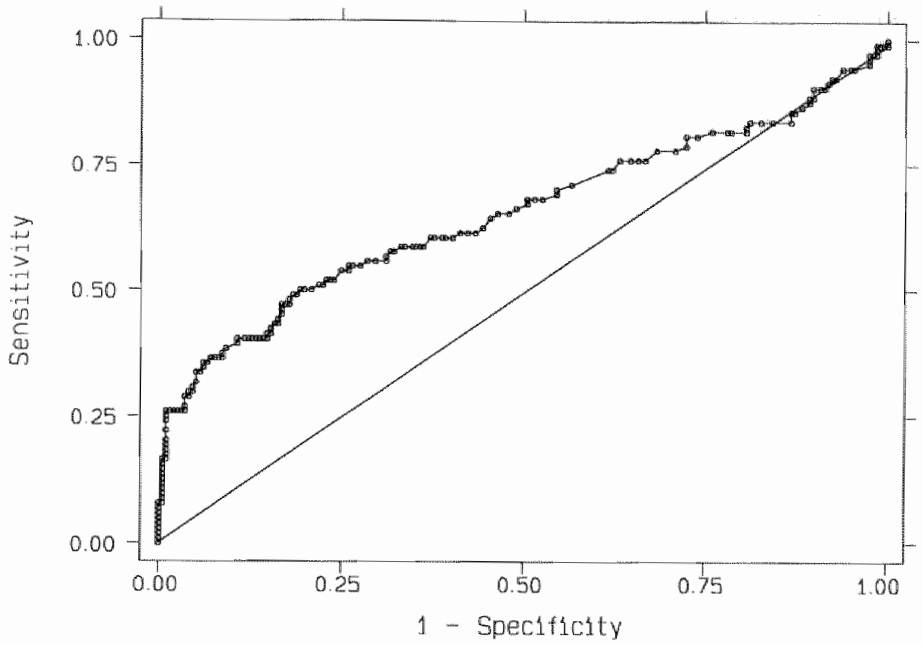
**Figure 1.** Primary patency rates represented by Kaplan-Meier curves of patient groups according to the initial PSV-ratio: group 1 (PSV-ratio <1.5), group 2 (PSV-ratio 1.5 to 2.0), group 3 (PSV-ratio 2.0 to 2.5), group 4 (PSV-ratio 2.5 to 3.0), and group 5 (PSV-ratio ≥3.0). On the abscissa T = 0 represents the time of the initial duplex examination.




**Grafts at risk**

| *Initial PSV-ratio* | | *0 months* | *6 months* | *12 months* | *18 months* |
|---|---|---|---|---|---|
| ≤1.5 | *(group 1)* | 203 | 149 | 95 | 65 |
| 1.5 to 2.0 | *(group 2)* | 30 | 20 | 11 | 7 |
| 2.0 to 2.5 | *(group 3)* | 18 | 13 | 7 | 5 |
| 2.5 to 3.0 | *(group 4)* | 14 | 8 | 3 | 3 |
| ≥3.0 | *(group 5)* | 35 | 7 | 3 | 1 |

**Figure 2.** Receiver operating characteristic (ROC) curves of the initial peak systolic velocity ratio (PSV-ratio) and its correlation with primary events during the first year.




**Duration of surveillance period**

For all grafts in this study (including grafts that were enrolled again after their first or second revision) the time of onset of "significant stenosis" (PSV-ratio ≥2.5), and of "event causing *de novo* stenosis" (revision or occlusion) is represented in Table I. Of all performed surveillance examinations the interval rates of significant *de novo* stenosis were 17%, 14%, and 10% at 6 weeks, 3 months, and 6 months. At the 9th and 12th month interval the incidence was considerably lower, 5% and 5% respectively. Event causing *de novo* stenosis occurred at the 6th week, 3rd month and 6th month interval in 8%, 8%, and 8%. At the 9th and 12th month interval this type of stenosis occurred in 4% and 7% of the grafts. Of the total of 111 event causing stenosis that occurred during the first year, 100 were associated with a revision and 11 with an occlusion.

In a second analysis of similar nature, grafts that underwent a revision were excluded after this primary event. In this assessment, in which second and third graft revisions were not considered, the interval rate of significant *de novo* stenosis at 9 and 12 months was 4% and 3% respectively, and significant progressive stenoses were

observed in 2% and 5% respectively. The interval rate of event causing *de novo* stenosis at the 9th and 12th month interval was 2% and 1% respectively (Table II). Of the total of 82 event causing stenoses that were observed in the first year 75 were associated with a revision and 7 with an occlusion. The sharp drop in the interval incidence of event causing *de novo* stenoses in previously unrevised grafts after 6 months is visualized in Figure 3. During the first year, of all event causing *de novo* stenoses, 84% had occurred within 6 months.

