PERCUTANEOUS TREATMENT OF PERIPHERAL ARTERIAL DISEASE

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PERCUTANEOUS TREATMENT OF PERIPHERAL ARTERIAL DISEASE

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CHAPTER 1

Introduction

BACKGROUND

Treatment options for Peripheral Arterial Disease (PAD) range from walking exercise programs to bypass surgery and percutaneous treatment. The general consensus is that all patients presenting with symptomatic PAD should initially be treated with walking exercise and only if symptoms fail to improve are invasive procedures considered. Both bypass surgery and percutaneous treatment, however, have their limitations. Percutaneous treatment is a relatively low risk and low cost procedure, but is associated with a fairly high restenosis rate which is highly dependent on the lesion type 1-12. Bypass surgery, on the other hand, is associated with a higher procedural risk, higher cost, and a longer convalescence period but is also associated with better long-term results which are relatively unaffected by the lesion type treated 13-15. The current view is that percutaneous treatment should be performed in patients presenting with short focal lesions, whereas bypass surgery should be performed in patients with more diffuse disease presenting with critical ischemia. The precise criteria, however, to determine the type of lesion are still under debate 1,3,4,11,16-37.

Besides lesion type other factors have been reported to be predictors of failure after percutaneous interventions. The predictive value of these factors and especially when multiple factors are seen together in one patient are still unclear. A better understanding of the prognostic value of baseline characteristics on the long-term outcome but also on the development of complications after percutaneous intervention may improve patient selection for percutaneous treatment and bypass surgery. This thesis presents two studies (**chapters 2 and 3**) examining the prognostic value of baseline characteristics.

Because of the limitations of current therapies, new endovascular treatment modalities are being developed 38-40. Given the performance of currently employed therapies, the criteria a new treatment has to meet to become preferred over current therapies can be determined 41,42.

Chapter 5 presents a study that explores the criteria that a new endovascular therapy for the treatment of femoropopliteal arterial disease has to meet to become more cost-effective than currently employed therapies.

An important issue in health care is the quality of care 43-53. Do interventions performed by different health care providers have comparable outcome or are there differences and if so can these differences be explained by differences in patient populations or are they due to differences in quality of care. **Chapter 4** presents a study that compares the outcome following percutaneous intervention for treatment of PAD across 6 hospitals in the Netherlands.

Besides issues mentioned above, this thesis addresses the issue of heterogeneity in outcome criteria applied in the literature to classify procedural outcome as success or failure and assesses the influence of varying outcome criteria on success percentages (**chapter 6**). Furthermore, **chapter 7** examines a method to limit the influence of potential selective loss to follow-up on the results in multi-center studies. Finally, **chapter 8** presents a review and meta-analysis of published long-term results of balloon dilation and stent placement for treatment of femoropopliteal arterial disease.

Most studies (5 out of 7) were based on the database of the Vascular Intervention Registry. This registry recorded the baseline characteristics and outcome of balloon dilations and stent placement performed in 6 hospitals in the Netherlands. Two studies, a meta-analysis (chapter 8) and a decision analytic model (chapter 5) were based on results reported in the literature.

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CHAPTER 2

Revisiting the Prognostic Factors associated with failure after Percutaneous Interventions for Peripheral Arterial Disease

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ABSTRACT

Purpose: To determine the independent predictors for the outcome of percutaneous intervention for peripheral arterial disease.

Materials and methods: The demographic, clinical and angiographic data of 847 balloon dilation and stent placement procedures involving 1058 limbs were prospectively recorded in a multicenter registry. Follow-up data was abstracted from medical records. Using multivariable Cox-regression analyses the independent prognostic value of 41 variables was evaluated. Two outcome measures were used: one based on symptomatic improvement as reported by the patient (symptomatic outcome) and one based on an improvement in ABI with more than 0.10 (hemodynamic outcome). From the multivariable Cox regression models the results for subgroups of patients were predicted.

Results: Independent predictors of both symptomatic and hemodynamic failure were: treatment for ischemia (OR for hemodynamic failure=1.4; 95%CI 1.1-1.9), treatment for gangrene (OR=5.4; 95%CI 2.8-10.4), diabetes (OR=1.3; 95%CI 1.1-1.6), infrainguinal location (OR=1.5; 95%CI 1.2-1.9), mild stenosis (OR=2.1; 95%CI 1.5-2.9), lesion length more than 10 cm (OR= 2.2; 95%CI 1.5-3.1), and the number of femoropopliteal arteries affected by PAD (OR range 1.6-4.0; 95%CI 1.3-13).

Conclusion: Ulceration, gangrene, diabetes, lesion length more than 10 cm, infrainguinal localization, mild stenosis, and poor femoropopliteal runoff are independent predictors of symptomatic and hemodynamic failure following percutaneous intervention for peripheral arterial disease.

INTRODUCTION

Balloon dilation and stent deployment are widely used percutaneous endovascular techniques in the management of patients with peripheral arterial disease (PAD) [1]. These percutaneous interventions are considered safe and effective in carefully selected patients [2]. The ideal candidates for percutaneous treatment of PAD are patients with claudication who have focal lesions [3]. Patients with more extensive disease are less likely to respond well in which case bypass surgery can be considered if the patient's general condition permits surgery and his/her symptoms warrant it.

Previous studies have reported the predictive value of lesion length, stenosis severity, arterial runoff, symptomatic status, concomitant disease such as diabetes mellitus, and previous revascularizations. However, because these studies commonly looked only at univariable analyses or a limited set of variables, the relation between these variables and the independent predictive value of each variable is not yet clearly understood [4-28].

In the Transatlantic Inter-Society Consensus on the management of PAD a classification based on lesion characteristics was recommended [3]. The Consensus recommended percutaneous endovascular treatment for patients with iliac or femoropopliteal lesions shorter than 3 cm of length and surgical treatment for patients with long lesions (>10 cm) or diffuse disease. For patients with iliac or femoropopliteal lesions 3-5 cm of length or iliac lesions extending to the common femoral artery, however, insufficient evidence was available to make a recommendation and it was concluded that more research was necessary. Furthermore, the recommendations are based only on lesion characteristics and clinical indication (claudication versus critical ischemia) and do not consider other factors such as diabetic mellitus age, cardiac history, or revascularization history. The purpose of the current study was to examine which factors are independent predictors of outcome in patients treated with percutaneous

endovascular interventions for PAD and to predict the probability of success for various subgroups in order to improve the selection of patients.

MATERIALS AND METHODS

On 1994, the Vascular Intervention Registry (VIR) was established for the purpose of the quality assessment and improvement of current medical practice by monitoring and analysis of percutaneous vascular interventions for PAD affecting the lower extremities and their outcome. Four teaching hospitals and two general hospitals in the Netherlands voluntarily participated. Data regarding each patient at the time of the intervention and details from the procedure were entered prospectively in the registry and follow-up data was obtained by abstracting medical records retrospectively. All data were recorded using standardized forms and entered in a computerized database (MS-Access 97).

A total of 1250 patients were registered from 1994 to 1998 who underwent 1347 consecutive procedures and were treated in 1671 limbs. Of the 1347 procedures 335 procedures were identified after cross-checking the VIR database with hospital based registries. Baseline data in these procedures were abstracted retrospectively from medical reports. Patients undergoing treatment for acute ischemia or undergoing treatment other than balloon dilation or stent placement were excluded from the analyses leaving 1583 limbs for the analyses presented here.

Two outcome measures were considered. Symptomatic outcome was based on the reported improvement in symptoms. Hemodynamic outcome was based on a change in ABI of more than 0.10 or, if performed, duplex imaging information. Technical failure and re-intervention were considered failures for both the symptomatic and hemodynamic outcome. Technical failure was defined as failure to enter the vessel, to cross the lesion, or to improve the arterial blood flow.

Data on the angiographic appearance of the lesions including localization, stenosis severity, length of the treated lesion, and the appearance of the outflow tract were available in 1058 of 1583 limbs. Correlation's between the angiographic features were evaluated by cross tabulation and the chi-squared test. The prognostic value of the angiographic features was assessed with a Cox proportional hazards regression model. Variables associated with a statistically significant value in univariable regression ($P<0.10$) were selected and entered in a multivariable model. Variables associated with a p-value>0.10 in the multivariable regression were removed. In the last step the threshold for statistical significance of 0.10 was chosen to minimize the chance that prognostic clinical variables were erroneously excluded. Stenosis severity was analyzed as both a continuous and categorical variable. For iliac lesions poor femoropopliteal runoff was determined by counting the number of arteries, including the common, superficial and deep femoral arteries and the popliteal artery, affected by PAD as defined by a stenosis more than 50%. For iliac and femoropopliteal lesions the poor crural runoff was determined by counting the number of crural arteries affected by PAD as previously defined.

Next the additional prognostic value of intervention type (stent deployment versus balloon dilation) and clinical data was examined by a process of univariable and multivariable regression analyses. The following clinical variables were tested: symptomatic status (categories: claudication, rest pain, ulceration, gangrene), diabetic status (insulin independent and insulin dependent), history of revascularizations (aorta-iliac bypass, femoropopliteal bypass, femoral-femoral bypass, other femoropopliteal surgical interventions, other iliac surgical interventions, femoropopliteal PTA and iliac PTA), cardiac history (angina pectoris, recent myocardial infarction, old myocardial infarction longer than 6 months ago, heart failure, coronary arterial bypass graft, percutaneous transluminal coronary angioplasty), cerebrovascular history (transient ischemic attack, reversible ischemic attack, cerebrovascular accident), renal history (creatinine level higher than 130 μmol/l, creatinine level higher than 530 μmol /l, haemodialysis, renal transplantation), hypertension history (diastolic blood pressure >90mmHg, antihypertensive drugs), smoking history

(never or past smoker more than 10 years ago, past smoker more than 1 year ago, past smoker less than 1 year ago, current smoker less than 20 cigarettes a day, current smoker more than 19 cigarettes a day), and ankle brachial index at rest. Clinical variables with a statistically significant additional prognostic value over and above the angiographic features (p-value <0.10) were selected and added to a multivariable model incorporating both angiographic and clinical data.

From the results of the multivariable Cox proportional hazards regression analyses the predicted outcomes of percutaneous intervention were estimated. The symptomatic and hemodynamic follow-up was, on average, 486 days and 314 days, respectively. Twenty percent and 24% of subjects were lost to follow-up at 1 year of symptomatic and hemodynamic follow-up, respectively. All analyses were performed in the SPSS statistical package.

RESULTS

Table 1 presents the baseline characteristics of the study population. Sixty-six percent of the patients were male, 22% had diabetes mellitus, 84% were current or past smokers, 41% percent of the limbs underwent stent placement, and 59 % underwent balloon dilation. Eighty-two percent of lesions were shorter than 5 cm.

Table 2 summarizes the groups of limbs classified by the presence or absence of angiographic features. Most procedures were performed for a short (<10cm) stenotic lesion located in the iliac artery in the presence of good femoropopliteal and crural runoff. Occlusions, infra-inguinal lesions, and impaired arterial runoff were only seen in a minority of the limbs. Occlusions were significantly (P<0.001) longer than stenoses. Ninety-two percent of the stenoses were shorter than 5 cm. Within the stenosis group no relation between stenosis severity and lesion length was found.

Table 3 presents the results of the multivariable analyses for the prediction of symptomatic and hemodynamic failure respectively. Both lesion length and stenosis severity were statistically significant independent prognostic factors.

Table 1. Baseline Characteristics of the Study Population (1058 limbs)

Characteristics	No./ no. available* (Proportion)
Sex	
Male	702/1058 (66%)
Female	356/1058 (34%)
Mean age (standard deviation)	61 (12)
Risk Factors	
Diabetes Mellitus	226/1032 (22%)
Hypertension/anti-hypertensive drugs	306/1058 (32%)
Smoking, past or current	858/1058 (84%)
Cardiovascular disease	294/1058 (28%)
Cerebrovascular disease	114/1026 (7%)
Renal Disease	72/977 (7%)
Presenting Complaint	
Intermittent Claudication	132/1058 (88%)
Restpain	25/1058 (2%)
Ulceration	97/1058 (9%)
Gangrene	10/1058 (1%)
Ankle Brachial Index in rest	
<0.5	182/909 (20%)
>=0.5-0.9	626/909 (69%)
>=0.90	182/909 (11%)
History of Revascularizations	
Aorta-iliac prosthesis	40/1058 (4%)
Femoropopliteal prosthesis	112/1058 (11%)
Other surgical aorta-iliac revascularization	15/1058 (1%)
Other surgical femoropopliteal revascularization	17/1058 (2%)
Aorta-iliac percutaneous revascularization	101/1058 (10%)
Femoropopliteal percutaneous revascularization	45/1058 (4%)
Amputation	16/1058 (2%)
Lesion length	
0-2 cm	493/1058 (47%)
2-5 cm	378/1058 (36%)
5-10 cm	117/1058 (11%)
>10cm	70/1058 (7%)
Severity of stenosis	
100%	217/1058 (21%)
90-99%	247/1058 (23%)
80-89%	221/1058 (21%)
70-79%	159/1058 (15%)
60-69%	91/1058 (9%)
<60%	123/1058 (12%)

* The denominator denotes the number of limbs with available data. Numbers between parentheses represent the percentage of limbs with that baseline characteristic.

Table2. Combinations of Angiographic Features ordered by the Frequency that these Combinations were seen in Patients treated with Balloon Dilation or Stent Placement

	Lesion Characteristics		Arterial Outflow distal to the artery that was treated		Frequency
Supra-/Infra-inguinal localization	Type	Length	Number of femoropopliteal arteries affected by PAD	Crural runoff *†	Number of limbs (percentage)
Supra	Sten	<10cm	0	Good	443 (42%)
Supra	Sten	<10cm	1	Good	178 (17%)
Infra	Sten	<10cm	NA	Good	142 (13%)
Supra	Occl	<10cm	0	Good	77 (7%)
Infra	Occl	<10cm	NA	Good	62 (6%)
Infra	Occl	>10cm	NA	Good	45 (4%)
Supra	Sten	<10cm	2	Good	42 (4%)
Infra	Sten	<10cm	NA	Poor	15 (1%)
Supra	Occl	<10cm	1	Good	11 (1%)
Supra	Occl	>10cm	0	Good	10 (1%)
Supra	Sten	<10cm	3	Good	7
Infra	Occl	<10cm	NA	Poor	6
Supra	Sten	>10cm	0	Good	4
Supra	Sten	>10cm	1	Good	4
Infra	Occl	>10cm	NA	Poor	3
Infra	Sten	>10cm	NA	Good	2
Supra	Occl	<10cm	2	Good	2
Supra	Sten	<10cm	4	Good	2
Infra	Sten	>10cm	0	Poor	1
Supra	Occl	>10cm	1	Good	1
Supra	Occl	<10cm	3	Good	1

Number between parentheses represent the percentage of limbs with a certain combination of angiographic features relative to the total number of 1058 limbs.
* Arteries with stenoses >=50% were considered affected by PAD.
Abbreviations: NA=Not applicable; Sten=stenosis; Occl=Occlusions; † Poor crural runoff was defined as 2 or more crural arteries (stenosis>=50%) affected by PAD

Table 3. Clinical Factors and Angiographic Variables Predicting Symptomatic and Hemodynamic Failure in Multivariable Analyses

	Symptomatic Failure		Hemodynamic Failure	
	Odds Ratio	P Value	Odds Ratio	P Value
Stenosis severity*				
100%	1		1	
90-99%	1.12(0.79-1.58)	0.045	1.10(0.80-1.52)	<0.001
80-89%	1.08(0.76-1.54)		1.44(1.05-1.96)	
70-79%	1.42(0.98-2.07)		1.81(1.30-2.53)	
60-69%	1.44(0.97-2.15)		1.83(1.28-2.63)	
<60%	1.66(1.13-2.44)		2.06(1.47-2.91)	
Lesion Length >10cm	1.47(0.39-2.20)	0.065	2.18(1.51-3.14)	<0.001
Infra-Inguinal Location	1.54(1.19-1.99)	0.001	1.50(1.20-1.90)	<0.001
Femoral and Popliteal Outflow (Number of diseased vessels)*†				
0	1		1	
1	1.36(1.04-1.77)	<0.001	1.60(1.27-2.03)	<0.001
2	2.38(1.54-3.67)		1.98(1.32-2.97)	
3	2.05(0.75-5.60)		3.96(1.26-12.5)	
Two or more diseased Crural vessels	-	NS	-	NS
Ischemic Ulceration	1.86(1.36-2.55)	<0.001	1.42(1.06-1.92)	0.020
Gangrene	7.33(3.76-14.3)	<0.001	5.36(2.77-10.4)	<0.001
Diabetes Mellitus	1.24(0.98-1.67)	0.075	1.33(1.08-1.64)	0.008
History of CVA	-	NS	1.28(1.06-1.55)	0.012
History of aorta-iliac bypass surgery	-	NS	1.71(1.13-2.57)	0.010
History of Revascularizations in the contra-lateral leg	1.32(1.06-1.65)	0.013	-	NS
ABI >=0.90	-	NS	2.42(1.96-2.97)	<0.001

NS = not significant (p-value>0.10)
* Stenosis severity and femoral outflow were analyzed as categorical variables
† Determined by counting the number of arteries affected by PAD as defined by a stenosis>50% including the common, deep and superficial femoral and popliteal arteries

Patients with short lesions (<10 cm) fared better than patients with long lesions. Within the group of limbs with lesions less than 10 cm in length, no statistically significant difference between lesions of less than 2 cm in length, 2-5 cm in length and lesions of 5-10 cm of length was found. The stenosis severity was significantly but inversely predictive of hemodynamic and symptomatic failure in the multivariable analysis, i.e. each step increase in diameter of the obstruction prior to intervention resulted in a higher hemodynamic success probability.