**Table I.** Stenoses occurring in all surveilled grafts, including grafts that were enrolled again after a 1st and a 2nd revision.

| *All grafts* | *6 week* | *3 month* | *6 month* | *9 month* | *12 month* |
|---|---|---|---|---|---|
| No. surveilled grafts | 244 | 244 | 238 | 221 | 210 |
| Significant graft stenosis[1] | | | | | |
| Total | 41 | 57 | 50 | 40 | 35 |
| *De novo*[2] | 41 | 34 | 23 | 11 | 10 |
| Progressive[3] | - | 23 | 27 | 29 | 25 |
| Event causing stenosis[4] | | | | | |
| Total | 20 | 31 | 32 | 12 | 16 |
| *De novo* | 20 | 20 | 19 | 8 | 15 |
| Progressive | - | 11 | 13 | 4 | 1 |
| Recurrent stenosis[5] | - | 4 | 5 | 6 | 9 |
| Event causing *de novo* stenosis / no. grafts (%) | 8 | 8 | 8 | 4 | 7 |

1. Significant stenosis is PSV-ratio ≥2.5; **2**. *de novo* stenosis is previous PSV-ratio <2.0; **3**. progressive stenosis is previous PSV-ratio ≥2.0 and increase of PSV-ratio ≥1.0; **4**. event causing stenosis is graft with revision or occlusion; **5**. recurrent stenosis is revised graft with secondary event causing stenosis.

**Table II.** Stenoses occurring in surveilled grafts with follow-up ending after a first revision.

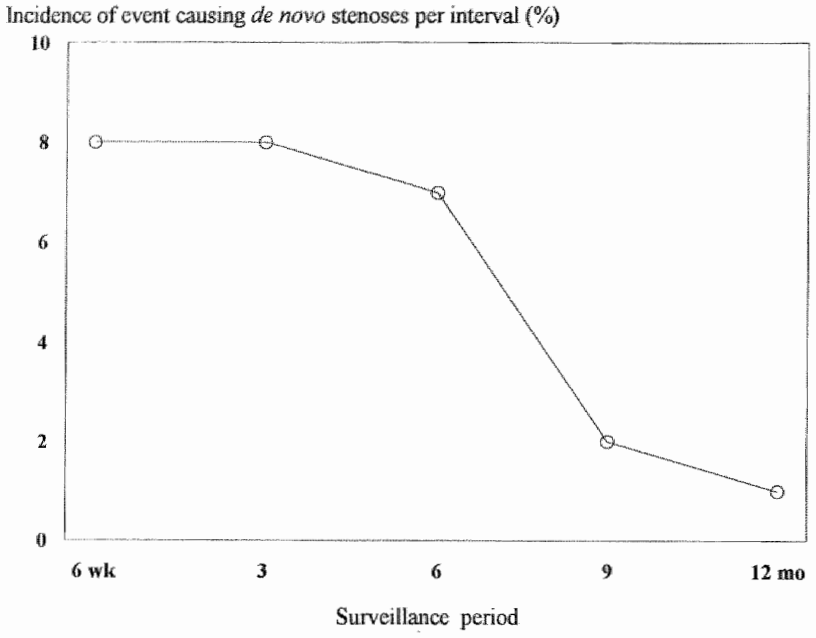
| ***Previously unrevised grafts*** | *6 week* | *3 month* | *6 month* | *9 month* | *12 month* |
|---|---|---|---|---|---|
| No. surveilled grafts | 244 | 224 | 203 | 169 | 152 |
| Significant graft stenosis[1] | | | | | |
| Total | 41 | 50 | 39 | 24 | 18 |
| *De novo*[2] | 41 | 31 | 18 | 6 | 5 |
| Progressive sten.[3] | - | 9 | 12 | 4 | 7 |
| Stable sten.[4] | - | 10 | 9 | 14 | 6 |
| Event causing stenosis[5] | | | | | |
| Total | 20 | 26 | 23 | 6 | 7 |
| *De novo* | 20 | 19 | 15 | 4 | 2 |
| Progressive | - | 7 | 8 | 2 | 5 |
| Event causing *de novo* stenosis / no. grafts (%) | 8 | 8 | 7 | 2 | 1 |

**1**. Significant stenosis is PSV-ratio ≥2.5; **2**. *de novo* stenosis is previous PSV-ratio <2.0; **3**. progressive stenosis is previous PSV-ratio ≥2.0 and increase of PSV-ratio ≥1.0; **4**. stable stenosis is previous PSV-ratio ≥2.0 and increase of PSV-ratio <1.0; **5**. event causing stenosis is graft with revision or occlusion.

## DISCUSSION

The usefulness of duplex scanning for follow-up of infrainguinal vein grafts has long been recognised, and several comparative studies have demonstrated that duplex scanning is superior to standard follow-up methods for detecting graft stenosis.[2,14-17] Some individual grafts are at greater risk of failure than others. Factors that were reported to be associated with this higher risk include: critical limb ischemia, diabetes, poor crural run-off, previous arterial reconstruction, composite or spliced vein grafts, non in-situ technique, and minimal graft diameter.[4,5,10,16] In the present study the risk of severe graft stenosis requiring intervention was significantly increased in grafts that had a PSV-ratio (≥2.5) at the initial duplex examination. It is likely that the development of stenoses in many patients begins at the time of surgery, and if progression is rapid, these lesions are associated with a high failure rate.

**Figure 3.** The incidence of event causing *de novo* stenoses per surveillance interval in previously unrevised grafts during the first postoperative year.




It has been suggested that the first duplex scanning is best performed at the completion of the operation or before discharge. Unrepaired early duplex abnormalities required later correction in 32% to 52%.[5-8,18] It is assumed that residual and minor defects in vein grafts may serve as a nidus for severe graft stenoses to develop later after implantation. It was hypothesized that if early postoperative duplex findings permitted distinction of grafts into low and high-risk groups, a more rational surveillance protocol may be instituted. Mills and coworkers found that 45% of lesions detected by intraoperative duplex scanning progressed to high-grade stenoses, that either required revision or occluded before an intervention was performed. In their study 23% of lesions remained stable, and 32% regressed.[6] These authors, as well as others suggested that an early separation of grafts into high-risk and low-risk groups was possible, allowing them to focus all surveillance attention to the higher risk group, while subjecting the other grafts to a less intensive or non-surveillance policy.[6,8] The outcome of the present prospective study supports the observation of these earlier studies, though not necessarily their conclusions. As expected, we found that early severe lesions (PSV-ratio $\geq 2.5$) quite often required a revision. Grafts with "early mild

to moderate lesions" represented by initial PSV-ratios between 1.5 and 2.5 follow a similar course with regard to primary patency as grafts in patients with completely normal PSV-ratios (<1.5). In addition it appears that patients with normal grafts by no means are safeguarded for a primary event at later follow-up, as the primary patency at 12 months was 71%. Therefore, excluding initially normal grafts from further surveillance would have resulted in a less effective surveillance protocol. These observations are supported by other studies, in which it was found that normal early duplex findings did not equate with the long-term absence of graft-threatening lesions.[19,20] Consequently, all grafts need to be followed from an early stage. At present we perform a full predischarge duplex scan in all patients. Whether this will improve on the information obtained by a 6-week scan as the initial examination, requires further evaluation. It is known that approximately one-third of early identified stenoses regress[6] negating the usefulness of their detection in the first postoperative week. The favorable overall outcome of revising identified severely stenotic lesions, which has been reported in many previous studies,[2,7,17,19] was confirmed in the present study. The secondary patency rate in the category with PSV-ratios ≥3.0 was 80%, which may be considered a satisfactory result.

Taylor *et al.* were among the first to propose in 1990 a rationalized surveillance program by limiting the duration.[9] In their study all stenoses were detected in the first year after operation and none occurred after this time. It was recognized that grafts will continue to fail in subsequent years, but this was at an annual rate of only 2% to 3%, which did not justify the cost involved with continuing surveillance of all grafts. At the present time many authors agree that routine graft surveillance is not indicated after 12 months of follow-up.[4,9,21] Erickson *et al.* in a recent analysis kept an opposite view.[13] They observed that of 236 grafts that developed surveillance abnormalities 21 had their initial defect more than 2 years after the initial bypass procedure. However, in this series, stenoses in the vein itself developed after a median follow-up period of 6 to 8.5 months, whereas inflow and run-off lesions developed after a median follow-up of 15 and 29 months, respectively. This difference in the time of onset of lesions in the vein conduit and in the arteries was explained by the different nature of the lesions, with slower progressing atherosclerosis being the dominant factor in the inflow and run-off segments.