The number of femoro-popliteal arteries affected by PAD in patients that underwent an iliac percutaneous intervention was a statistically significant predictor of failure. The number of crural arteries affected by PAD was not associated with a statistically significant prognostic value in multivariable analysis.

Entering symptomatic status (ulceration, gangrene) to the multivariable model changed the prognostic value associated with the crural runoff from borderline significant to non-significant. Restricting the population to patients undergoing infra-inguinal procedures did not increase the prognostic value of crural runoff.

Ischemic symptoms prior to treatment (categories: ulceration and gangrene), and diabetes mellitus (insulin dependent and insulin independent diabetes pooled in one category) were statistically significant independent predictors for both symptomatic and hemodynamic failure. Positive histories for aorta-iliac bypass and cerebrovascular accidents were independent predictors for hemodynamic failure. An ABI of 0.9 or higher prior to treatment was a predictor for developing hemodynamic failure, i.e. limbs with an ABI lower than 0.9 had a higher probability that the ABI increased by more than 0.10 after treatment.

Table 4 shows the impact that severity of stenosis and the number of femoropopliteal arteries affected by PAD had on both the symptomatic and hemodynamic outcome of supra-inguinal interventions. For example, the 1-year symptomatic success probability after treatment of iliac occlusions with good femoropopliteal outflow is 82% whereas the 1-year symptomatic success probability after treatment of a mild iliac stenosis (<60%) was 72%.

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Table 4. Success Probabilities in Patients with an Iliac Lesion Shorter than 10 cm presenting with Claudication, an ABI lower than 0.9, and no Comorbidity, depending on Lesion Severity and Femoro-Popliteal Outflow

Severity of Stenosis (%)	Number of femoral/popliteal arteries affected by PAD	Symptomatic success (%)			Hemodynamic success (%)		
		1 year	2 year	3 year	1 year	2 year	3 year
100	0	82	74	66	75	66	59
80-90	0	81	72	64	66	56	47
<60	0	72	66	57	55	43	34
100	1	76	66	57	63	52	43
80-90	1	75	64	55	52	39	30
<60	1	64	51	40	39	26	18
100	2	62	49	38	57	45	35
80-90	2	60	46	35	44	31	22
<60	2	46	30	20	31	19	12

Table 5 shows the impact that lesion length, diabetes mellitus, and stenosis severity had on the outcome of infra-inguinal interventions. For example, the 1-year hemodynamic success probability after treatment of a short femoropopliteal occlusion in patients without diabetes was 65% whereas treatment of a long femoropopliteal lesion (>10cm) in a diabetic patient was associated with a 1-year hemodynamic success probability of only 29%.

Table 5. Success Probabilities in Patients with an Infra-Inguinal Lesion presenting with Claudication, an ABI lower than 0.9, and no Comorbidity, depending on Lesion Length, Diabetic status, and Stenosis Severity

Lesion length	Diabetes	Stenosis Severity (%)	Symptomatic success(%)			Hemodynamic success(%)		
			1 year	2 year	3 year	1 year	2 year	3 year
<10cm	No	100	74	63	53	65	54	45
		80-90	72	61	50	54	42	32
		<60	60	46	35	41	28	19
	Yes	100	69	56	46	56	44	35
		80-90	67	54	43	44	31	22
		<60	46	43	27	31	19	11
≥10cm	No	100	64	51	39	39	26	18
	Yes	100	57	43	32	29	17	10

Table 6 shows the influence of stenosis severity, lesion localization and diabetic status on the success rate of intervention in patients presenting with ulceration. Patients with ischemic ulcers, short femoral stenoses (90-100) and with diabetes had a symptomatic and hemodynamic 1-year success probability of 45% and 41%, respectively.

In the appendix we present an equation for calculating the long-term symptomatic and hemodynamic success probabilities depending on the presence or absence of predictive baseline patient characteristics.

Table 6. Success Probabilities in Patients presenting with Ulceration and an ABI lower than 0.9, and a Lesion shorter than 10 cm of Length, depending on Lesion Localization, Diabetic status, and Stenosis Severity

Lesion localization	Diabetes	Stenosis Severity	Symptomatic success(%)			Hemodynamic success(%)		
			1 year	2 year	3 year	1 year	2 year	3 year
Supra*	No	100	69	57	46	66	56	47
		90-100	66	53	42	64	53	44
	Yes	100	63	50	39	58	46	37
		90-100	60	46	34	55	43	33
Infra	No	100	57	42	31	54	42	32
		90-100	53	38	27	51	38	29
	Yes	100	50	34	23	44	31	22
		90-100	45	30	19	41	28	19

Abbreviations: Supra = Supra-inguinal; Infra = Infra-inguinal
*The femoral and popliteal outflow were assumed to be unaffected by PAD

DISCUSSION

On this study the prognostic value of 41 variables representing symptoms prior to treatment, co-morbidity, and angiographic features was evaluated. In multivariable analysis ulceration, gangrene, diabetes, lesion length (≥ 10 cm), infrainguinal localization, mild degree of stenosis, and poor femoropopliteal runoff were independent prognostic variables for both symptomatic and hemodynamic failure.

Contrary to what we expected from the literature [6-15], we found in multivariable analyses that occlusions were associated with a higher probability of symptomatic and hemodynamic success than stenoses.

Within the group of stenoses, each step increase in stenosis severity prior to intervention was associated with an increase in probability of symptomatic and hemodynamic success. Although somewhat counter intuitive, this finding has been reported before [12, 16, 17]. An explanation may lie in the potential gain that can be achieved through treatment of the lesion. In patients with only a moderate stenosis, successful dilation may not achieve the same degree of improvement as successful dilation of a severe stenosis or successful recanalization. (The same reasoning can be applied to explain the finding that an ABI less than 0.9 prior to treatment was associated with a higher hemodynamic success.) An alternative but somewhat speculative explanation may be that occlusions and severe stenoses may generally be hard calcified and stable plaques whereas mild stenosis may more often be soft vulnerable plaques that may be more prone to progression of disease even after treatment.

Available literature on the prognostic influence of the number of crural arteries affected by PAD showed conflicting results [6, 7, 9-13, 15, 18-24]. Some authors found this variable to be associated with prognostic value whereas others did not. Only a few studies, however, analyzed the prognostic value of crural runoff in multivariable analysis [6, 7, 11, 12, 15, 23]. In 4 studies the number of crural arteries was found to be associated with independent statistically significant prognostic value [7, 11, 15, 23] whereas in the remaining 2 studies this was not the case [6, 12]. In the current study we found that entering the variables representing ulceration and gangrene to the model changed the prognostic value of the crural runoff affected by PAD from borderline significant to non-significant indicating that the clinical presentation already captures the prognostic information associated with crural runoff. Restricting the population to infra-inguinal procedures and thus excluding supra-inguinal procedures did not increase the prognostic value of crural runoff.

As far as we know, only a few studies have examined the influence of the femoral runoff for the outcome of supra-inguinal interventions [17, 25]. In these studies, patients with a superficial or deep femoral artery affected by PAD, were found to have a worse prognosis compared with those with

a good femoral runoff. In the current study the number of femoral and popliteal arteries affected by PAD, including the common, superficial and deep femoral artery and the popliteal artery, was found to be predictive of failure following a supra-inguinal procedure.

Another factor that is reported to be an important predictor of outcome is lesion length [4, 6, 9, 10, 18, 20, 22, 26]. Treatment of short lesions is reported to be associated with a better prognosis compared with treatment of long lesions. The threshold value to distinguish short and long lesions, however, still has to be determined. Comparison of the published results on the effect of lesion length is difficult because of the different threshold values that are used to categorize lesion length. In the current study we found that patients with lesions shorter than 10 cm fared better than patients with lesions longer than 10 cm. Within the group of patients with lesions shorter than 10 cm (subgroups; 0-2cm, 2-5 cm and 5-10cm) no difference in prognosis was detected. The sample size of the subgroup with 5-10 cm lesions, however, was probably inadequate to detect a small difference if present. Diabetes mellitus [9, 11, 16, 20, 27, 28] and symptoms prior to intervention [10, 11, 14, 16, 27, 29] have also been reported to be predictors of outcome of percutaneous intervention. We found that ulceration and tissue loss had a worse prognosis compared with patients presenting with claudication. Patients with rest pain did not have a significant different prognosis than patients with claudication. An explanation for this finding may lie in the definition of rest pain that was applied. In the current study we used the symptoms as reported by the patient. Others, however, prefer a definition of rest pain based on ankle blood pressure measurements which may be a more stringent criterion for rest pain [28, 30].

Diabetes mellitus was found to be an independent prognostic factor. The type of diabetes (insulin dependent versus insulin-independent) did not provide additional prognostic information.

This study may be limited by the large number of procedures involving 571 limbs that were excluded from the analyses because of missing values in the angiographic data. More than half of the procedures with missing

angiographic data (300 of 525 limbs) were identified after cross-checking our database with hospital based registries. In these procedures baseline characteristics were abstracted retrospectively from medical reports. The written reports of the intervention however, did not provide enough detail to record all angiographic features. Cross-tabulating the technical failures with retrospective registration revealed a higher technical failure rate of 5.5% in the retrospectively registered limbs compared with a technical failure rate of 3.5% in the prospectively registered limbs. Although not statistically significant (P-value=0.092) this does indicate that some selection for registration may have occurred.

The large variation in success rates found in the current study indicates that patient selection can have a huge influence on the outcome following the intervention. The TransAtlantic Inter-Society Consensus document on the management of PAD recommended that patients with iliac or femoropopliteal stenoses shorter than 3 cm should be treated with a percutaneous intervention. For patients with 3-5cm iliac or femoropopliteal stenoses, iliac or femoropopliteal occlusions, or iliac lesions that extend to the common femoral artery, however, insufficient evidence was available to make firm recommendations. The results of the current study indicate that all stenoses and occlusions shorter than 5 cm should be treated percutaneously. Furthermore, in contrast to the recommendations of the Transatlantic Inter-Society Consensus document, we would suggest that presenting symptoms, diabetes, stenosis severity, and femoral and popliteal outflow should also be considered when deciding whether to treat a patient with a percutaneous intervention.

In conclusion, ulceration or gangrene prior to treatment, diabetes, lesions longer than 10 cm in length, infrainguinal localization, mild degree of stenosis, and poor femoropopliteal runoff are independent predictive factors for symptomatic and hemodynamic failure following percutaneous treatment of peripheral arterial disease. Patients with claudication or rest pain and a supra- or infra-inguinal severe stenosis or occlusion shorter than 5 cm are suitable candidates for percutaneous treatment. Similar patients with a 5-10 cm lesion can be treated percutaneously but the

evidence for success is less firm. In patients with poor femoropopliteal outflow below an iliac lesion, ulceration or gangrene, and in patients presenting with a long lesion (>10cm) percutaneous treatment should only be considered as an adjunct procedure to bypass surgery or as a temporary palliative measure if bypass surgery is not feasible.

APPENDIX

Based on the results of multivariable Cox proportional hazards regression analysis (tables 3 and 4) the long-term symptomatic and hemodynamic success probabilities ($S(t)$) for all subgroups depending on the presence or absence of predictive baseline patient characteristics can be calculated using the following equation:

$S(t) = S_0^{\Pi OR}$

S_0 denotes the success percentage at time t in the group of patients that was chosen as reference group in the proportional hazards regression analyses. These baseline success percentages are presented in table 4 in the first row, depending on the follow-up time (t) and the outcome measure symptomatic or hemodynamic success that was considered.

The term ΠOR represents the product of the odds ratios associated with the baseline characteristics that are present in the subgroup for which $S(t)$ is being calculated. These odds ratios are presented in table 3.

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CHAPTER 3

Complications Associated with Angioplasty and Stent Placement for Peripheral Arterial Disease

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ABSTRACT

Purpose: To evaluate the complication rate associated with percutaneous treatment for peripheral arterial disease and to identify patient groups at a high risk for developing a complication.

Methods: Baseline characteristics and outcomes of 1186 procedures recorded in a multicenter registry were evaluated. The relation between risk factors, symptomatic status, procedural data, and complications were analyzed and patients at a higher risk for complications were identified. The prognostic value of baseline factors was evaluated using multivariable logistic regression.

Results: The overall 30-day complication rate was 7.2% (SE=0.7%), the 30-day local complication rate was 5.2% (SE=0.6%), the systemic 30-day complication rate including mortality was 2% (SE=0.4%), and 30-day mortality was 1.1% (SE=0.3%). Multi-variable analyses demonstrated that symptoms prior to treatment (critical ischemia vs claudication OR= 7.81, 95% CI= 3.24; 18.85) and a high creatinine level (>130 µmol/l; OR= 4.46, 95% CI 1.83;10.86) were independent predictors for 30-day systemic complications.

Conclusion: In patients presenting with claudication and a low creatinine level, percutaneous treatment of peripheral arterial disease is a safe procedure. In patients presenting with critical ischemia and an elevated creatinine level, the systemic complication and mortality rates are substantial.

INTRODUCTION

Balloon dilatation and stent placement are established techniques for treating short, focal obstructions of the iliac, femoral, and popliteal arteries. One of the advantages of these percutaneous therapies is that they are associated with fairly low morbidity and mortality rates compared with bypass surgery. Reported complication rates vary from 2.3% to 10.8% for iliac interventions and from 2.4% to 6.3% for femoropopliteal interventions [1]. A few patient characteristics have been identified that predict the risk of a complication. These include the type of lesion (occlusion vs stenosis) and the symptomatic status prior to the intervention (critical ischemia vs claudication) [2]. It seems plausible, however, that patients with other manifestations and risk factors of cardiovascular disease are also at a higher risk for complications.
The purpose of this study was to identify patient groups that are at a high risk for complications associated with angioplasty and stent placement for peripheral arterial disease.

METHODS

In 1994, the Vascular Intervention Registry (VIR) was established for the purpose of the quality assessment and improvement of current medical practice by monitoring and analysis of percutaneous vascular interventions for peripheral arterial disease (PAD) affecting the lower extremities and their outcome. Six teaching hospitals (four university and two non-university hospitals) in the Netherlands participated. All patients that were scheduled for percutaneous intervention for treatment of PAD affecting the lower extremities were registered. Data regarding each patient at the time of the intervention and details of the procedure were entered prospectively in the database. Data regarding post-procedural follow-up were collected on the basis of the medical records. All data were recorded using standardized forms.

Risk factors

We recorded the history of smoking (defined as current, former, none) and renal failure (defined as none, moderate or severe if the serum creatinine was 0-129 µmol/l, 130-530 µmol/l, > 530 µmol/l respectively), renal dialysis or renal transplantation and hypertension (defined as a diastolic blood pressure (90 mmHg). The symptomatic status before the intervention was categorized as claudication, rest pain, ulceration, gangrene, or threatened bypass.

The following risk-factors related to cardiovascular disease were registered: diabetes mellitus (defined as non-insulin dependent or insulin dependent diabetes mellitus), angina pectoris (AP), heart failure, myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary arterial bypass grafting (CABG), haemodialysis or renal transplantation, transient ischemic attack (TIA), reversible ischemic neurological deficit (RIND), cerebrovascular accident (CVA), percutaneous or surgical interventions for PAD and amputations, oral anti-coagulation use, beta-blocker or aspirin use.

Procedural parameters

The ankle-brachial index (ABI) at rest and after exercise prior to the procedure was recorded. The following data about the intervention were entered in the database: diameter of the treated artery, type of intervention, procedural medication, local and generalized complications, technical outcome, and additional vascular interventions. Post-procedural measurements included: change in symptoms compared with pre-procedural, ABI measurements at rest, walking distances, peak systolic ratios measured with duplex scanning, vascular (re)interventions, and all late complications. All data were entered into a computerized database (Microsoft Access 97).

Definition of complications

All events that occurred within 30 days after the procedure and that required additional medical care were considered complications. For example, hematomas were considered complications only if additional diagnostic tests were performed (duplex ultrasound), hospitalization was prolonged, or additional surgical or radiological intervention or blood transfusion was required. Hematomas that did not require treatment or increased level of care were not considered significant complications.

Several outcome measures were evaluated: the local complication rate, the systemic complication rate (which included 30-day mortality), the overall complication rate (which was the combined local and systemic complication rate), and the 30-day mortality rate. Furthermore, the relation between baseline characteristics with cardiovascular complications, renal complications, and with bleeding complications was evaluated. In addition, the relation between the occurrence of complications and the occurrence of technical failures was analyzed. Technical failures were defined as inability to enter the vessel, cross the lesion, or improve blood flow.

Analyses were performed using the chi-square test and logistic regression analysis. We used the SPSS statistical package (version 9 SPSS Inc, Chicago, Illinois).

Variables associated with a statistically significant or borderline significant prognostic value (P-value<0.10) in univariable analyses were selected and entered in a multivariable regression model. Using backwards stepwise logistic regression analyses all variables that were not associated with a statistically significant prognostic value in the multivariable analyses were removed from the model (P-value>0.05; likelihood ratio test). Because of the limited number of systemic complications that occurred (24 events) a maximum of 2 prognostic factors were allowed in the final model to avoid overmodelling. The creatinine level was not available in 103 procedures. In these procedures we assumed that the creatinine level was lower then 130 µmol/l. To explore the effect of this assumption a sensitivity analysis was performed in which these procedures were excluded and the results were compared.

RESULTS

Study population

The study population consisted of 1250 patients who underwent 1347 procedures. A total of 161 procedures were excluded: in 71 procedures no follow-up data were available and in 90 procedures the treatment consisted of trombolysis or thromboembolectomy. Thus, 1186 procedures were included in the current analysis. Comparison of the baseline characteristics of the 1186 procedures included in the analysis and the 71 procedures without follow-up did not show a statistically significant difference in age, gender, creatinine level, ankle-brachial index and lesion type (stenoses versus occlusion). Table 1 summarizes the baseline characteristics of the study population.