Grafting technique is suggested to make a difference for the time of onset of stenoses. In a series, exclusively consisting of in situ bypasses only 2 of 117 grafts needed a revision after 6 months of follow-up.[22] Unfortunately not many series will exclusively consist of in situ bypasses, as this type of bypass requires a greater saphenous vein with a good caliber throughout its entire length. We found that grafts with treated stenoses are at increased risk of developing a recurrent stenosis or a second stenosis at another location. After revision a venous bypass should be followed by regular duplex examination for at least another 6 months as a recurrence can be

expected in about one out of four grafts.[9,23,24] However, the majority of grafts do not require an intervention within 6 months after operation, and if there is no evidence of a stenosis and the maximum PSV-ratio is less than 2.0, intensive surveillance can be safely stopped, which was the crucial observation in the present study. Only 2% of surveilled patients without previous revision at 9 months and in 1% at 12 months developed an event causing *de novo* stenosis. Moreover, it has been reported that *de novo* lesions that develop after 6 months tend to be stable, and infrequently require revision.[25,26]

In conclusion, the typical time course of vein graft failure and intervention appeared to be related to the onset and progression of graft lesions. Our current protocol after discharge includes examinations at 6 weeks, 3 months and 6 months. Thereafter, in the absence of previous revisions or duplex abnormalities, discretionary clinical examinations may be scheduled annually just to check on the return of symptoms.

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*Chapter* **8**

# General Discussion

## GENERAL DISCUSSION

This thesis describes the experience with color-flow duplex surveillance of autologous vein grafts to detect vein graft stenosis.

In the retrospective part (chapter 3) the results of a study, published in 1993, are presented. In this study standardized methods for duplex surveillance were used throughout the study period, allowing valid conclusion on parameters and criteria for the diagnosis of critical vein graft stenosis. It demonstrated that durable long-term improvement in patency rates of up to 19% can be achieved by the implementation of a systematic program of color-flow duplex surveillance and selective secondary intervention in critical lesions. A large number of studies have demonstrated the beneficial effect of graft surveillance on patency.[1-4]

In the prospective part of the thesis the results are presented of a study which was supported by a Grant from the Commission of Investigative Medicine of the Dutch National Health Insurance Council. This study started in 1993 and was performed in three hospitals (Catharina Hospital Eindhoven, Academic Hospital Maastricht, and St. Antonius Hospital Nieuwegein). The protocol defined a number of questions that need to be addressed and the analysis of these questions form the basis of the prospective part of this thesis.

The first question was the influence of patient and graft factors on the development of vein graft stenoses and their significance for clinical management (chapter 4). Of all the different factors tested the minimal graft diameter was the only significant factor that had a significant correlation with the occurrence of graft stenosis. Although the minimal graft diameter is a predictor of graft lesion development, the specificity is still too low to deny vein graft surveillance to patients with grafts greater than 4.5 mm. In grafts with a minimal diameter of greater than 4.5 mm 25% had developed a significant graft stenosis at one year after the operation. In the present series factors representing the general vascular status of the patient (indication for operation, presence of diabetes mellitus, of coronary artery disease, of hypertension, etc) did not have a significant correlation with the development of vein graft stenoses. In contrast, a local graft factor such as the minimal graft diameter had a strong correlation with vein graft stenosis development and this observation supports the view that vein graft stenoses may be caused by local graft-related factors. These factors may consist of pre-existing vein pathology and intraoperative microlesions of the conduit. There is increasing data that the quality of the graft immediately after implantation may be the most important factor for durable vein graft function.[5,6]

The second question related to the diagnostic accuracy of the several investigated surveillance parameters to detect vein graft stenoses (chapter 5). The accuracy was assessed with angiography as the gold standard. All investigated duplex and ankle

brachial pressure-derived parameters, except for the volume flow, had a significant difference at univariate analysis for the group with DSA confirmed lesions <70%, and the group with ≥70% DR. Using multivariate analysis the PSV-ratio and the ankle blood pressure (ABP) appeared independent predictors of stenoses of ≥70%, overtoning all other parameters. The combination of these two variables, however, provided hardly a better sensitivity and specificity to identify graft stenosis ≥70% than the PSV-ratio alone. A PSV-ratio ≥3.0 was a reasonable indicator of the presence of a stenosis ≥70% with a sensitivity of 80% and a specificity of 84%. These observed results are in agreement with those reported by other authors.[7-9]

The third question was: Is vein graft stenosis revision without angiography justified and what criteria should be used (chapter 6). Replacing angiographic evaluation of vein graft stenoses prior to revision by duplex scanning would be advantageous. It would result in less delay of the revisional procedure and it would also reduce the overall costs of graft surveillance programs. On the basis of the PSV-ratio a two-parameter algorithm is presented which has the best combination of efficiency (limitation of the number unnecessary revisions), safety (minimal number of correctable lesions missed) and reduction of angiograms. This algorithm included a PSV-ratio <2.5 to delineate patients in which a conservative approach without angiography or revision was appropriate, a PSV-ratio ≥4.0 to indicate patients in which vein graft revision without angiography could be scheduled, and a group with PSV-ratios between 2.5 and 4.0 in which an angiogram was to be performed to determine clinical management on the basis of the stenosis severity. In addition it resulted in a reduction of the number of angiograms of 49% compared with a policy of angiographies in all patients with a PSV-ratio ≥2.5. There are recent studies in which a revision is performed solely on the basis of the PSV-ratio.[9,10] In the future we will probably use the PSV-ratio as the intervention criterium and not the angiographic degree of stenosis. Replacing prerevisional angiography with duplex parameters is an important issue and needs to be studied in the future.

The fourth question was: Are their ways to limit the graft surveillance program, in other words how can graft surveillance programs be economized (chapter 7). Two strategies were examined. The first strategy to investigate this question was to assess the predictive role of the first postoperative duplex scan for any subsequent vein graft stenosis development. Some reports have described that the majority of vein graft stenoses may develop soon after the operation.[11,12] Therefore we examined whether the initial duplex scan can be used as a criterion to categorize grafts into a high and a low-risk category for the development of a vein graft stenosis. Although subgroups of grafts with initial PSV-ratios demonstrated statistical correlation with later vein graft stenosis development, it appeared that patients with "normal grafts" (initial PSV-ratio <1.5) are by no means safeguarded for a primary event at later follow-up, as the primary patency at 12 months is 71%. Excluding normal grafts from further surveillance would

obviously have resulted in a less effective surveillance protocol. These observations are supported by other studies, in which it was found that normal early duplex findings did not equate with the long-term absence of graft-threatening lesions.[10,13] Consequently all grafts need to be followed from an early stage.
In the second strategy the possibility to limit the duration of duplex surveillance was investigated. It appeared that 84% of all "event causing *de novo* stenoses" had occurred before six months. The majority of grafts that did require an intervention after six months postoperatively had previous evidence of a stenosis with a PSV-ratio ≥2.0. In grafts that were normal at 6 months surveillance, usually no stenoses developed at a later time. Only in 2% of surveilled patients without previous revision at 9 months and in 1% at 12 months a *de novo* stenosis was identified. Moreover, it was reported that *de novo* lesions that develop after 6 months tend to be stable, and infrequently require a revision. These findings are in accordance with those of other authors.[11,14-16] On the basis of these observation it is recommended that surveillance is stopped if vein grafts are found normal at 6 months and did not require a revision in the first half year.

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*Chapter* **9**

# Summary

# &

# Samenvatting

## SUMMARY

*Definition:* Surveillance of infrainguinal autologous vein bypasses is a structured schedule for use of diagnostic methods to detect stenoses in these grafts or adjacent to the bypasses. Early repair of graft stenoses may prevent graft thrombosis.

*Chapter one* is the preface of the study. It describes how graft surveillance had started. It gives an outline of the design of the retrospective and of the prospective studies. In addition, the questions that were investigated in the prospective part of the study (aims of the study) are formulated.

*Chapter two* contains a review of the literature on various aspects of postoperative infrainguinal graft surveillance.

*Chapter three* focussed on the contribution of color-flow duplex surveillance to improve infrainguinal autologous vein graft patency in two patient groups. Patency rates were compared between a group followed by color-flow surveillance group and a group that were subjected to clinical follow-up only. The assisted primary graft patency rates was improved by 19% with the use of a color-flow duplex surveillance and repair of detected significant stenotic lesions.

*Chapter four* discussed the influence of various clinical and graft factors on the development of stenotic lesions in infrainguinal autologous vein bypasses, and to investigate wether this may lead to modifications to rationalise duplex surveillance programs or surgical techniques of these bypass procedures. The minimal graft diameter appeared to be the only significant factor that correlated with the development of a vein graft stenosis during follow-up. Several other systemic factors, previously documented to be associated with infrainguinal autologous vein graft failure or stenoses development, failed to show any correlation. The 1-year secondary patency rate of composite vein and arm-vein grafts with a minimal diameter $\geq 3.5$ mm was significantly better than that of single greater saphenous grafts with a minimal graft diameter $<3.5$ mm (94% and 76% respectiveley, $p = 0.03$). Although the minimal graft diameter is an important risk factor for stenoses development in infrainguinal autologous vein bypasses, it was not practical for use in tailoring duplex surveillance programs with respect to the risk of failure. However it may have significance in guiding the surgeon to make use more often of composite vein and arm-vein grafts.