Table 1. Baseline Characteristics of the Study Population (1186 procedures)

Mean age (standard deviation)	62 (12) years
Female	34 %
Critical ischemia *	18.2%
Tissue loss †	14.5%
Smoker (current/ever)	54%/78%
Diabetes ‡	22%
Hypertension	25%
Cardiovascular history §	22.8%
Renal disease ¶	9.4 %
Previous revascularization for PAD #	45%
Occlusions	20%

* Critical ischemia included restpain, ulceration and gangrene.
† Tissue loss included ulceration and gangrene.
‡ Diabetes included non-insulin dependent and insulin dependent diabetes mellitus.
§ Cardiovascular history included myocardial infarction, heart failure, angina pectoris, percutaneous transluminal coronary angioplasty, or coronary arterial bypass grafting in the history.
¶ Renal disease included patients with a serum creatinine blood level ≥ 130(mol/l, those on hemodialysis, and those with a renal transplant.
# Previous revascularization included percutaneous and surgical interventions and amputations.
PAD: peripheral arterial disease.

In 45% of the procedures the patient had a history of previous revascularization for PAD. Eighteen percent of the procedures were carried out in patients with critical ischemia and twenty percent of lesions treated were occlusions. The overall complication rate including local and systemic complications combined, was 7.2% (SE=0.7%).

Systemic complications

Table 2 gives an overview of the systemic complications that occurred.

Table 2. Systemic Complications (1186 procedures)*

	Number
30-day mortality	13
CVA/TIA	1
Myocardial infarction	1
Heart failure	2
Arrythmia's	2
Renal failure †	2
Cholesterol emboli	1
Bronchospasm	1
Pneumonia	1
Total	24

* If multiple complications occurred only the worst was tabulated. The complications are listed in decreasing order of severity.
† Renal failure was defined as the need for dialysis.

A wide variety of systemic complications occurred. Thirteen patients died within 30 days after the intervention (1.1% SE=0.3%). Of these thirteen patients, two died after bypass surgery and two patients died after an amputation procedure, and one after percutaneous urokinase treatment that followed the percutaneous procedure. In the remaining 8 case fatalities death was preceded by renal failure (1 patient), heart failure and CVA (1 patient), heart failure (2 patients), and a malignancy (1 patient).

The remaining three patients were relatively young patients, had no history of cardiovascular disease, two of them were severe smokers, and two of them had a bypass operation.
In 24 procedures the treatment was followed with a systemic complication, resulting in a systemic complication rate of 2% (SE=0.4%). Five procedures were followed by multiple systemic complications; for these procedures only the worst complication was tabulated.

Local complications

Table 3 presents the local complications that occurred during or after the intervention.

Table 3. Local Complications (1186 procedures)

		Management					
Type	No. of complications	Obs/ US	PTA/ stent	Thromb- ectomy	Surgical	Blood transfusion	Medication
Hematoma	20	13			6	1	
Dissection	4			1	3		
Distal embolus	4		1		3		
Thrombus	11		2	2	7		
Local infection	5	1			2		2 *
False aneurysm	13	5			8		
Otherwise	6 †	2	1		2		1
Total	62	21	4	3	31	1	3

Obs= observation
US = Ultrasound
* = one time morphine
† This included hypergranulation (1) requiring medication, subintimal stent placement (1) requiring additional stent placement, abdominal pain requiring observation (2), and in one procedure part of the guiding catheter broke off requiring retrieval with a Dormier catheter.

In 62 procedures local complications occurred. Five procedures had multiple local complications. Bleeding complications such as hematomas, thrombi and false aneurysms were most often seen (4.0%, SE=0.6%). Distal emboli, local infections, or dissections that required surgical treatment or a second percutaneous procedure occurred only rarely (1.9%, SE=0.4). The overall local complication rate was 5.2% (SE=0.6%).

Prognostic factors

In uni-variable analyses the following variables were significant predictors of both the occurrence of a systemic complication and 30-day mortality; age, betablok use, critical ischemia, renal insufficiency, and cardial insufficiency. In addition smoking (preventive effect) and femoropoliteal localization of the lesion were associated with a statistically significant value in predicting the occurrence of a systemic complication. Diabetes was a statistically significant predictor for 30-day mortality. Table 4-6 presents the results of multi-variable analyses of the prognostic factors.

Table 4. Independent Predictors of Systemic Complications and 30-day Mortality (Multivariable Analysis)

	Odds ratio	Odds ratio
	Systemic complications	30-day mortality
Creatinine level > 130Ámol /l	4.46 (1.83-10.86)	5.36 (1.70-19.97)
Critical ischemia	7.81 (3.24-18.85)	20.19 (4.35-93.61)

Numbers in parenthesis represents the 95% confidence interval.

In multi-variable analysis symptoms prior to the intervention (critical ischemia vs claudication) and elevated creatinine level (≥130 µmol/l) were independent predictors of systemic complications and mortality. Table 5 shows the observed complication rate stratified for these prognostic factors and compares the observed rates with the predicted rates based on the multivariable model. The observed systemic complication rate ranged from 0.7% in patients with claudication and a creatinine level <130 µmol/l to 18.9% in patients with critical ischemia and an elevated creatinine level (≥130 µmol/l). The observed and predicted rates did not differ substantially.

Table 5. Comparison of Observed Systemic Complications and 30-day Mortality rate with Predicted rates based on the Results of Multivariable Logistic Regression Analyses

	Number of procedures	Systemic complications		30-day mortality	
		Observed	Predicted	Observed	Predicted
Claudication					
- Creatinine level <130 µmol/l	903	0.7% (6)	0.7%	0.2% (2)	0.2%
- Creatinine level ≥130 µmol/l	67	3% (2)	3%	0 (0)	0.8%
Critical ischemia					
- Creatinine level <130 µmol /l	179	5% (9)	5%	2.8% (5)	3.1%
- Creatinine level ≥130 µmol/l	37	18.9% (7)	19%	16.2% (6)	14.7%
Total	1186				

Expected rates based on multivariable model.
Numbers in parenthesis represent the absolute numbers.

Table 6. Independent Predictors of Local Complications (Multivariable Analysis)

	Odds ratio	P-value
Localization: Supra vs infra-inguinal	3.82 (1.51-9.65)	0.01
History of Cerebro Vascular Disease		0.03
History of TIA/RIND	2.18 (0.89-5.34)	
History of Cerebro Vascular Accident	2.69 (1.15-6.27)	

TIA =Transient Ischaemic Attack
RIND = Reversible Ischaemic Neurological Deficit
Numbers between parenthesis represent 95% confidence interval.

In uni-variable analysis examining the prognostic factors for local complications demonstrated that stent placement, localization, history of oral anti-coagulantion use, diabetes, history of transient ischemic attack, and a history of cerebrovascular accident were associated with a statitically

significant prognostic value. Mutivariable analyses showed that localization and a history of cerebrovascular accident were independent predictors for local complications (Table 6).

DISCUSSION

The current study reports the complications that occurred in a series of 1186 procedures performed for the treatment of PAD in 6 hospitals in the Netherlands. We found a 30-day mortality rate of 13/1186=1.1%, a non-fatal systemic complication rate of 11/1186=0.9% and a local complication rate of 62/1186=5.2%. Predictors for the occurrence of a systemic complication and 30-day mortality were renal insufficiency and the presence of critical ischemia. Predictors for the occurrence of a local complication were iliac localization and a history of cerebrovascular disease.

The analysis of the prognostic factors for complications following percutaneous interventions was limited by the low occurrence rate of complications. To overcome this problem complications were grouped by severity (local, systemic, and mortality alone), type and bleeding complication. The number of complications did not allow a more detailed classification of complications. Another limitation may lie in the 77 procedures that did not have any follow-up and that were thus excluded from the analysis which may have introduced some degree of selection bias. Comparison of baseline patient characteristics with those that were included, however, did no reveal any major differences suggesting that the presence of selection bias is unlikely.

Table 7 gives an overview of previously published complication rates associated with PTA and stent placement for PAD [2-10]. The published overall complication rate varies from 2.6% to 11.3% and the mortality rate varies from 0% to 3.7%. The multitude of definitions for complications applied in these studies, however, makes comparison of the published rates difficult.

Table 7. Summary of Published Complication Rates Associated with Angioplasty and Stent Placement for Peripheral Arterial Disease

Author	Year	Proc/(Pat)	Compl (%)	30-day mort (%)	Critical Ischemia (%)
Belli AM et al [3]	1990	1642 (1141)	2.6%	0.1%	26.5%
Capek P et al [4]	1991	217 (152)	10%	1.4%	26%
Struk DW et al [5]	1993	350 (235)	6%	NR	NR
Krikorian RK et al [6]	1997	293 (206)	11.3%	NR	NR
Matsi PJ et al [2]	1998	410 (295)	5% major 10.5% total	2.7%	35%
Martin DR et al [7]	1999	(88)	4.5%	1%	26%
Uher P et al [8]	1999	(82)	7.4% major	3.7%	34%
Cheng SWK et al [9]	2001	69 (55)	8.3%	0%	43%
Saha S et al [10]	2001	61 (50)	3.2% minor	1.6%	19.7%
Muradin et al [11]	2002	1186	7.2%	1.1%	18.2%

[3] Complications were divided into complications that required therapy and non-vascular complications such as femoral nerve damage. Time of occurrence of complications and mortality is unknown.

[4] Only superficial femoral arteries and popliteal arteries were treated. Mortality was defined as hospital death. Complication rate was based on total number of patients. Percentage critical ischemia included also patients with severe claudication.

[5] Major complications are those that required treatment by a physician or a change in patient status from outpatient to inpatient. All but one complication occurred within one day after the procedure.

[6] In-hospital complications were defined as hematoma involving the puncture site and/or requiring surgery, acute reocclusion, need for urgent bypass surgery or repeat PTA, and associated post-procedural death, myocardial infarction, stroke, amputation, or renal failure requiring dialysis. Complication rate included only hematomas that required surgery.

[7] Major complications included those that required surgical or some other type of active treatment or significantly influenced the patient's hospital stay (30-day mortality not included). Total complication rate included major and minor complications together. Only femoropopliteal arteries were treated.

[8] Exclusion of patients undergoing PTA of grafts and those having repeated angioplasty of native vessels. Rates based on number of patients. Complications were not defined.

[9] Only treatment of aortoiliac disease. Primary stenting or stenting following failed PTA. Complication rate and 30-day mortality based on patients. Complications were not defined.

[10] Only procedures involving the superficial femoral artery. In all cases one or more stents were placed in the SFA. Startingpoint was a successful PTA. Complications were not defined. Time of occurrence of complications is unknown.

[11] Aortic and iliac stenosis were treated with primary or secondary stenting. Complications were not defined. Complications and death within 30 days after intervention.

Proc: procedures, Pat: patients, Compl: complications, 30-day mort: 30 day mortality, NR: not reported. Complication and mortality percentages are procedure-related unless otherwise specified.
Pooled complication rate (random effects model) was 6.3%. Pooled 30-day mortality rate (random effects model) was 1.1%.

One would expect that mortality would be independent of variation in outcome criteria. Some authors, however, report procedural mortality but do not report what criteria were applied to determine whether the cause of death was due to the procedure. Others report a 30-day mortality including both procedural and non-procedural mortality. The latter may include deaths not attributable to the procedure but overcomes the potential bias associated with determining whether the mortality was procedure- related or not. A large study in which outcome criteria comparable with those applied in the current study were used is the study performed by Matsi [2]. Our study showed a slightly higher non-fatal overall complication rate (6.1 % vs 5%) but a lower 30-day mortality rate (1.1% vs 2.7%). These differences in complication rates may be explained by differences in the procedures performed. Matsi et al included mainly balloon dilatations and only eight stent placements. In our study the percentage of stent placements was higher and we found that in univariable analysis stent placement was associated with a significantly higher local complication rate compared with balloon dilatation.

The complication rate in the current study and reported in previously published studies indicate that the complication rate associated with balloon dilatation and stent placement is relatively low when compared with bypass surgery (Table 7). Reported mortality rates associated with proximal bypass surgery for patients with claudication can be presumed to be close to 1% (operative mortality rate) [1]. In our study the 30-day mortality rates for patients with claudication was 0.2%. Published thirty-day mortality rates associated with bypass surgery in patients with critical ischemia varied from 3.3% [11] to 5.7% [12]. In our study we had a 30-day mortality rate of 5.1% for patients with chronic lower limb ischemia but this included four patients who died after bypass surgery or amputation that followed the percutaneous intervention.

Two very strong predictors for systemic complications and 30-day mortality were renal insufficiency and critical ischemia. Renal insufficiency has previously been shown to be associated with an increased risk of complications presumably due to delayed excretion of contrast medium

[13-15]. Infrainguinal bypass grafting in dialysis- dependent patients and patients with elevated creatinine levels was associated with a high major complication rate, 13% and 29% respectively [13]. Another retrospective study for infra-inguinal bypass grafting reported a 30-day mortality rate of 4.9% in dialysis-dependent patients and a major complication rate of 11% [14]. Amputation in these groups of patients is also associated with a high risk. Lower extremity amputation in patients with end-stage renal disease was associated with a hospital mortality rate of 24% and post- operative morbidity of 54% [15].

Surprisingly, we found that supra-inguinal percutaneous treatment had a significantly higher local complication rate in comparison with infra-inguinal percutaneous treatment. In the literature reported local complications occur predominantly during and after infra-inguinal interventions because of the smaller vessel diameter in comparison with supra-inguinal vessels. A potential explanation may lie in the selection process for percutaneous treatment. In general percutaneous treament for femoropopliteal arterial disease is only performed when the lesions are short and focal whereas in the iliac arteries percutaneous treatment is also considered for more extensive disease [1]. Also the relationship of local complications with a history of cerebrovascular disease is difficult to explain. This predictor may indicate that the patient had severe atherosclerotic disease and was therefore prone to developing complications.

In conclusion, percutaneous treatment is associated with a low 30-day mortality and low overall complication rate. Patients with critical ischemia and renal insufficiency have a relative high risk for developing a systemic complication or dying within 30 days after the intervention.

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CHAPTER 4

Quality assessment and Registries: Experience with a Registry of Percutaneous Interventions for Peripheral Arterial Disease in the Netherlands

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ABSTRACT

Purpose: To monitor the outcomes of percutaneous interventions for peripheral arterial disease and to compare outcomes across hospitals with adjustment for differences in case-mix.

Materials and Methods: From 1994 to 1998 baseline characteristics of patients undergoing percutaneous interventions performed in 6 hospitals in the Netherlands were registered prospectively. Follow-up was abstracted from the medical records and data were analyzed using multivariable Cox-proportional hazard models. Procedures were classified as successful if patients reported symptomatic improvement and if sustained improvement in ABI with more than 0.10 was recorded. Sensitivity analyses were performed to explore the potential influence of missing baseline values and the influence of censoring.

Results: A total of 1347 balloon dilation and stent placement procedures involving 1583 limbs were recorded. Multivariable Cox proportional hazards analyses with adjustment for differences in case-mix demonstrated that the difference in outcomes was statistically significant across hospitals ($P<0.05$). The performance of one hospital was associated with a statistically significant higher hazard rate (hazard ratio=1.3; 95% CI: 1.1-1.6) compared with the overall performance and was ranked last. In this hospital patients with more severe disease were treated raising the question whether the Cox regression adjustment method for differences in case-mix across hospitals was adequate. Further exploration of the influence of the uncertainty in estimates for the performance of hospitals on the rank of this hospital demonstrated a 95% rank interval ranging from rank 3 to 6 indicating substantial uncertainty in rank order.

Conclusion: after considering the differences in case-mix and the uncertainty in ranking, we concluded that the results did not demonstrate a difference in performance across hospitals.

INTRODUCTION

Reported results of percutaneous interventions for peripheral arterial disease (PAD) show a considerable variation in success rates [1, 2]. Part of this variation can be explained by the limited precision of the estimates, differences in reporting methods, and differences in case-mix. Another explanation for the variation in reported success rates, however, may be that the performance across hospitals differs.

During the past decade considerable attention has been paid to the monitoring of quality of care and studies comparing the performance across hospitals in a variety of areas have been published [3-13]. In order to assess the effect of hospital care on patient outcomes, it is essential to take into account the differences across hospitals in the type of patients treated and their severity of illness [14-16]. Unless adjustments are made for these potential differences in case-mix across hospitals no valid comparisons can be made. Ignoring or inadequately dealing with differences in case-mix may result in erroneously singling out hospitals as "bad apples". Careful analysis with adjustment for differences in case-mix, on the other hand, may provide valid information on the performance of a hospital and can be used to assess the quality of care, information that can be used to optimize the level of care.

In the light of these considerations a registry for percutaneous interventions for PAD was started in the Netherlands. The purpose of the current study was to monitor the outcomes of percutaneous interventions performed for peripheral arterial disease and to compare the outcomes across hospitals with adjustment for case-mix.

MATERIALS AND METHODS

Data collection

In 1994, the Vascular Intervention Registry (VIR) was established for the purpose of the quality assessment and improvement of current medical practice by monitoring and analysis of percutaneous vascular interventions

for PAD affecting the lower extremities and their outcome. Four teaching hospitals and two general hospitals in the Netherlands participated voluntarily. Three hospitals registered for 3 years, 2 for 2 years, and one for one year.
Data regarding patients at the time of the intervention and details from the procedure and its outcome were entered prospectively in the registry. A total of 1012 procedures were registered prospectively. From 1998 to 2000 follow-up data was obtained by abstracting medical records retrospectively. Cross-checking the VIR registry with hospital based registries identified another 335 procedures that had not been registered. For these procedures baseline data were abstracted retrospectively from medical records. All data were recorded using standardized forms. A total of 1250 patients were registered from 1994 to 1998 who underwent 1347 consecutive procedures and in whom 1671 limbs were treated. Limbs with acute ischemia or undergoing treatment other than balloon dilation or stent placement were excluded from the analyses resulting in a study population of 1583 limbs. All data were entered in a computerized database (Microsoft Access 97). Two outcome measures were considered: a symptomatic outcome based on whether the patient reported symptom improvement and a hemodynamic outcome based on a change in Ankle Brachial Index (ABI) by more than 0.10 or, if performed, duplex imaging information. Technical failure and re-intervention were considered failures for both the symptomatic and hemodynamic outcome. Technical failure was defined as inability to enter the artery, to cross the lesion, or to improve the blood flow. The reproducibility and validity of the data analyzed was assessed in a random sample of 59 patients by comparing the baseline data from the VIR database with data abstracted retrospectively from medical records. In 66% and 23% of the validation set the VIR database recorded identical information or more detailed information, respectively, compared with the information recorded in the medical records. In 11% of the validation set items were recorded differently.

Data-analysis:
differences in case-mix

To assess whether performance differed between hospitals, Kaplan Meier curves were constructed and the log-rank test was performed.To evaluate whether differences in performance between hospitals could be explained by differences in the case-mix, Cox proportional hazard regression models were constructed. By a process of univariable and multivariable regression analyses with symptomatic outcome as the dependent variable in one analysis and hemodynamic outcome as the dependent variable in another analysis, the prognostic variables for the model were selected. Forty-one candidate variables were evaluated including: age, gender, myocardial infarction more than 6 months ago, myocardial infarction less than 6 months ago, angina pectoris, heart failure, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, creatinine level (≥130 μmol/L, creatinine level ≥530 μmol/L, renal transplantation, dialysis, transient ischemic attack/reversible ischemic neurological deficit, cerebrovascular accident, never smoker or past smoker more than 10 years ago, past smoker less than 10 years ago, past smoker < 1 year ago, current smoker 1-19 cigarettes package per day, current smoker 20 or more cigarettes a day, aspirin use, oral anticoagulant treatment, use of beta-blockers, use of anti-hypertensive drugs, elevated diastolic blood pressure (>90 mmHg), insulin dependent diabetes mellitus, non-insulin dependent diabetes mellitus, ABI, claudication, rest pain, ischemic ulceration, gangrene, asymptomatic (treatment indication bypass at risk), asymptomatic (primary treatment indication: symptoms in contralateral leg), type of lesion (stenosis versus occlusion), localization of lesion (aorta-iliac, femoropopliteal, infra-popliteal), and previous revascularization (aorta-iliac prosthesis, femoral prostheses, cross-over prosthesis, infra-inguinal percutaneous intervention, supra-inguinal percutaneous intervention, other surgical revascularization in the aorta-iliac segment, other surgical revascularizations in the femoropopliteal segment). Variables associated with a statistically significant or borderline significant prognostic value (P-value<0.10) in univariable analyses were selected and entered in a multivariable regression model. Using backwards stepwise Cox proportional hazard regression analyses, all variables that were not associated with a statistically significant prognostic value in the

multivariable analysis were removed from the model (P-value>0.10; likelihood ratio test). The threshold of 0.10 was chosen to minimize the possibility of excluding important clinical predictors from the multi-variable analyses. We used the SPSS statistical package (version 10.0.7) SPSS Inc, Chicago, Illinois. The unit of analysis for all results reported was treated limbs.

Data-analysis:
Comparison of hospitals

First we assessed whether performance differed between hospitals , Kaplan Meier curves were constructed and the log-rank test was performed. Next the additional prognostic value associated with hospitals was tested in the multivariable regression analysis by adding a variable indicating the hospital effect in the models with adjustment for differences in case-mix. The prognostic value associated with the individual hospitals was tested by comparing the hospital effects with the overall performance across all hospitals using the Wald test.

Missing values & sensitivity analysis

Complete data on the selected variables for the final multivariable model were available in 88% of the population for the symptomatic model (1391 limbs out of 1583 limbs) and in 79% of the population (1253 limbs out of 1583 limbs) for the hemodynamic model. The percentage of limbs that was censored during the first year of symptomatic follow-up and hemodynamic follow-up was 21.7% (302/1391) and 22.7% (285/1253), respectively. During the first year of follow-up 6.4% of limbs were censored because of mortality or severe comorbidity including health problems, such as malignancies, cerebrovascular accidents, disabling cardiac symptoms, or hip fractures, making it irrelevant from the clinician's perspective to evaluate the outcome of the intervention for PAD.

To explore the influence of missing data on our results, we performed various sensitivity analyses. In the first set of sensitivity analyses we explored the effect of missing baseline values by imputing the missing ABI values and by substituting the missing values in dichotomous variables with first "no" and subsequently "yes" in two separate analyses. In the second set of sensitivity analyses we explored the effect of selective loss to

follow-up on our results by assuming that the patients who were lost to follow-up did not have a change in ABI or symptoms for the remaining period of that year, and, in another analysis, by assuming that all patients who were censored before 90 days had deterioration of the symptomatic and hemodynamic status. In the third sensitivity analysis we explored the influence of including angiographic details including distal arterial runoff, length of the lesion and severity of the stenosis in the models. Angiographic data were available in 1058 limbs and unavailable in the majority of procedures identified by cross-checking our database with hospital base registries.
Ranking of hospitals was performed according to the hazard ratios that tested the hospital effects adjusted for significant clinical variables. Because the hazard ratios were associated with standard errors, the ranking of hospitals was also associated with a certain degree of uncertainty. To explore this uncertainty, hospital rank intervals were constructed by randomly drawing 10.000 point estimates from the multivariable distributions of the hospital specific hazard ratios and computing the ranking of hospitals in each sample. The 95% rank intervals for the individual hospitals were computed by taking the 95% percentiles of the samples.

RESULTS

Differences in case-mix

Table 1 compares the clinical indication for treatment across hospitals. Nearly 24% of the limbs undergoing treatment in hospital F had critical ischemia (restpain or tissue loss) which is an important predictor for the outcome of percutaneous interventions, whereas the percentage of limbs with critical ischemia in the other hospitals was much lower. The mean ABI prior to treatment was also the lowest in hospital F. Table 2 shows the differences in hospital population with regard to other manifestations of vascular disease and risk factors that can potentially influence the outcome of treatment.

Table 1. Comparison of Hospital Populations by Clinical Indication

	Hospital						
	A	B	C	D	E	F	Overall
Claudication (%)	83.3	82.3	80.5	73.1	74.8	69.7	76.1
Restpain (%)	3.1	5.5	2.7	3.2	1.3	4.5	3.0
Tissue loss (%)	8.8	6.4	8.9	11.9	9.6	19.0	11.1
Asymptomatic, indication bypass at risk (%)	0.0	3.2	2.7	4.3	6.5	1.2	3.7
Symptoms predominately in contralateral leg (%)	4.7	2.7	5.3	6.5	6.2	3.9	5.0
Mean ankle brachial index prior to treatment	0.72	0.74	0.71	0.73	0.77	0.65	0.73

The difference in distribution of clinical indications was statistically significant between hospitals

Hospital populations differed significantly in the percentage of subjects with diabetes and the percentage of subjects with a positive revascularization history. The patient population undergoing treatment in hospital F was associated with the highest mean age, the highest percentage of occlusions, and relatively high prevalence of diabetes, cardiac disease, and cerebrovascular disease.

A process of univariable and multivariable regression analyses excluded 30 of the candidate prognostic variables. The variables that were independently associated with both symptomatic and hemodynamic outcome in the multivariable analysis were age, clinical indication (categories: claudication, rest pain, ischemic ulceration, gangrene, asymptomatic but bypass at risk, symptoms predominantly in contralateral leg), localization of the lesion (supra versus infra-inguinal), diabetic status of the patient, a history of femoropopliteal bypass surgery, and a history of other surgical revascularization in the femoropopliteal segment. In addition, the cardiac and renal histories were independently associated with the symptomatic outcome. Finally, ABI and aspirin use were independently associated with the hemodynamic outcome.

Table 2. Comparison of Baseline Characteristics across Hospitals

	Hospital						
	A	B	C	D	E	F	Overall
Number of limbs	194	220	113	93	626	337	1583
Male (%)/Female (%)	33/67	36/64	31/69	37/63	33/67	37/63	34/66
Mean age (years)*	57	58	60	60	62	63	61
Ever-smoking †	84	85	81	75	85	81	83
Diabetes (%)*	13	21	18	16	24	23	21
Hypertension/antihypertensive medication (%)*	36	27	36	38	26	29	30
Cardiac disease (%)	30	24	34	25	27	32	28
Renal disease (%)*	8	11	13	4	7	11	9
Cerebrovascular disease (%)	8	8	9	16	11	14	11
Previous percutaneous intervention for PAD (%)*	16	25	9	22	11	19	16
Previous aorta-iliac surgical revacularization (%)*	7	14	10	8	5	7	8
Previous femoropopliteal surgical revascularization (%)*	4	13	16	12	17	11	13
Amputation (%)	3	3	2	0	1	2	2
Previous revascularization in contralateral leg (%)*	23	36	21	27	23	30	26
Lesion type: occlusion (%)*	14	26	23	23	19	33	22

* Difference in percentage of limbs was statistically significant across hospitals
† Ever smoking was defined as current smokers or past smokers less than 10 years ago

Comparison of hospitals

Figure 1[a,b] compares the Kaplan Meier curves associated with the individual hospitals. In unadjusted analyses, the difference in outcome between hospitals was statistically significant (log-rank-test: p-value< 0.04). Hospital F was associated with the lowest symptomatic and hemodynamic success curve in the unadjusted analysis.

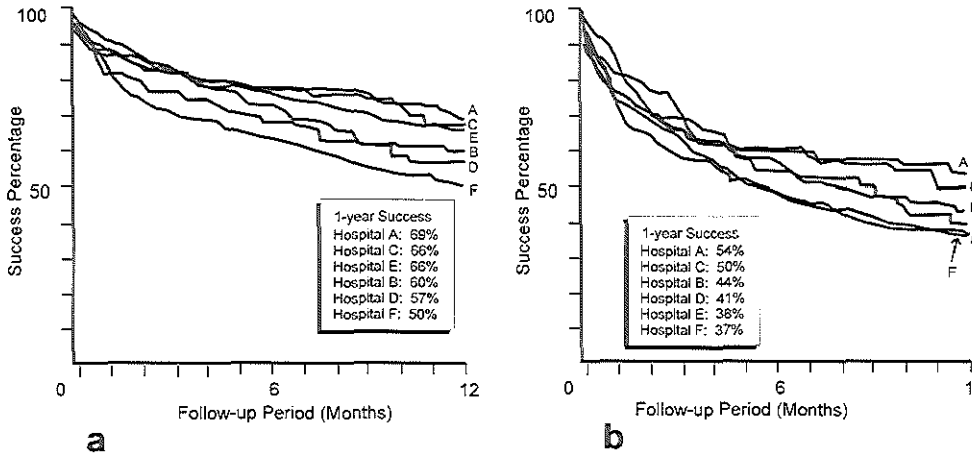
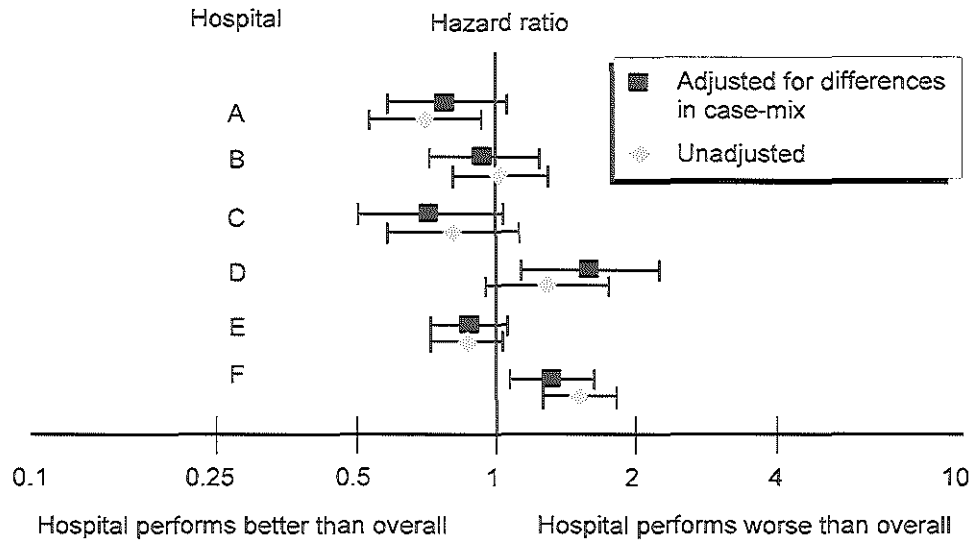


Figure 1a/b. a) Crude Symptomatic Success Percentages, **b**) Crude Hemodynamic Success Percentages

In the Cox-regression model adjusting for differences in case-mix did not change the statistically significant overall prognostic effect of the hospitals on the symptomatic outcome (P-value 0.002). The relation between overall hospital effect and the hemodynamic outcome, however, changed from significant to borderline significant (P-value 0.054).

Figure 2 [a,b] illustrates the differences in performance between hospitals, before and after adjustment for differences in case-mix, depending on the outcome considered. After adjustment for case-mix the hospitals A,B,C,and E were not significantly better or worse than the overall mean independent of the outcome considered. Hospital F was, however, both in adjusted and unadjusted analyses and independent of the outcome considered, associated with a statistically significant hazard ratio compared with the mean performance across all hospitals (P<0.01). Hospital D was not associated with a statistically significant different hazard rate compared with the overall performance in unadjusted analyses.



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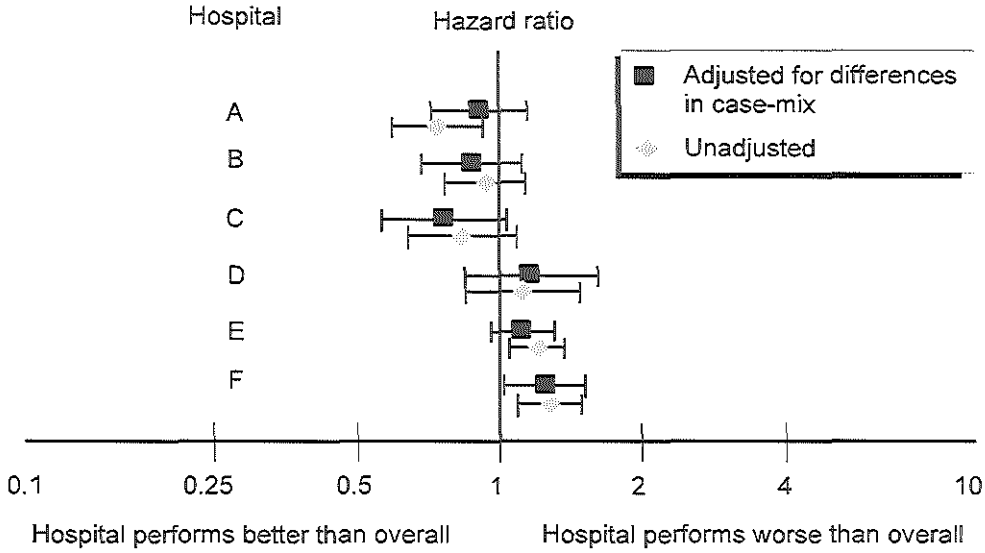

b

Figure 2a/b. a) Symptomatic Outcome, **b)** Hemodynamic Outcome

After adjustment for case-mix, however, hospital D became (P=0.008) associated with a statistically significant hazard ratio but only for the hemodynamic outcome.

Sensitivity analysis

Most sensitivity analyses did not change the results considerably (Table 3) with the exception of the sensitivity analysis with hemodynamic outcome in which we assumed that all censored patients remained asymptomatic.

Table 3. Range in Results found in the Sensitivity Analyses that explored the potential influence of Missing Values, depending on the Outcome that was considered

Symptomatic Outcome			Hemodynamic Outcome		
Hospital	Hazard Ratio*	95%CI †	Hospital	Hazard Ratio*	95%CI †
A	0.78-1.02	0.58-1.29	A	0.82-0.99	0.65-1.26
B	0.78-1.05	0.56-1.34	B	0.83-0.93	0.62-1.21
C	0.66-0.95	0.47-1.33	C	0.73-0.85	0.54-1.18
D	1.26-1.61	0.90-2.27	D	1.06-1.29	0.75-1.74
E	0.68-0.90	0.57-1.08	E	0.98-1.20	0.84-1.14
F	1.27-1.55	1.04-1.93	F	1.16-1.42	0.95-1.70

* Range in hazard ratio found in the various sensitivity analyses that were performed: In all comparisons the reference was the overall performance of all hospitals.
† The lowest and highest limit of the 95% confidence intervals associated with the hospital specific hazard ratio found in the sensitivity analyses.

In this analysis hospital effect was not associated with a statistically significant additional prognostic value (P=0.1) and hospital F was not associated with a significantly higher hazard ratio compared with the overall performance of all hospitals.

Table 4 shows the results of ranking hospitals according to the adjusted hazard ratios and the results of exploring the uncertainty in the hazard ratios on the rank of each hospital. Hospital E which included the largest number of patients, was associated with a 95% rank interval ranging from rank 1 to rank 4 for the symptomatic outcome and from rank 3 to rank 6 for the hemodynamic outcome.