*Chapter five* assessed the diagnostic accuracy of a number of surveillance parameters, all previously described in the literature, to detect stenoses in infrainguinal autologous vein bypasses. Surveillance parameters were compared with angiography as the gold

standard. Except for volume flow-related variables all other variables showed significant differences at univariate analysis between angiographic stenosis <70% and ≥70% diameter reduction. Using a logistic regression analysis it was found that the PSV-ratio was the best parameter to grade vein graft stenosis by non-invasive examination. A PSV-ratio with a cutoff value of 3.0 had the best sensitivity and specificity to detect a stenosis with an ≥70% angiographic diameter reduction. Other surveillance parameters than the PSV-ratio had lower sensitivities and specificities and were not usefull in clinical practice.

*Chapter six* investigated wether revision of stenoses in infrainguinal autologous vein bypasses without angiography was justified and what criteria should be used. From the investigation described in chapter five of this thesis, it appeared that the PSV-ratio was the best indicator of a high-grade vein graft stenosis. Therefore a series of cutoff values of this parameter were correlated with the occurrence of primary clinical events by cumulative hazard analysis with transient state method and Kaplan-Meier graphs. It appeared that for clinical application an algorithm based on a single surveillance parameter (single PSV-ratio cut-off value) to differentiate between intervention and non-intervention was not sufficiently accurate to replace prerevision angiography. It was demonstrated that the best combination of efficacy (limitation of the number of unnecessary revisions), safety (minimal number of correctable lesions missed) and reduction of angiograms was obtained by a two-parameter surveillance algorithm. This algorithm included a PSV-ratio <2.5 to delineate patients in which a conservative approach without angiography or revision was appropriate, a PSV-ratio ≥4.0 to indicate patients in which vein graft revision without angiography could be scheduled, and a group with PSV-ratios between 2.5 and 4.0 in which an angiogram was to be performed to determine clinical management on the basis of the stenosis severity. This algorithm had a positive predictive value (PPV) of 93% and a negative predictive value (NPV) of 89%. In addition it resulted in a reduction of the number of angiograms of 49% compared with a policy of angiographies in all patients with a PSV-ratio ≥2.5.

*Chapter seven* investigated two different strategies to reduce the need for frequent duplex scanning of infrainguinal autologous vein grafts.
In the first strategy it was attempted to reduce the number of patients for continued surveillance by identifying grafts with a possible higher risk of significant stenosis development, indicated by the presence of early duplex abnormalities. The presence of moderate abnormalities at the initial duplex scan did not identify patients with a high-risk of an event, as initial PSV-ratios of 1.5 to 2.0 and 2.0 to 2.5 (early mild-moderate lesions) had comparable 12-month primary patencies as patients with a PSV-ratio <1.5 (completely normal grafts): (63%, 73%, and 71% respectively). Considered the fact that grafts with a initial PSV-ratio <1.5 was associated with a fairly high incidence of

primary events (12 month primary patency 71%) it was concluded that initially normal grafts may develop stenotic lesions sometime after the procedure. Therefore, it is not justify to withold a regular surveillance program to initially normal infrainguinal autologous vein bypasses.
In the second strategy the effects of reducing the duration of the surveillance program per patient was examined. The interval incidence of "event causing *de novo* stenoses" was 8% of the total number of duplex tests performed at 3 months, and also 8% at 6 months after the operation. In patients that had no previous intervention for stenosis a sharp drop in this incidence was seen at 9 and 12 months, with "event causing *de novo* stenoses" in only 2% and 1% of all duplex tests. The duration of the surveillance period may be restricted to the first six months after operation in patients that have a normal infrainguinal autologous vein bypass during that time period, as only few vein graft stenoses will be missed by this policy.

*Chapter eight* provides the general discussion.

## SAMENVATTING

*Definitie:* Surveillance van infrainguinale autologe veneuze bypasses is een gestructureerd programma voor gebruik van diagnostische methoden voor het detecteren van stenosen in deze bypasses of in hun naburige arteriële segmenten. Tijdige correctie van deze stenosen kan bypass trombose voorkomen.

*Hoofdstuk 1* was het voorwoord van de studie. De gedachten achter de start van vene-bypass surveillance, de retrospectieve studie en de opzet van de prospectieve studie werden besproken. Ook werden de vragen die onderzocht werden in het prospectieve deel van de studie (doelstellingen van de studie) geformuleerd.