Hospital F, which was singled out as the worst performer in the Cox regression analysis, was associated with a 95% rank interval ranging from rank 4 to rank 6 for both outcomes, indicating that the low rank assigned to this hospital may be due to limited precision of the hazard ratios.

Table 4. Ranking and 95% rank interval of Hospitals According to the Hospital Specific Hazard ratios after Adjusting for Differences in Case-mix, Depending on the Outcome that was Considered

	Ranking (95% rank interval)*	
Hospital	Symptomatic Outcome	Hemodynamic Outcome
A	2(1-4)	3(1-4)
B	4(1-4)	2(1-4)
C	1(1-4)	1(1-3)
D	6(5-6)	5(2-6)
E	3(1-4)	4(3-6)
F	5(4-6)	6(4-6)

*The 95% rank intervals represent the uncertainty in hospital rank due to the limited precision of the hospital specific hazard ratios. These intervals were constructed by drawing 10.000 samples from the distributions of the hazard ratios and by ranking hospitals in each sample. The range of hospital ranks that occurred in 95% of samples were included in the interval.

DISCUSSION

In the current study performance of hospitals in daily clinical practice was evaluated by prospective recording of baseline characteristics and by chart review to determine the outcome of the procedure. We found that hospitals were associated with a statistically significant prognostic value in addition to the prognostic factors that reflected differences in case-mix. One hospital (F) demonstrated a statistically significant higher hazard rate compared with the overall mean for both the symptomatic outcome and

the hemodynamic outcome. Four hospitals did not show any statistically significant difference compared with the average performance and one hospital showed a statistically higher hazard rate when considering the symptomatic outcome but not when considering the hemodynamic outcome. The 95% rank intervals that were constructed, however, revealed that the rank of all hospitals was associated with substantial uncertainty. The main limitations of this study were related to the fact that clinical practice registries only record variables that are collected in daily routine practice. First, not all patients had complete follow-up or baseline data. To explore the potential influence of these missing values we performed sensitivity analyses. Imputing the missing ABI values and substituting all other missing values with "no" or "yes" or making assumptions for patients lost to follow-up did not change the results based on the symptomatic outcome considerably. Exploring the potential influence of censoring on the hemodynamic outcome by assuming that censored subjects remained asymptomatic, however, changed the prognostic value of hospital effect to non-significant indicating that the results change considerably when extreme assumptions are made on the patients that are lost to hemodynamic follow-up. The results based on symptomatic follow-up data were not substantially affected by the potential influence of missing follow-up data.

Second, although we adjusted for differences in case-mix across hospitals and although the main proportion of procedures and baseline characteristics were recorded prospectively, it may be possible that the results were affected by residual confounding. Examination of the baseline characteristics of the hospital populations revealed that the patient population undergoing treatment in hospital F was associated with a highest mean age, the highest percentage of occlusions, a relatively high prevalence of diabetes, cardiac disease and cerebrovascular disease, the lowest mean pre-treatment ABI, and highest percentage of patients presenting with critical ischemia. Not surprisingly this hospital was associated with the lowest success probabilities in unadjusted analyses. In multivariable analyses after correcting for differences in case-mix this hospital was still associated with a statistically significant worse performance compared with the overall performance. A possible explanation for this may be that the patient population of hospital F

differed too much from the other hospital populations and that the applied statistical and epidemiological methods could not adjust completely for this difference. Furthermore, exploration of the uncertainty in the ranking of hospitals using 95% rank intervals demonstrated that the observed rank of hospitals might for a large part be due to the limited precision of the hazard ratios. This was certainly the case for hospital F which was associated with a 95% rank interval ranging from rank 4 to rank 6.

A third limitation may be that symptomatic and hemodynamic outcome are only part of the spectrum of clinically relevant outcomes for patients undergoing percutaneous treatment for PAD. An important measure of performance that was not evaluated in the current study was the patients' perception of care. The results of the current study can therefore not be generalized to all aspects of hospital performance.

Previous studies comparing performance across hospitals used short-term outcomes such as for example 30-day mortality or morbidity rates to evaluate differences in outcome [3, 6-8]. The current study focussed on the long-term results of percutaneous interventions for PAD. The 30-mortality rate, systemic complication rate and local complication rate, however, were also recorded, and were 1.1%, 2% and 5.2%, respectively, in the total population. These rates did not differ significantly across hospitals. As far as we know, no other studies comparing the outcome of percutaneous treatment for PAD across hospitals have been published thus far.

Our major finding was that 5 hospitals did not differ in performance from the overall performance and showed considerable uncertainty in the ranking in either the symptomatic outcome or the hemodynamic outcome. The one hospital that differed from the overall performance treated patients with more severe disease compared with patients treated in the other hospitals. The finding that this hospital was associated with a higher hazard ratio may be due to residual confounding. Furthermore, sensitivity analysis suggested that the low rank may be due to chance. Nevertheless our results indicated that major differences in practice patterns across hospitals in the Netherlands probably exist and that treatment strategies vary per hospital. Which treatment strategy is optimal and which patients should be selected for percutaneous treatment must be determined in cost-effectiveness studies that consider all treatment options and consider

sufficient patient characteristics to evaluate the complete spectrum of disease.

In conclusion, registries that record daily clinical practice are useful in assessing differences in practice patterns and outcomes across hospitals. Great care must, however, be taken in the statistical analysis of the results to avoid inadvertently labeling a hospital as a bad performer. After considering the differences in case-mix and the uncertainty in ranking, the outcome of percutaneous intervention for PAD did not differ between the 6 hospitals included in the current study.

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CHAPTER 5

Cost and Patency Rate Targets for the Development of Endovascular Devices to Treat Femoropopliteal Arterial Disease

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ABSTRACT

Purpose: To determine the criteria that would make use of an endovascular device cost-effective compared with bypass surgery and percutaneous transluminal angioplasty in the treatment of femoropopliteal arterial disease.

Materials and methods: A decision model was developed to compare treatment with the use of a hypothetical endovascular device to treatment with established therapies. Cost-effectiveness from the perspective of the health care system was considered. Outcome measures were lifetime costs and quality adjusted life years. With the use of net health benefit and threshold analysis, combinations of costs and patency rates were determined that would make the device cost-effective compared with established therapies. In subgroup and sensitivity analyses, the effect on decision making of sex, age, indication, lesion type, procedural risk and society's willingness to pay for incremental gain in health were explored.

Results: Use of a device that costs $ 3,000 would be cost-effective compared with bypass surgery for critical ischemia if the five-year patency rate is 29-46%. The same device would be cost-effective compared with angioplasty for disabling claudication and a stenosis if the five-year patency rate is 69-86%.

Conclusions: The target combinations of costs and patency rates found in this study are probably attainable, and further development of such endovascular devices seems warranted.

INTRODUCTION

Although bypass surgery and percutaneous transluminal angioplasty (PTA) are commonly used revascularization procedures in the treatment of femoropopliteal arterial occlusive disease, both procedures have disadvantages [1]. Percutaneous transluminal balloon angioplasty is a low risk and low cost procedure, but is associated with a fairly high restenosis rate [2-5]. Primary stent placement does not improve the patency rate of PTA performed for femoropopliteal arterial disease and is thus currently used only to salvage a failed balloon angioplasty procedure [6, 7]. Bypass surgery, on the other hand, has higher long term patency rates but is also associated with a higher procedural risk, higher cost, and a longer convalescence period [4, 5]. In general, PTA is performed as primary treatment of short focal lesions of the femoropopliteal artery, whereas bypass surgery is the primary treatment in diffuse disease.

Endovascular devices are currently being developed as alternative interventions to overcome the problems of established procedures. Important considerations in choosing the optimal treatment strategy are the effectiveness of the device, the risks of the procedures, and the costs. These parameters are generally unknown during the development of a new technology. In particular, the patency and cost estimates associated with endovascular devices are uncertain and may even change with time. It is difficult, if not impossible, to predict what the precise values for the parameters of a new technology will be. Given the outcome and cost of established procedures, however, we can calculate under what conditions a new technology can become cost-effective compared with the established procedures, thereby setting standards for the new device. The merit of such an approach is that it can potentially focus the development of new therapeutic technology [8, 9]. This applies not only to femoropopliteal interventions but also to many other procedures such as abdominal aortic endoprothesis and carotid stenting.

The purpose of this study was to determine the criteria that would make the use of an endovascular device for the treatment of femoropopliteal arterial disease cost-effective compared with PTA and bypass surgery. A secondary objective was to illustrate how decision and cost-effectiveness analysis can be used to focus the development of new technologies.

MATERIALS AND METHODS

Overview Decision Model

Previously, a decision analytic model was developed to examine the choice between bypass surgery and PTA for femoropopliteal arterial occlusive disease [10]. The model considered different types of patients (age, sex, and other risk factors), varying severity of disease (disabling claudication, rest pain, and tissue loss), and different types of lesions (stenosis and occlusion) and to combine literature data on risks, benefits, and costs. The main outcome measures were quality-adjusted life expectancy and life-time cost for each strategy, depending on patient characteristics, clinical indication, and lesion type.

In the current study, another treatment option was added to the model, namely, treatment with a hypothetical endovascular device. We compared three treatment strategies. Each strategy allowed at most two treatments. Initial revascularization was accomplished with balloon angioplasty, with autologous saphenous vein bypass surgery, or use of the hypothetical endovascular device. Secondary treatment for primary failure was undertaken with bypass surgery if the initial treatment was angioplasty or use of the endovascular device, or with surgical revision if the initial treatment was bypass surgery.

Because the procedural risk, cost, and patency curves of the endovascular device are unknown, the following assumptions were made. The patency curve of the endovascular device was assumed to relate, through a proportional hazards model, to that of PTA, which implies that the curves of the endovascular device and PTA were similar in shape but different in

height. The 5-year patency rate was used as measure for the height of the patency curve. The risk and complications of an endovascular device and the procedural cost, excluding the cost of the device itself, will ideally be approximately the same as those of PTA or lower. However, since the procedural risk of a hypothetical device is unknown, we assumed that the morbidity, mortality, and convalescence period associated with an endovascular device will be 1.5 times higher than that of PTA. The procedural cost of the device (excluding that of the device itself) was assumed approximately the same as that of PTA. Threshold analysis was performed to determine criteria (ie, combinations of 5-year patency rates and costs) that would make the device equivalent in terms of cost-effectiveness compared with bypass surgery and PTA.

The model was developed from the perspective of the health care system. All costs were adjusted to 1999 U.S. dollars with use of the medical care specific consumer price index.

Data and Data Sources

Estimates of procedural mortality, morbidity, amputation rate, quality-of-life adjustments, costs, and patency rates following femoropopliteal PTA and bypass surgery were based on findings from a published meta-analysis and decision analysis [4, 10]. The meta-analysis involved a combination of literature data published between 1985 and 1993 and pooled patency results following bypass surgery and PTA for the treatment femoropopiteal arterial disease, with the use of a method based on the proportional hazards model and the actuarial life-table approach [4]. The decision-analysis involved a combination of literature data published in 1995 and earlier and an examination of the choice between bypass surgery and PTA for femoropopliteal arterial disease [10].

Table 1 presents the data on bypass surgery and PTA incorporated in the model. The costs for angioplasty and bypass procedures, physician services, noninvasive testing during outpatient follow-up, amputation plus rehabilitation, and annual costs of treatment after an amputation or with major morbidity were based on published and unpublished data on charges from the Brigham and Women's Hospital Vascular Service [10, 11].

TABLE 1. Data on Currently Used Femoropopliteal Revascularization Procedures

Parameter	Bypass Surgery	Angioplasty
Procedural mortality		
Claudication	0.8%	0.2%
Critical ischemia	4.7%	3.2%
Procedural nonfatal systemic morbidity	8.5%	1.3%
Time lost due to convalescence	7 days	2 days
Procedural cost		
Claudication	$ 20,531	$ 10,168
Critical ischemia	$ 25,881	$ 18,171
Primary patency, 1-y/5-y (%)		
Claudication and stenosis	91/80	79/68
Claudication and occlusion	91/80	53/35
Critical ischemia and stenosis	84/66	62/47
Critical ischemia and occlusion	84/66	28/12

* In 1999 U.S. dollars. Costs are from the perspective of the health care system and include materials used, personnel, equipment, administration, overhead, professional fees, and room and board. The cost of surgical revision of a bypass was assumed to be in the same order of magnitude as that of primary bypass surgery.

All data on charges were adjusted with the use of cost-to-charge ratios specified by cost center and fiscal year. Quality-of-life adjustments were based on the experience of two vascular surgeons, two interventional radiologists (including M.G.M.H.), and an internist who estimated the various health states related to peripheral arterial disease with the use of an abbreviated form of the Health Utilities Index. This index is used to rate physical function, role function, social and emotional well-being, and general health [10].

The amputation rate following revascularization was assumed to depend on the initial symptomatic status. Each year, on average, 1.2% of patients

with claudication, 2.3% of patients with rest pain, and 6.4% of patients with tissue loss underwent amputation [12, 13]. Of these patients, an estimated 11.5% did not survive the amputation, and another 38% experienced major morbidity [14-16]. The convalescence period following amputation was approximately 82 days [16]. The total cost of amputation, including cost of rehabilitation, was estimated to be $ 34,384 US [17, 18]. Follow-up of patients after revascularization cost on average $ 543 in the 1st year, $ 182 annually thereafter if the artery or bypass remained patent, and $ 543 annually if failure occurred [10]. The annual cost of long-term care and treatment in patients who underwent amputation of a lower limb was estimated to be $ 48,877 per year [17, 19-21]. The cost of care and treatment of patients with major morbidity following revascularization or amputation was estimated to be $ 11,947 [22].

The relative risk of overall mortality of patients with peripheral arterial disease was estimated to be 3.1 compared with that of the general population matched for age and sex [12, 23]. In view of the recommendations of the Panel on Cost-effectiveness in Health and Medicine, both costs and benefits were discounted at a discount rate of 3% [24].

Determination of Criteria and Threshold Analysis

A strategy was considered cost-effective compared with another if the gain in quality adjusted life-years (QALYs) justified the additional monetary costs. The trade-off between QALYs and additional monetary cost was considered justified if it did not exceed society's maximum willingness to pay for an incremental gain of 1 QALY.

To facilitate the calculation of the threshold values for patency and cost, the net health benefit approach (NHB) was used to compare the use of the hypothetical endovascular device with currently used interventional strategies [25]. The NHB is used to combine costs, QALYs, and an estimate of society's willingness to pay (λ) for an incremental gain of 1 QALY in one expression. For each strategy, we computed the NHB with the use of the eqation $NHB = QALYs - {}^{Costs}/_{\lambda}$ [25].

Two strategies were considered equivalent in terms of cost-effectiveness if they yielded the same NHB.

The NHB makes a trade-off between QALYs gained and monetary expense. In essence, the use of the NHB is the same as the use of incremental cost-effectiveness ratios, but technically, the use of NHB is more practical. The difference between the use of the NHB approach and the incremental cost-effectiveness ratio approach is that in the use of incremental cost-effectiveness ratios, society's willingness to pay can be considered after the results are obtained, whereas in the use of the NHB approach, an estimate of society's willingness to pay must be incorporated in the calculation. For a given estimate of society's willingness to pay, however, the conclusions with the use of either method will be the same. To estimate the effect of the chosen willingness to pay value, one can repeat the analysis for a range of values. Published estimates for willingness to pay range from $ 20,000 to $ 100,000 per QALY gained, and we therefore considered this range in our calculations [25].

Baseline and Sensitivity Analysis

The baseline case used in the analysis was that of a 65-year-old male with femoropopliteal arterial disease without co-morbidity or other risk factors. In our baseline analysis, we assumed society's willingness to pay to be $ 20,000 per QALY gained. In subgroup analysis, we explored the effect of disease severity (disabling claudication, rest pain, tissue loss) and lesion type (stenosis and occlusion).

In one-way sensitivity analysis, we explored the effect of varying age (55 and 75 year), sex, society's willingness to pay for gain of 1 QALY ($50,000 and $ 100,000), and the discount rate (2% and 5%) on our results. Furthermore, we performed one-way sensitivity analyses to explore the effect of a lower and higher (1 and 2 times that of PTA) procedural risk of the device, including morbidity, mortality, and time lost due to the intervention. We assumed that the morbidity, mortality, and time lost due to the intervention of the endovascular device would not exceed that of bypass surgery. Finally, we explored the effect of varying age, sex, society's

willingness to pay and procedural risk simultaneously in a four-way sensitivity analysis.

RESULTS

Whereas bypass surgery yielded the highest NHB (Table 2) in patients with chronic critical ischemia (rest pain or tissue loss) and a femoropopliteal occlusion, PTA yielded the highest NHB in stenotic femoropopliteal lesions irrespective of the clinical indication.

TABLE 2. Health Effects, Costs, and NHB of Currently Available Therapies for Femoropopliteal Arterial Disease

Indication and Lesion	Initial treatment	QALE (QALY's)	Cost ($)	NHB (QALY-equivalents)
Claudication				
Stenosis	PTA	5.85	22,758	4.71
Stenosis	Bypass	5.46	33,229	3.80
Occlusion	PTA	5.59	32,131	3.99
Occlusion	Bypass	5.46	33,229	3.80
Rest pain				
Stenosis	PTA	5.26	42,372	3.14
Stenosis	Bypass	5.00	44,694	2.76
Occlusion	PTA	4.83	55,074	2.08
Occlusion	Bypass	5.00	44,694	2.76
Tissue loss				
Stenosis	PTA	5.20	48,589	2.77
Stenosis	Bypass	4.92	53,346	2.25
Occlusion	PTA	4.74	65,578	1.46
Occlusion	Bypass	4.92	53,346	2.25

Note. QALE = quality adjusted life expectancy; All costs are from the perspective of the health care system and included hospital and physician costs for the initial and secondary procedures, treatment of complications, follow-up, long-term care, and amputation and rehabilitation.

The Figure presents the target values that would make the use of an endovascular device cost-effective compared with currently used procedures.

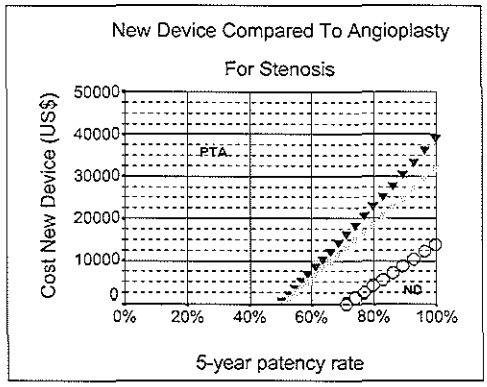

Figure 1a

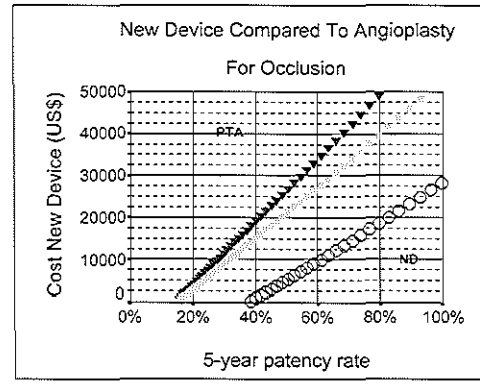

Figure 1b

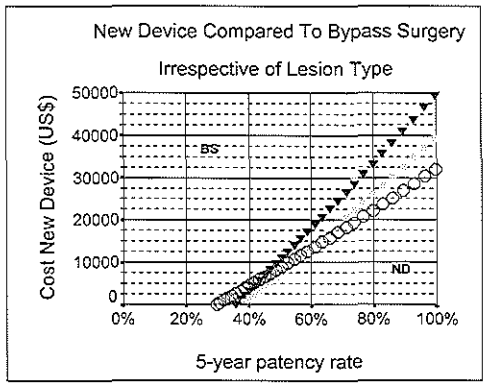

Figure 1c

Figure 1. Target values that would make an endovascular device cost-effective compared with **(a)** angioplasty for a stenosis, **(b)** angioplasty for occlusions, and **(c)** bypass surgery. The x axis represents hypothetical 5-year patency rates of the endovascular device and the y axis, hypothetical costs of the device. The lines represent combinations of 5-year patency rates and costs that would make the endovascular device equivalent to the therapy to which it is being compared in terms of cost-effectiveness, depending on clinical indication: tissue loss (▼), rest pain (▩) and claudication (O).

Area below the lines represents the target combinations of patency rates and costs that would make the device **(ND)** more cost-effective then the therapy to which it is being compared. Area above the lines represent combinations that would make either bypass surgery **(BS)** or angioplasty **(PTA)** more cost-effective.

For example, the Figure, part a, shows that an endovascular device that costs $ 2500 and that is associated with a 5-year patency rate of 80% would be cost-effective compared with PTA for the treatment of a femoropopliteal stenosis, independent of the clinical indication. However, an endovascular device with the same long-term patency but with a cost of $ 7500 would not be cost-effective compared with PTA for the treatment of a stenosis and claudication, whereas it would be cost-effective

for the treatment of a stenosis and critical ischemia. Figure, part b, shows that the lines are more to the left compared with those in part a, which implies that for the treatment of occlusions, the target 5-year patency rates are less stringent.

By considering the treatment of critical ischemia and an occlusion, the graphs show that for any given cost of the endovascular device the patency rates needed to make use of the device cost-effective compared with bypass surgery (Figure, part c) were higher than those required to make the device cost-effective compared with PTA (Figure, part b). This is consistent with the findings presented in Table 2, which shows that bypass surgery yielded a higher NHB than PTA in treatment of critical ischemia and occlusion.

A striking finding was the high acceptable cost for an endovascular device, provided that it is associated with a high long-term patency rate. For example, the Figure, part c, shows that, if an endovascular device has a 5-year patency rate of 80%, the cost of the device may increase to $ 20,000, and it would still be cost-effective compared with bypass surgery, irrespective of the clinical indication.

The results are shown in more detail in Table 3 for two endovascular devices, one device that costs $ 3000 and a second device that costs $ 6000. For clarity, rest pain and tissue loss were replaced by critical ischemia to take into account the highest patency rate required. Table 3 shows the 5-year patency rates and the associated 1-year patency rates that would make an endovascular device equivalent in terms of cost-effectiveness compared with currently employed procedures. For example, the 5-year patency rate that would make a device that costs $ 3000 cost-effective compared with bypass surgery for the treatment of critical ischemia was 43% in the baseline analysis.

Results of one-way sensitivity analyses demonstrated that with an increase in society's willingness to pay, female sex, and a younger age, lower patency rates would be acceptable for an endovascular device. A higher procedural risk and a higher age increased the required patency rates. The tabulated ranges (Table 3) indicate the lowest and highest required patency rates

found when age, sex, procedural risk, and society's willingness to pay were varied simultaneously in a sensitivity analysis.

TABLE 3. Primary Patency Rates Required to Make a New Endovascular Device Equivalent to Currently Available Treatments in Terms of Cost-Effectiveness

Procedure and Indication	Patency (%) with $ 3000 Device		Patency (%) with $ 6000 Device	
	1-year	5-year	1-year	5-year
Bypass surgery				
Claudication	53(41-57)	37(25-41)	59(44-64)	44(28-49)
Critical ischemia	58(45-61)	43(29-46)	63(47-68)	48(31-54)
PTA for occlusion				
Claudication	60(53-65)	45(36-51)	66(54-73)	52(38-61)
Critical ischemia	36(28-39)	20(13-22)	42(29-46)	25(14-29)
PTA for stenosis				
Claudication	85(79-91)	77(69-86)	89(80-98)	84(70-96)
Critical ischemia	69(61-72)	55(46-60)	72(62-78)	60(47-67)

Patency rates were determined in baseline analysis. Numbers in parenthesis represent the range of patency rates found after performing a four-way sensitivity analysis with simultaneously varying sex, age (55, 65 and 75 years), society's willingness to pay ($20,000, $50,000 and $100,000 per quality adjusted life year) and procedural risk of the new device (1, 1.5 and 2 times that of PTA).

Variation of the discount rate from 2% to 5% in one-way sensitivity analyses resulted in an absolute difference of, at most, 1% when these rates were compared with the 5-year patency rates found in the baseline analyses.

DISCUSSION

We report target values of primary patency rates and costs that a hypothetical endovascular device for the treatment of femoropopliteal arterial disease would have to attain to be cost-effective compared with currently employed therapies. The results help predict under what conditions an endovascular device would be the most promising and can help focus future technological development of endovascular devices. As previously demonstrated, the results illustrate that, when currently used procedures are considered, PTA is more cost-effective compared with bypass surgery in the treatment of milder forms of femoropopliteal arterial disease, and bypass surgery is the treatment of choice in more severe disease [10]. When an endovascular device is considered, the results suggest that the target 5-year primary patency rate that would make a device that costs $ 3000 equivalent in terms of cost-effectiveness compared with bypass surgery ranges from 25% to 46%. The 5-year patency rates that would make a device that costs $ 3000 equivalent in terms of cost-effectiveness compared with PTA in the treatment of claudication and a femoropopliteal stenosis ranged from 69% to 86%. Furthermore, the results suggest that use of a hypothetical endovascular device, with a 5-year patency rate of 80 %, would be cost-effective compared with bypass surgery, even if the device cost up to $ 20,000, irrespective of clinical indication.

Caution should be exercised when conclusions are made about cost-effectiveness. Cost-effectiveness is always relative. In the current study, we compared treatment with use of an endovascular device with bypass surgery and PTA. If more than one endovascular device were to be made available on the market, they would have to be compared with each other. Thus, an expensive currently available device may have a cost-effectiveness ratio just below the threshold willingness to pay compared with bypass surgery or with PTA, whereas in the future, the device may no longer be cost-effective if another device yields nearly the same effectiveness at lower costs.

Limitations of the analysis lie within the assumptions of the model. First, we did not update the data concerning the currently used procedures in the model. Although the patency rates and risks of both PTA and bypass surgery are continually improving, a major improvement in the past 5 years is unlikely [26]. Therefore, we assumed that the data used in the 1995 model were still valid. Furthermore, there is evidence that the cost of femoropopliteal revascularization has not changed considerably during the last few years [5]. Second, the data on costs associated with current therapies were collected in a teaching hospital in the United States. Caution should be exercised when the results are generalized to non-teaching hospitals or hospitals in other countries. Third, we assumed that the procedural risk (complications and mortality) of an endovascular device would be 1.5 times higher than that of PTA. We assumed this because, ideally, the procedural risk of an endovascular treatment would be the same as that of PTA or lower. However, to make the baseline results also applicable for an endovascular treatment associated with less favorable morbidity and mortality rates, we assumed that the procedural risk associated with the new device was 50% higher than that of PTA. In sensitivity analyses, we explored the effect of varying the procedural risk and the convalescence period, ranging from one to two times that of PTA, and found that an increase in procedural risk and convalescence period resulted in more stringent target values for the endovasular device.
Fourth, the hypothetical patency curves of the endovascular device were based on the patency curve of PTA. By doing this, we assumed that most failures occur during the 1st year after the procedure. We assumed this because both are endovascular treatments, but the true curve is unknown. Fifth, the choice of the threshold value of society's willingness to pay. Estimates of society's willingness to pay are highly dependent on the societal and decision context [27]. In the baseline analyses of the current study, we assumed society's willingness to pay to be $ 20,000 per QALY gained, and we explored the influence of choosing a threshold of $ 50,000 per QALY gained and that of a threshold of $ 100,000 per QALY gained on our results.

Because we chose a higher threshold, which implies the acceptance of higher costs for the same health effect, the results yielded less stringent criteria for the hypothetical endovascular device.

Current research on endovascular devices to treat femoropopliteal arterial disease focuses on the problem of intimal hyperplasia, which causes secondary obstruction after an angioplasty procedure or stent implantation. The idea is to prevent secondary obstruction by covering the arterial wall with prosthetic material, such as polytetrafluoroethylene, now often used as the conduit material in bypass surgery. Primary patency rates reported thus far associated with such stent-grafts range from 73% at 12 months, 59% at 18 months to 46% at 24 months [28-30]. One group of investigators recently reported less favorable results (12-month patency rate, 29%) [31]. The results in the current analysis suggest that the target 12-month primary patency rate for an endovascular device that costs $ 3000 is approximately 41%-61%. This finding suggests that, if the assumptions in this study hold true, the use of these devices may already be cost-effective compared with bypass surgery. The precision of the reported patency rates in these initial studies was, however, low because the sample sizes were limited and because data on long-term results were not available.

The methods used in this study can be applied to many situations where investigators are developing new therapeutic technologies. Other examples of new technologies under development are endovascular devices for the treatment of abdominal aortic aneurysms or catheter techniques with the use of coiling devices for the treatment of cerebral aneurysms. Perhaps the first step in investigations of new technologies, both therapeutic and diagnostic, should be to establish clear-cut goals for the performance of such technologies compared with existing ones. Such analyses could help focus research and the development of new technologies and thereby help to save valuable resources [8, 9].

In conclusion, the results of this cost-effectiveness analysis in which target cost and patency rates were estimated demonstrate that there is a place for a new endovascular therapy in the treatment of femoropopliteal arterial disease.

The target values of patency rates and costs determined in this study that would make the use of an endovascular device cost-effective compared with the currently used therapies are probably attainable, and further development of such devices seems warranted.

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CHAPTER 6

Reporting Results after Percutaneous Treatment for Peripheral Arterial Disease: The Impact of Outcome Criteria

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ABSTRACT

Purpose: To assess the influence of varying outcome criteria on the results of percutaneous intervention for peripheral arterial disease and to suggest a reporting method that can be used in studies that report results of daily clinical practice.

Methods: The outcome of 1347 consecutive procedures recorded in a multicenter registry involving 6 hospitals in the Netherlands was analyzed. Six sets of outcome criteria were evaluated including one based on symptomatic change, 3 based on ankle brachial index measurements (ABI), and 2 based on combining the symptomatic and ABI outcome. Agreement between outcome measures was compared using the Kappa statistic and by comparing the results from Kaplan-Meier survival analysis.

Results: The 3 outcome measures based on the ABI showed good agreement (kappa .74-.94) and yielded comparable Kaplan-Meier results. The symptomatic outcome measure yielded a substantially higher 1-year success rate compared with the ABI outcome measures (difference 18-24%) and the agreement was only fair (kappa .52-.60). The agreement between symptomatic outcome and ABI outcome was poor in patients with a pre-treatment ABI at rest of more than 0.90 (kappa .20). Combining symptomatic outcome and ABI measurement with the logical operator "OR" showed good agreement with the symptomatic outcome alone (kappa .97) and using "AND" showed good agreement with the ABI outcome alone (kappa .87).

Conclusion: In patients with a pre-treatment ABI at rest higher than 0.9 classifying procedures using a criterion based on improvement in ABI with more than 0.10 is inaccurate and underestimates the actual treatment effect. Furthermore, combining subjective symptomatic improvement and improvement in ABI does not yield more information than reporting them separately.

INTRODUCTION

Comparison and interpretation of published results associated with revascularization for peripheral arterial disease (PAD) have been hampered by the different outcome criteria that are applied to classify outcome in success or failure [1-4]. To standardize the classification of outcome, Rutherford et al proposed a set of criteria to report outcome following therapeutic intervention for PAD [5-7] which are now widely accepted as a standard reporting method [1,8]. According to the published recommendations, two types of outcomes should be distinguished: a clinical-hemodynamic outcome based on the patient's ability to finish a standardized treadmill exercise in combination with ankle brachial pressure index (ABI) measurements and a patency outcome that requires segmental pressure measurements or imaging of the vessel.

The proposed criteria and reporting standards, however, were designed for highly protocolized studies such as randomized clinical trials but not for use in studies and registries that evaluate daily clinical practice. Extensive evaluation is not likely to be performed in all patients in routine medical care after an apparently successful intervention. Clinicians rely on history and physical examination including ABI's, and only if warranted will additional tests such as duplex ultrasound, standardized segmental pressure measurements, and angiography be performed.

The purpose of the current study was to evaluate outcome measures that are available in daily clinical practice and explore how results change when different outcome criteria are applied.

METHODS

In 1994, the Vascular Intervention Registry (VIR) was established for the purpose of the quality assessment and improvement of current medical practice by monitoring the outcomes of percutaneous vascular

interventions for peripheral arterial disease (PAD) affecting the lower extremities. Six teaching hospitals in the Netherlands participated. All consecutive patients that were scheduled for percutaneous intervention for treatment of PAD affecting the lower extremities were registered. Data regarding each patient at the time of the intervention and details about the procedure performed were entered prospectively in a vascular interventional radiology registry. Data regarding post-procedural follow-up were abstracted from medical reports. All data were recorded using standardized forms and entered into a computerized database (Microsoft Access 97).

Six different outcome measures were constructed. In all outcome measures, procedures that ended in technical failure or limbs that underwent revascularization during follow-up were classified as failures. Technical failure was defined as failing to enter the vessel, cross the lesion, or improve blood flow. A procedure was considered successful if

a) the patient reported continued symptomatic improvement,
b) the ABI was consistently more than 0.10 above the pre-procedural level
c) the ABI was consistently more than 0.15 above the pre-procedural level
d) the ABI was consistently above 0.90
e) the patient reported continued symptomatic improvement **or** the ABI was consistently more than 0.10 above the pre-procedural level
f) the patient reported continued symptomatic improvement **and** the ABI was consistently more than 0.10 above the pre-procedural level.

This last outcome measure was similar to the clinical-hemodynamic outcome proposed by the TASC Working Group [1] and only differed in that it was not based on the patient's ability to complete a standardized treadmill exercise test but on the patient's self-evaluation of his or her symptomatic change.

In all but the first outcome measure information obtained with duplex scanning or angiography was also considered. If duplex or angiography

was performed, the results of the intervention was classified according to the peak systolic velocity ratio or the severity of stenosis respectively, irrespective of the ABI. Peak systolic flow ratio's larger than 2.5 or angiographic stenosis of 50% or were defined as procedural failures.
To determine whether procedures were classified differently when different outcome measures were applied, two by two tables were constructed and kappa calculations were performed to determine the level of agreement between the outcome measures.
Subgroup analyses were performed to assess whether the estimates for kappa depended on localization of the treated lesions (iliac versus femoropopliteal), clinical indication (claudication versus critical ischemia), or pre-treatment ABI at rest (ABI<=0.9 versus ABI>0.9). In addition, because some patients had a longer symptomatic follow-up than ABI follow-up and vice versa, a subgroup analysis was performed including those patients with at least one year of symptomatic and one year ABI follow-up. The mean symptomatic follow-up was 18 months and the mean ABI follow-up was 15 months.
We used the SPSS statistical package (version 10.0.7) SPSS Inc, Chicago, Illinois.

RESULTS

A total of 1250 consecutive patients who underwent 1347 percutaneous endovascular procedures in 1671 limbs were registered. Patients treated for acute ischemia were excluded leaving 1634 limbs for the analyses presented here. Table 1 shows the baseline characteristics of the study population. The majority of interventions were performed for treatment of iliac disease (69%). Infra-inguinal interventions were performed in 31% of the population. Sixty-two percent of the population underwent balloon dilation and 34% underwent stent placement. The remaining four percent underwent either thrombolytic therapy or thrombo-embolectomy.