In *hoofdstuk 2* werd er een literatuur overzicht gegeven over de verschillende aspecten van postoperatieve infrainguinale bypass surveillance.

*Hoofdstuk 3* evalueerde het effect van een kleuren duplex surveillance programma op de verbetering van de patency van infrainguinale autologe veneuze bypasses. De patencies van deze bypasses werden vergeleken tussen een groep patiënten die met een kleuren duplex scanner werden vervolgd en patiënten die alleen met klinisch-onderzoek gecontroleerd werden. Het bleek dat de geassisteerde primaire patency van de infrainguinale autologe veneuze bypasses verbeterd werd met 19% door gebruik te maken van een kleuren duplex surveillance programma en herstel van gevonden significante stenotische afwijkingen.

*Hoofdstuk 4* handelde over de invloed van verschillende patiënt- en bypass faktoren op de ontwikkeling van stenosen in infrainguinale autologe veneuze bypasses en de eventuele aanpassing van het surveillance programma of chirurgische technieken van deze bypass procedures. De gemeten minimale bypass diameter bleek de enigste factor te zijn die significant gecorreleerd was met het ontstaan van stenosen in deze bypasses gedurende follow-up. Verschillende andere systemische faktoren, die voorheen werden beschreven als gerelateerd met bypass occlusie of stenose vorming, bleken niet gecorreleerd te zijn met stenose vorming. De 1-jaars secundaire patency van samengestelde veneuze en arm-vene bypasses met een minimale bypass diameter >3.5 mm was significant beter dan die van een complete vena saphena magna bypass met een minimale diameter <3.5 mm (94% en 76% respectievelijk, $p = 0,03$). Alhoewel de minimale bypass diameter een belangerijke risico faktor is voor stenose ontwikkeling in infrainguinale autologe veneuze bypasses, is het praktisch niet mogelijk het duplex surveillance schema op basis hiervan aan te passen. Maar het kan wel zódanig gebruikt worden waardoor de chirurg vaker samengestelde vene bypasses en arm-vene bypasses kan gebruiken.

*Hoofdstuk 5* beschreef de diagnostische accuraatheid van verscheidene surveillance parameters om stenosen in infrainguinale autologe veneuze bypasses te detecteren. De surveillance parameters werden vergeleken met de angiografie als gouden standaard. Behoudens de volume flow gerelateerde parameters toonden alle andere parameters een significant verschil bij een univariate analyse tussen een angiografische stenose van <70% en ≥70% diameterreductie. Een logistische regressie analyse toonde aan dat de PSV-ratio de beste parameter is om stenosen in infrainguinale autologe veneuze bypasses non-invasief te graderen. Een PSV-ratio van 3.0 is het criterium met de beste sensitiviteit en specificiteit om stenosen van ≥70% angiografische diameterreductie te detecteren. Andere surveillance parameters dan de PSV-ratio hebben een lage sensitiviteit en specificiteit en zijn daarom niet bruikbaar in de praktijk.

In *hoofdstuk 6* werd onderzocht of revisie van stenosen in infrainguinale autologe veneuze bypasses zonder angiografie gerechtvaardigd was en welke criteria daarbij dienen te worden gebruikt. Uit de onderzoekingen beschreven in hoofdstuk 5 van dit proefschrift bleek dat de PSV-ratio de beste indicator was voor een hoog-gradige veneuze bypass stenose. Er werden verschillende drempelwaarden van de PSV-ratio gecorreleerd met het optreden van primaire klinische gebeurtenissen door middel van cumulatieve risico analyse met "transient state" methoden en Kaplan-Meier curves. Het bleek dat voor klinisch gebruik een algoritme gebaseerd op één surveillance parameter (één enkele PSV-ratio drempelwaarde) om te onderscheiden tussen wel of geen interventie niet accuraat genoeg bleek te zijn om een pre-revisie angiografie te vervangen. Er werd aangetoond dat de beste combinatie van efficiëntie (limiteren van het aantal onnodige revisies), veiligheid (minimaal aantal gemiste corrigeerbare laesies) en reductie van het aantal angiogrammen bereikt werd door een twee-parameter surveillance algoritme. Dit algorithme bestaat uit een PSV-ratio <2.5 om patiënten te classificeren bij wie een conservatief beleid zonder angiografie of revisie juist is, een PSV-ratio ≥4.0 om patiënten te identificeren bij wie een bypass revisie zonder angiografie gepland kan worden en een groep met PSV-ratios tussen 2.5 en 4.0 waarbij een angiografie verricht zal moeten worden om een klinisch besluit te kunnen nemen op basis van de stenosegraad. Dit algoritme had een positieve voorspellende waarde van 93% en een negatieve voorspellende waarde van 89%. Tevens resulteerde dit in een reductie van 49% in de aantallen verrichte angiogrammen vergeleken met een beleid waarbij alle patiënten met een PSV-ratio ≥2.5 een angiografie zouden ondergaan.

In *hoofdstuk 7* werden twee verschillende strategieën onderzocht om de noodzaak tot herhaaldelijk duplex onderzoekingen van infrainguinale autologe veneuze bypasses te reduceren.

Bij de eerste strategie werd geprobeerd het aantal patiënten die voortdurende surveillance ondergaan te reduceren door identificatie van bypasses die een hoog risico hadden voor een significante stenose, aangegeven door de aanwezigheid van vroege duplex afwijkingen. De aanwezigheid van matige afwijkingen bij de initiële duplex scan identificeerde geen patiënten met een hoog risico voor een gebeurtenis, omdat patiënten met een initiële PSV-ratio van 1.5-2.0 en 2.0-2.5 (matige lesies) vergelijkbare 12-maands primaire patencies hadden als die met een initiële PSV-ratio van <1.5 (volledig normale bypasses): (63%, 73% en 71% respectievelijk). Gezien het feit dat infrainguinale autologe veneuze bypasses met een initiële PSV-ratio van <1.5 geassocieerd waren met een tamelijk hoge incidentie van primaire bypass gebeurtenissen (occlusie of revisie van een stenose) in het eerste postoperatieve jaar (12-maands primaire patency van 71%), werd geconcludeerd dat ook initieel normale bypasses niet gevrijwaard zijn van de ontwikkeling van stenotische afwijkingen. Daarom is het niet gerechtvaardigd om initieel normale infrainguinale autologe veneuze bypasses een regulier duplex surveillance programma te onthouden.
Bij de tweede strategie werd onderzoek verricht naar het effect van reductie van de duur van het surveillance programma per patiënt. De interval incidentie van "gebeurtenis veroorzakende *de novo* stenosen" was 8% van het totaal aantal duplex onderzoekingen verricht bij 3 maanden en eveneens 8% bij 6 maanden na de operatie. Bij patiënten die geen eerdere interventie ondergingen, werd er een scherpe daling van de incidentie gezien bij 9 en 12 maanden, waarbij "gebeurtenis veroorzakende *de novo* stenosen" in slechts 2% en 1% van alle duplex onderzoekingen werden geïdentificeerd. De duur van de surveillance periode kan dus beperkt worden tot de eerste 6 maanden na de operatie bij patiënten die een normale infrainguinale autologe veneuze bypass hadden gedurende deze periode, aangezien bij dit beleid maar sporadisch een bypass stenose gemist zal worden.

*Hoofdstuk 8* gaf de algemene discussie.

## DANKWOORD

Op de afdeling Algemene Heelkunde van het Catharina Ziekenhuis te Eindhoven, zijn de studies zoals beschreven in dit proefschrift geïnitialiseerd. De studies zijn uitgevoerd in nauwe samenwerking met de afdelingen Algemene Heelkunde van het Academisch Ziekenhuis te Maastricht en het St. Antonius Ziekenhuis te Nieuwegein. Aan het tot stand komen van dit proefschrift hebben vele mensen bijgedragen:

Dr. J. Buth, mijn co-promotor. Hij leerde mij de methoden voor het verrichten van klinisch-wetenschappelijk onderzoek en heeft een essentiële bijdrage geleverd aan het tot stand komen van dit proefschrift. Ik ben hem dankbaar voor alle hulp, adviezen en ondersteuning die hij mij de afgelopen jaren heeft gegeven.

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## CURRICULUM VITAE

| | |
|---|---|
| 26 juli 1964 | Geboren te Paramaribo, Suriname. |
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Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door de financiële ondersteuning van de volgende bedrijven: Abbott bv, Acuson®, Advanced Technology Laboratories Nederland bv, Aloka®, Asta Medica bv, Bard Benelux nv, Bauerfeind Benelux bv, Boston Scientific Coorporation, Convatec®, Gambro bv, W.L Gore & Associates bv, Hewlett-Packard Nederland bv, Karl Storz Endoscopie, Mathys Medical Nederland bv, Schering Nederland bv, Sigma Medical bv en Stöpler Instrumenten bv.

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