Table 1. Baseline Characteristics of the Study Population

Mean Age in years (standard deviation)	62 (12)
Sex (female/male)	33% / 67%
Smoker (current/ever)	53% / 77%
Diabetes	22%
Hypertension	25%
Renal Disease	10%
Cardiovascular History	32%
Previous Revascularization for PAD	44%
Claudication/Critical ischemia	86% / 14%
Supra / Infra-Inguinal procedures	69% / 31%
Balloon dilation/Stent Placement	62 / 34%*

* The remaining four percent underwent either thrombolytic therapy or thrombo-embolectomy.

Table 2 shows the variation in results when applying different outcome criteria. The patency at 1 year ranged from 37% to 61%. The highest patency rates were achieved by applying the patient's subjective self-evaluation of his symptomatic status.

Table 2. The Impact of Varying the Outcome Criterion on the Success Rate

Outcome Criterion	Success Rate at 12 months
Symptomatic Improvement	61%
ABI > 0.90	43%
Δ ABI > 0.10	41%
Δ ABI > 0.15	37%
Δ ABI > 0.10 AND Symptomatic Improvement	36%
Δ ABI > 0.10 OR Symptomatic Improvement	61%

The differences in results when the different criteria based on ABI were applied were small (range 1-year success rates 37%-41%).
To assess whether these different outcome measures classified the same patients as successes or failures the kappa statistic was calculated (Table 3).

Table 3. Level of Agreement (Kappa) Between the Different Outcome Measures that were Applied

	Outcome Measures					
Success if:	Symptomatic Improvement	ABI > .90	Δ ABI > .10	Δ ABI > .15	Δ ABI > .10 And Symptomatic Improvement	Δ ABI > .10 OR Symptomatic Improvement
Symptomatic Improvement	1					
ABI > . 90	.60 (.58-.68)	1				
Δ ABI > .10	.55 (.53-.74)	.74 (.71-.79)	1			
Δ ABI > .15	.52 (.50-.71)	.74 (.71-.79)	.94 (.94-95)	1		
Δ ABI > .10 AND Symptomatic Improvement	.68 (.65-.85)	.69 (.68-.77)	.87 (.82-.90)	.84 (.79-.85)	1	
Δ ABI > .10 OR Symptomatic Improvement	.97 (.95-.99)	.62 (.60-.68)	.58 (.55-.75)	.55 (.52-.72)	.69 (.67-.86)	1

Numbers between parentheses represent the range of estimates for the kappa value found in subgroup analyses: iliac versus femoral and claudication versus critical ischemia
The standard error associated with the kappa is 0.01-0.02

The agreement between the outcome measures based on ABI measurements was good (kappa 0.74-0.94; standard error, 0.02). In particular the two outcome measures based on a change in ABI showed a very high level of agreement (kappa 0.94). However, the agreement between symptomatic improvement measures and the ABI measures was only moderate (kappa 0.52-0.60; standard error, 0.020).

Combining symptomatic improvement and improvement in ABI of more than 0.10 in one outcome measure using the logical operator "AND" showed good agreement with the outcome measure based on the same improvement in ABI alone (kappa .87; standard error .01). Combining symptomatic improvement and change in ABI using the logical operator "OR" showed a good agreement with the outcome measure based on symptomatic improvement alone (kappa 0.97 standard error 0.02). Subgroup analyses exploring the influence of localization and differences in follow-up duration did not have a substantial impact on the agreement between outcome measures (maximum absolute change in kappa =<0.06). In the subgroup of patients with critical ischemia, however, all kappa values increased with a maximum change of 0.19. Furthermore, subgroup analyses in patients with a pre-treatment ABI at rest of 0.9 or less versus those with an ABI higher than 0.9 showed a large difference in the kappa values (Table 4) and also in the hemodynamic success rate.

Table 4. The Relation between the Symptomatic Improvement and Change in ABI by more than 0.10 depending on the ABI Prior to Treatment

ABI prior to treatment <= 0.9					ABI prior to treatment > 0.9				
		Symptomatic Improvement					Symptomatic Improvement		
		Yes	No				Yes	No	
Δ ABI > 0.10	Yes	410	68	478	Δ ABI > 0.10	Yes	53	8	61
	No	139	423	491		No	115	95	210
		549	491	1040			168	103	271
		Kappa: 0.60 (0.02)					Kappa: 0.20 (0.04)		

Number between parentheses represents the standard error associated with kappa value.

Restricting the population to patients with a low ABI resulted in only a moderate increase in kappa values (Table 4), no influence on the symptomatic success rate and an increase in hemodynamic success rate from 40% to 47% at 1-year follow-up.

DISCUSSION

This study explored the outcome measures available to report results of percutaneous interventions for PAD performed in daily clinical practice. Authors reporting results of these procedures use a multitude of outcome measures making comparison of results difficult. To overcome this problem the TASC Working Group [1] proposed a standard for reporting results based on treadmill testing or imaging tests. These tests, however, are not routinely performed in routine daily clinical practice. In fact, in the current study we found that only 37% and 30% of the population underwent a treadmill test or imaging study during follow-up, respectively, making reporting results obtained in daily practice using these proposed standards impossible.

Tests that are used routinely in daily clinical practice include the ABI and the patient's self-evaluation of symptoms. From the patient's perspective, and probably also the treating physician's perspective, the most relevant outcome is the symptomatic outcome. Symptomatic change, however, is highly subjective. Symptoms may be affected by the patient's attitude to his health status, the placebo effect, and the patient -doctor relationship. The ABI, on the other hand, is not affected by these potential biases. A major disadvantage of the ABI, however, is that it is not of primary interest, neither to the patient nor to the physician performing the intervention. Furthermore, the precision of an ABI measurement is limited [9, 10]. Clinicians, however, still frequently use the ABI to assess the patient's status because it is an easy and inexpensive tool that yields results which are unbiased by the patient's attitude. The limited precision of one ABI measurement may result in misclassification but, because of the random nature of the measurement error, it does not introduce a bias.

The current study highlighted another disadvantage associated with an outcome based on change in ABI. In patients with a pre-treatment ABI at rest higher than 0.9 the agreement between a change in ABI by more than 0.10 and symptomatic improvement was poor, whereas in patients with an

ABI of 0.9 or lower the agreement was good. Although symptomatic improvement cannot be considered a gold standard, of all patients with a high pre-treatment ABI who reported symptomatic improvement, a large proportion did not have a change in ABI of more than 0.10. This is easily explained by the fact that the potential gain in ABI that can be achieved in patients with a high ABI prior to treatment is limited and does not reflect the potential gain in symptomatic status. Another explanation may lie in the measurement error of the ABI. It is possible that these patients actually had an ABI lower than 0.9 but that due to the random error in measurement the measured ABI was higher. In these patients an improvement in ABI of more than 0.10 is difficult to achieve because the measured pre-treatment ABI was higher than the actual ABI. Irrespective of the cause, in patients with a high ABI prior to treatment assessing outcome by assessing the change in ABI seems inaccurate and excluding patients with a high ABI prior to treatment resulted in a higher hemodynamic success rate.

To overcome the problems associated with symptomatic outcome and ABI measurements some propose to combine these outcomes into one outcome measure [5]. In the current study combining symptomatic outcome and ABI measurement using the logical operator "AND" showed a good agreement with the outcome measure based on a change in ABI by more than 0.10 alone. Together with the finding that the curves associated with these two outcome measures did not deviate much this indicated that combining the outcomes using the "AND" operator does not yield more information than applying an outcome measure based on change in ABI alone. Similarly, combining symptomatic improvement with change in ABI using the logical operator "OR" showed good agreement with symptomatic improvement alone.

These results suggest, that combining symptomatic outcome with hemodynamic outcome with either the logical operator "AND" or "OR" does not provide more information. Reporting symptomatic outcome and change in ABI separately, on the other hand increases the clarity of the methods by giving a direct answer to the questions 1) what proportion of

patients had symptomatic improvement, which is subjective but extremely relevant to the patient and the treating physicians, and, b) what proportion had objective proof that the treatment had effect, which is not affected by the patients' and physicians' attitudes.

This study was limited by the lack of a reference standard. As previously discussed imaging studies during follow-up were performed in only a small proportion of the patients and an outcome measure based on imaging studies could therefore not be used. The authors of a previous study that also examined the impact of varying outcome criteria, albeit in a small patient population, reported similar results as found in the current study [2]. They reported that applying outcome criteria based on symptomatic outcome resulted in higher success rates compared with applying an outcome based on an improvement of ABI. Furthermore, the authors reported similar success rates after applying an outcome based on improvement of ABI alone and after combining symptomatic and ABI improvement by using the logical operator "AND". Although the authors did not use kappa calculations or other statistics to examine the agreement between outcome measures and although their study population was small (106 patients) their findings support our finding that combining symptomatic improvement and improvement in ABI does not provide more information than reporting them separately.

Another limitation was that we could not explore the influence of combining objective symptom improvement measured by a standardized treadmill test and ABI measurements into one outcome. As far as we know no studies exploring the influence of combining objective symptom improvement and ABI measurements into one outcome or reporting them separately have been published.

In conclusion, in patients with an ABI higher than 0.9 prior to treatment classifying procedures using a criterion based on improvement in ABI with more than 0.10 is inaccurate to assess the outcome of intervention of peripheral arterial disease. Applying an ABI criterion in this group of patients may underestimate the actual treatment effect. Furthermore, the results of the current study indicate that combining subjective

symptomatic improvement and improvement in ABI does not yield more information than reporting them separately. To preserve the distinct perspective that each represents and to ensure clarity of the results we recommend reporting subjective symptomatic and ABI improvement separately.

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CHAPTER 7

Multicenter Registries and Selective Loss to Follow-up: Methods to Assess the Validity of the Results

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ABSTRACT

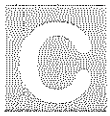
Purpose: To suggest a new method to limit the influence of potential censoring in multicenter registries.

Methods: The follow-up data of 1347 percutaneous interventions performed for treatment of peripheral arterial disease in 6 hospitals in the Netherlands were analyzed by I) pooling all follow-up data and II) pooling only the follow-up data yielding valid estimates per hospital.

Results: Method I resulted in 2 year and 3 year symptomatic success percentages of 54%(standard error 2%) and 46%(standard error 2%), respectively. At 2 year and 3 year follow-up, however, the maximum underestimation of the success rate due to potential informative censoring was 7% and 11%, respectively. Method II on the other hand resulted in a 3-year estimate of 51%(standard error 2%). The maximum underestimation of this 3-year success percentage was at most 6%.

Conclusion: Pooling only the data that is relatively unaffected by censoring resulted in more valid estimates over a longer follow-up period compared with pooling all data.

INTRODUCTION



urrently, more and more multi-center registries examining the results of treatment of peripheral arterial disease (PAD) are being published [1-4], and also in other areas of medical research an expanding number of multi-center registries are initiated [5-7]. The main reason to initiate a registry is to assess variations in daily practice and outcome of daily medical care. However, the often large number of patients included in multi-center registries also offers the possibility to assess the independent prognostic value of baseline characteristics. A disadvantage associated with these registries, however, is that they cannot impose a rigorous follow-up protocol other than accepted in current practice which may make a registry susceptible to loss to follow-up and may limit the validity of the estimates [8].

In daily clinical practice patients that are cured are discharged from follow-up whereas only patients with residual complaints remain under specialist medical care. Because those that are discharged are asymptomatic, informative censoring may occur resulting in an underestimation of the results. Overestimation of the results, on the other hand, may occur if patients who did not respond to treatment did not return to the clinician.

Suggested reporting methods that deal with censoring and enable evaluation of the validity of the results include presenting the standard error together with the number of patients that are still under study [9]. This reporting method, however, does not explore the influence that the potential bias may have on the results and some advocate the use of sensitivity analyses to estimate the extent of the potential bias [10-12].

The purpose of this study was to evaluate the available methods to deal with censoring in multicenter registries recording daily clinical practice and to suggest a method to limit the influence of potential informative censoring.

METHODS

In 1994, the Vascular Intervention Registry (VIR) was established for the purpose of the quality assessment and improvement of current medical practice by monitoring the outcome of percutaneous vascular interventions for peripheral arterial disease (PAD). Four teaching hospitals and two general hospitals in the Netherlands participated. Data regarding each patient at the time of the intervention and details from the procedure were entered prospectively in the registry. Data regarding post-procedural follow-up were abstracted from medical records. All data were recorded using standardized forms and entered into a computerized database (MS-Access 97).

A total of 1250 consecutive patients were registered from 1994 to 1998 who underwent 1347 procedures and were treated in 1671 limbs. Eighty-eight limbs with acute ischemia or undergoing treatment other than balloon dilation or stent placement were excluded from the analyses. In 112 limbs no FUP was recorded. These procedures were excluded leaving 1471 limbs for the analyses reported here. Table 1 summarizes the baseline characteristics of the study population.

Table 1. Baseline Characteristics of Study Population (1471 limbs)

Sex	Male / Female	66% / 34%
Mean age (standard deviation)		61(12)
Risk Factors	Diabetes Mellitus	21%
	Smoking. less than 10 years ago or current	84%
Presenting Complaint	Intermittent Claudication	86%
	Restpain	3%
	Ulceration	10%
	Gangrene	1%
Localization of Lesion	Supra-inguinal / Infra-Inguinal	68% / 32%
History of Revascularizations		41%

Comparison of the baseline characteristics of the 1471 limbs included in the analyses and the 112 limbs without follow-up did not show a statistically significant difference in symptomatic status, ankle brachial index, lesion type (stenoses versus occlusion), length of lesion and crural runoff.

First (method I) we focused on the standard methods to evaluate the presence of selective loss to follow-up [9-12]. That is, patients from all hospitals were pooled in one data set and analyzed together using Kaplan Meier survival statistics. We report the patency, the standard errors, and the percentage of patients censored relative to the number of patients at baseline. As endpoints we considered technical failure of the procedure, detoriation or recurrence of symptoms, and a second revascularization procedure during follow-up. Furthermore, in sensitivity analysis we explored the uncertainty in the estimates caused by loss to follow-up by assuming that censored subjects remained asymptomatic, except if they developed severe co-morbidity (such as paralysis or life threatening malignancy) making their PAD problem from a clinical perspective irrelevant, in which case they were assumed to be censored at random. Estimates were considered invalid if the maximum underestimation of the success rate due to potential informative censoring was more than 6% or if more than 20% of subjects were lost to follow-up.

Next (method II) we explored the influence of applying methods to evaluate selective loss to follow-up before pooling and analyzing the data. In this method the follow-up period of each hospital was divided into 2 periods: an initial period in which the data were considered valid and a second period in which the data was considered potentially too much affected by selective loss to follow-up. Only the data from the initial period were pooled and jointly analyzed.

To define which data were considered valid and thereby distinguish the 2 periods, we used two criteria. The first criterion took into account the number of patients that were censored relative to the total number of patients, i.e., if more than 20% of the total study population were censored the initial period ended and the second period started.

The second criterion considered the potential effect of selective loss to follow-up on the estimates as determined by the sensitivity analysis described above. If the patency curve based on the assumption that all patients who were censored remained asymptomatic deviated more than 6% from the curve obtained using the standard statistical methods, the initial period ended.
Finally the results obtained by using method I and II were compared with respect to the validity of the estimates and the length of follow-up that was associated with valid estimates. All reported success percentages apply to the end of the interval. All analyses were performed using the SPSS statistical package.

RESULTS

Table 2 shows the results obtained by applying standard analyses and reporting methods stratified for localization of the lesion (supra-inguinal versus infra-inguinal). After one year follow-up 13% and 18% of subjects were censored depending on the localization of the lesion. The 1-year symptomatic success rate of treatment of supra and infra-inguinal disease was 66% and 47%, respectively. The maximum potential underestimation of these 1-year success rates due to informative censoring varied from 2% to 3% at 1-year follow-up. This, together with the fairly low percentage of censored subjects, indicated that the 1-year estimates for the results of treatment for supra-inguinal estimations may be considered valid. The maximum underestimation of the 3-year success rates, on the other hand, was 10-11% and were based on a population of which 30-46% was censored indicating that the uncertainty in the estimates of the success rates at later years may be considered too large.

Table 2. Symptomatic Success Rates for Percutaneous Treatment obtained by Pooled Analysis of all available data and using Sensitivity analyses to explore the Maximum Underestimation of the Results due to Censoring.

Localization of lesion	Interval (year)	No at risk at beginning of interval (limbs)	Number of events	Censored subjects per interval	Cumulative percentage of censored subjects (%)*	Cumulative symptomatic improvement rate (%)*	Maximum underestimation of symptomatic improvement rate (%)†
Supra-Inguinal	0-12	1050	324	193	18	66(2)	3
	12-18	533	48	89	27	59(2)	5
	18-24	396	32	84	35	54(2)	7
	24-36	280	35	113	46	46(2)	11
	36-48	132	19	86	54	36(3)	19
Infra-Inguinal	0-12	499	225	64	13	47(2)	2
	12-18	183	22	24	18	41(2)	3
	18-24	137	13	19	21	36(3)	5
	24-36	105	23	41	30	26(3)	10
	36-48	41	4	23	34	22(3)	13

Number between parentheses represent the standard error of the estimate.

* The numbers represent the cumulative percentage of censored subjects and symptomatic improvement at the end of each interval.

† Obtained by assuming that all censored limbs remain asymptomatic.

Abbreviations: No= number.

Table 3 compares the results of assessing the validity of the reported estimates after pooled analysis of all data versus assessing validity per hospital before pooling data and only including the valid considered data per hospital in the pooled analysis. The validity criterion applied allowed at most 6% underestimation in the success rates. Applying this criterion after pooling all data resulted in a follow-up period of 18 months and 24 months associated with valid estimates depending on the localization of the lesion whereas applying this criterion before pooling and only including the valid considered data per hospital in the pooled analysis

Table 3. Results of Assessment of the Validity of the Estimates by Applying a Validity Criterion that Allowed a Potential Underestimation of the Success Rates of at most 6% depending on whether this criterion was applied After or Before Pooling data on the success rates per hospital

Success rate (%) *

Interval (months)	Supra-inguinal lesions		Infra-inguinal lesions	
	After pooling data	Before pooling	After pooling	Before pooling
0-12	66	66	47	47
12-18	59	59	41	41
18-24	NV	55	36	36
24-36	NV	51	NV	29
36-48	NV	NV	NV	NV

All standard errors were smaller or equal to 3%

* The numbers represent the cumulative percentages at the end of each interval

Abbreviations NV= not valid:

resulted in a follow-up associated with valid estimates of 36 months. Similar findings were found when applying a validity criterion that allowed at most 20% potentially informative censored subjects (table 4). Here applying the validity criterion before pooling data resulted in an increase of the follow-up period associated with valid estimates by 6 months compared with the follow-up period associated with valid estimates obtained by pooling all available follow-up data.

Table 4. Results of Assessment of the Validity of the Estimates by Applying A Validity Criterion that allowed 20% censoring depending on whether this criterion was applied after or before pooling data on the data set per hospital

	Success rate (%)*			
	Supra-inguinal lesions		Infra-inguinal lesions	
Interval (months)	After pooling data	Before pooling	After pooling	Before pooling
0-12	66	67	47	47
12-18	NV	63	41	41
18-24	NV	NV	NV	36
24-36	NV	NV	NV	NV
36-48	NV	NV	NV	NV

All standard errors were smaller or equal to 3%.
* The numbers represent cumulative percentages at the end of each interval
Abbreviations NV=not valid;

DISCUSSION

Clinical registries record the large number of procedures performed in daily clinical practice providing the opportunity to assess variations in practice patterns and to compare outcomes across health care providers. Recording daily practice, however, and not imposing rigorous follow-up protocols makes the estimates of registries susceptible to informative censoring. In our series 67% and 47% of the patients with a supra-inguinal stenosis reported symptomatic improvement at 1 year and 3 year follow-up, respectively. These estimates were low compared with previously published success rates (success rate 77-92% at one year and 60-82% at three years)[13]. The fairly high precision of our estimates (the

standard error was 2%) could not explain the difference. The high percentage of subjects censored, however, 19% and 46% at 1 and 3-year, respectively, indicated the possibility of informative censoring. To assess the maximum underestimation possible due to informative censoring sensitivity analyses were performed in which all patients that were censored were assumed to remain asymptomatic yielding a 2% higher symptomatic success rate at 1 year and a 5% higher rate at 3 years. This indicated that the potential influence of informative censoring on the 1-year estimate was limited and that the results found in the current study are lower than reported thus far. The potential underestimation of the success rates at later years, however, indicated that these were potentially too much affected by selective loss to follow-up.

Because in some hospitals patients had a more complete follow-up than patients in other hospitals, we explored the influence of applying various validity criteria per hospital before pooling the data and analyzing only the data considered valid. This resulted in a more efficient use of the data available and resulted in a longer follow-up period associated with valid estimates. The follow-up period associated with valid estimates increased from 8 to 16 months.

We used two different criteria to determine what data was useful and valid. The first was based on the percentage of subjects that was lost to follow-up. The other was based on the influence that selective loss to follow-up might have on the estimates for success. In the latter we assumed that selective loss to follow-up would result in an underestimation of the results. A criterion based on the assumption that all censored subjects had a failure was not used because from discussions with specialists and from the process of abstracting medical records it was learned that patients who reported a complete relief of symptoms were discharged from specialist medical care and advised to return only if symptoms recurred. These patients had a relative short follow-up compared to patients who reported improvement but still had some complaints and who regularly visited the specialist for evaluation. Furthermore, our patency rates were rather low compared to previously

published estimates [14, 15] making it likely that censored subjects were successfully treated patients. Finally, applying the validity criterion that was based on the percentage of patients who were censored and not on the direction of the bias resulted in higher estimates than the estimates based on all data, indicating that the loss to follow-up resulted in an underestimation of results.

Other methods available to deal with selective loss to follow-up are based on completing the follow-up in a random sample of censored subjects with a more rigorous data collection method or through correction of the bias based on measured prognostic factors for censoring [16-18]. These methods aim to adjust the estimates for the information that is lost when subjects are censored and involve advanced statistical methods, which are still under development. The method suggested in the current paper does not adjust the estimates but it merely restricts the follow-up period to a period that is considered relatively unaffected by informative censoring yielding more valid estimates. The method is easy to apply and is in essence not different from previously published methods to evaluate the validity of the estimates with the exception that in the current study these methods are applied in multicenter studies before pooling the data making it an integral part of the analysis. [9-12]. In a recent published multicenter study examining the risk factors for a complication after endovascular treatment of aortic aneurysms used a comparable method[5]. In this study all follow-up data of centers that had too many censored subjects were excluded from the analysis. The criteria that were used to determine whether too much censoring occurred, however, were not specified and excluding all follow-up data of a center may be an inefficient use of the available data.

The current study was limited by the 112 limbs in which no follow-up was recorded. Comparison of the baseline characteristics of these 112 limbs with the baseline characteristics of the 1471 with follow-up did not show a statistically significant difference in symptomatic status, ankle brachial index, lesion type (stenosis versus occlusion), lesion length, and crural runoff. Another limitation may be the selection of the validity criterion for

including data in the analysis. Ideally all subjects have complete follow-up. Allowing some degree of potential informative censoring makes the estimates susceptible to bias. The acceptable degree of uncertainty due to potential informative censoring should be chosen in the clinical context of the subjects analyzed. In the current study we chose to express the degree of uncertainty in potential underestimation of the estimate and potential number of informative censored subjects. We chose to allow an underestimation in success rate of at most 6% and to allow a percentage of censored subjects of at most 20%. These thresholds, however, are arbitrary. Choosing a lower threshold, for example allowing an underestimation in success rate of at most 1.5% or allowing at most 10% potential informative censoring would result in a shorter follow-up period associated with valid estimates but decreases the influence of potential informative censoring . Given the wide range of published success rates of percutaneous revascularization procedures and the limited precision of the reported estimates we chose for thresholds that were less stringent [13]. This study explored the methods to evaluate the influence of potentially informative censoring on the results. We concluded that in multicenter studies pooled analysis of only the data from the follow-up period per hospital that is relatively unaffected by the potential effect of selective loss to follow-up increases the validity of the reported results and yields a longer follow-up period associated with valid estimates compared with pooled analysis of all follow-up data.

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CHAPTER 8

Balloon Dilation and Stent Implantation for Treatment of Femoropopliteal Arterial Disease: Meta-analysis

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ABSTRACT

Purpose: To perform a meta-analysis of long-term results of balloon dilation and stent implantation in the treatment of femoropopliteal arterial disease.

Materials and methods: The English-language literature was searched for studies published between 1993 and 2000. Inclusion criteria for articles were presentation of long-term primary patency rates, standard errors (explicitly reported or derivable), and baseline characteristics of the study population. Two reviewers independently extracted data, and discrepancies were resolved by consensus. Primary patency rates were combined using a technique that allows adjustment for differences across study populations. Analyses were adjusted for lesion type and clinical indication.

Results: Nineteen studies met the inclusion criteria, representing 923 balloon dilations and 473 stent implantations. Combined 3-year patency rates after balloon dilation were 61% (standard error, 2.2%) for stenoses and claudication, 48% (standard error, 3.3%) for occlusions and claudication, 43% (standard error, 4.1%) for stenoses and critical ischemia, and 30% (standard error, 3.7%) for occlusions and critical ischemia. The 3-year patency rates after stent implantation were 63%-66% (standard error, 4.1%) and were independent of clinical indication and lesion type. Funnel plots demonstrated an asymmetric distribution of the data points associated with stent studies.

Conclusions: Balloon dilation and stent implantation for claudication and stenosis yield similar long-term patency rates. For more severe femoropopliteal disease, the results of stent implantation seem more favorable. Publication bias could not be ruled out.

INTRODUCTION

Treatment and prognosis of peripheral arterial disease is influenced by lesion and patient characteristics, such as the site of the lesion, type of lesion (stenosis or occlusion, lesion length), arterial runoff, and clinical manifestation [1]. Estimates of the 5-year patency rate of balloon dilation for femoropopliteal arterial disease range from as low as 12% in patients with an occlusion and critical ischemia to 68% in patients with a stenosis and claudication [2]. Bypass surgery for femoropopliteal arterial disease is associated not only with higher long-term patency rates but also with a higher procedural morbidity, mortality, and a longer hospital stay [3]. The development of a new therapy that combines the relatively low risk of an endovascular procedure with a higher patency rate than those currently associated with balloon dilation would be desirable.

In the recent past, many new endovascular techniques, such as laser-assisted balloon angioplasty and atherectomy, as well as several types of stents, have been developed and tested [4-10]. Until now, however, these devices have not demonstrated improvement in the long-term results of balloon dilation in the femoropopliteal artery. Of these techniques, only stent placement is currently used, and it is used only as a "bailout" procedure after a failed balloon dilation procedure.

At present, new endovascular stent-graft systems are being developed [8, 11, 12]. To enable comparison of the results of a new therapy with established therapies, data on benefits and costs of the established procedures must be available. To our knowledge, the last meta-analysis on the long-term results of femoropopliteal balloon dilation dates from 1993 and did not consider femoropopliteal stent implantation [2]. Although major improvements in the long-term results of balloon dilation seem unlikely, the use of stents as an adjunct to balloon dilation may have improved the patency rate of percutaneous revascularization. Furthermore, the continuous development and improvement of materials and skills, as well as possible changes in the indications for performing

balloon dilation, may have influenced the long-term results.
The aim of this study was to review the currently available data on the long-term results following balloon dilation and to assess the influence of stent placement in the treatment of femoropopliteal arterial disease.

MATERIALS AND METHODS

Data Sources

e performed a systematic review of the literature that was published between January 1993 and August 2000. We restricted our review to this period for two reasons. First, a previous meta-analysis included balloon dilation articles that were published between January 1985 and January 1993 [2]. Second, we expected only a limited number of stent implantation studies to have been published before 1993, and these studies were likely to be small [13]. Whereas the baseline analysis of the current meta-analysis included studies published between January 1993 and August 2000, in a sensitivity analysis we also included the studies identified in the previous meta-analysis [2].
To identify studies that were published from 1993 to 2000, we performed a comprehensive search of abstracts of English-language articles in the MEDLINE database, using the search terms "interventional radiology," "balloon dilation," "stents", "arterial occlusive diseases," "arteriosclerosis," "claudication," "ischemia," "limb salvage," "femoropopliteal," "femorodistal," "femoral," "popliteal," "infrainguinal," "above-knee," "survival analysis," "actuarial analysis," "patency," "patencies," "life table," "failure rate," "follow-up studies," and "recurrence."
In addition to the abstract search in the Medline database, references were obtained from the bibliographies of retrieved articles. If the abstract of an article provided sufficient information to conclude that the authors did not report results after femoropopliteal percutaneous transluminal angioplasty or stent placement, the full article was not retrieved. These articles were excluded on the basis of the abstract alone. All other articles were retrieved

and reviewed. To avoid double counting, both data extractors (G.S.R.M. and J.L.B.) compared the articles for participating institutions and inclusion criteria. If overlap of study populations was suspected, the most complete report fulfilling the study selection criteria (specified in the next section) was included. Unpublished research was not included.

Study Selection

Studies that reported data on the long-term results after balloon dilation or stent implantation were included if: (a) at least 90% of all procedures were performed for femoropopliteal arterial disease; (b) primary patency data and standard errors were presented or such data could be estimated from the data presented; (c) the study follow-up was at least 1 year; (d) the number of subjects at the start of follow-up was at least 20 patients, and (e) the number of initial failures was reported.

To adjust for differences in populations between studies, articles were required to include data on the case mix of the study population. Since it is unlikely that all articles report all relevant prognostic factors to qualify for inclusion, we required that authors reported a minimum set of data on the case mix of the study population that both were well-known prognostic factors and were likely to be reported in the majority of studies [2]. The minimum set consisted of clinical indication (percentage with claudication vs percentage with critical ischemia) and lesion type (percentage with stenosis vs percentage with occlusion).

Data Extraction

Two readers (G.S.R.M. and J.L.B.) abstracted the data from each article independently by using a standard form. The following data were recorded: (a) number at risk at the start of the follow-up, (b) percentage of subjects with claudication versus percentage with critical ischemia (rest pain and tissue loss), (c) percentage of subjects with a stenosis versus percentage with an occlusion, and (d) patency rates and standard errors or data sufficient to derive patency rates and/or standard errors, such as life tables or survival curves listing the number at risk at several points in time.

Furthermore, the following factors that may reflect differences in study populations and methods between studies were extracted: (e) percentage of femoral lesions versus percentage of popliteal lesions, (f) percentage of subjects with poor arterial runoff (one or no patent crural vessel), (g) data on length of the lesions, (h) methods and criteria used for assessment of vascular patency, and (i) unit of observation used in reporting the patency (ie, lesions, limbs, procedures, or patients).

If the article reported a life table or a patency curve listing the number at risk at several time points but did not report the standard errors, we estimated the standard errors by using an actuarial life-table approach and the Greenwood formula [14]. We assumed that where stepped survival curves were used, the lowest of the two data points at the end of each interval represented the fraction of patients at the end of that interval, unless explicitly stated otherwise in the methods section of the article.

Some articles reported multiple patency rates at the same point in time, based on different definitions of patency. To increase the uniformity in the definition of patency across the various studies, we extracted the data associated with the patency definition that corresponded best with the criteria for a marked change in clinical status following an intervention for peripheral arterial disease that were proposed by the Society for Vascular Surgery and International Society for Cardiovascular Surgery (SVS/ISCVS) [15].

Differences in the extracted data were resolved in discussion. Only minor discrepancies in the extracted data were found. In most cases, these were small differences in the patency rate extracted from survival-curves. The remaining discrepancies were found to be due to misinterpretation of the reported data. Both authors resolved these by examining the articles together.

Funnel Plot

To detect the presence of publication bias (i.e., the bias resulting from the greater likelihood of publication of studies reporting a positive result compared with the likelihood for studies with a negative result), we

constructed a funnel plot. In a funnel plot, a measure of the study size is plotted as a function of the measure of interest [16]. In the current study, we plotted the number of patients that underwent femoropopliteal intervention as a function of the reported 1-year primary patency rate. If publication bias is absent, the distribution of the data points will be symmetric and funnel shaped. Visual inspection of the plot may, however, reveal an asymmetric distribution of data points, which may result from a paucity of smaller studies reporting negative results. In that case, the plot indicates the presence of publication bias.

Data Synthesis

All patency rates reported at multiple times were analyzed together by using weighted multiple linear regression according to the method described by Dear [17]. The dependent variable in the regression models was the reported patency rate, and independent variables were the times of the reported patency rates. In the regression models, we adjusted for the correlation between the reported patency rates within the same study, and the inverse-squared standard errors were used as weights. In the regression model, both balloon dilation and stent implantation had their own time-dependent treatment effect.

To adjust for differences in case mix between the study populations, we included the baseline characteristics of clinical indication (claudication vs critical ischemia) and lesion type (stenosis vs occlusion) in the model. Because the results after balloon dilation and stent implantation may be affected differently by clinical indication and lesion type, we also included interaction terms that allowed treatment-type-specific effects for these factors.

The percentage of subjects with a femoropopliteal occlusion and critical ischemia and who were undergoing stent implantation were modeled as continuous variables. With use of multivariate stepwise backward regression, variables and interaction terms with a P value larger than .05 were eliminated. The models were fitted using SAS Proc Mixed (SAS System for Windows, release 6.12; SAS Institute, Cary, NC).

Heterogeneity

To detect residual heterogeneity in the reported patency rates that could be explained in terms of differences between studies other than differences in the percentage of subjects with critical ischemia, occlusion, or undergoing stent implantation, an interaction term representing study effects within the two treatment groups was added to the model and tested in a multivariate analysis. We found that heterogeneity was present in the model. Therefore, additional explanatory variables-namely, age, sex, lesion site, status of distal arteries, long-term use of oral anticoagulant treatment after the intervention, definition of patency, and unit of observation used in reporting patency-were tested in multivariate analyses for their contribution to the explanation of reported heterogeneity in treatment effect. Only those studies that reported data on the covariables incorporated in the regression model were included in each of these analyses.

Sensitivity Analyses

To test for the dependence of results on the patency rates reported in a single study, sensitivity analyses were performed by analyzing the data with a jackknife type of procedure; that is, the analysis was repeated multiple times, each time with removal of a single study from the baseline group of studies.

Second, to explore the robustness of our results and to detect a trend in reported patency results over time, we extended our data set with the articles identified in the previous meta-analysis [2] that met our inclusion criteria. These additional articles were all balloon dilation studies. To identify the trend in patency rates over time, a term representing the year of publication was added to the model. This variable was modeled as a continuous variable and in another analysis as a dummy variable (score of 0 for studies identified in the previous meta-analysis, score of 1 for studies identified in the current study). All variables were tested at a significance level of .05.

Third, in an additional sensitivity analysis, we investigated the influence of

primary stent implantation on our patency estimates by excluding the two studies that reported primary stent implantation results [10, 18].
Finally, in some studies, patency results were reported separately for patients with occlusions and for patients with stenoses[19-21]. In most studies, however, patency results were reported for stenoses and occlusions combined. To explore the effect on our results of inclusion of the overall patency results instead of the results by subgroups, we performed a sensitivity analysis using, where available, the patency data by subgroups.

RESULTS

Selected Articles

A total of 533 citations published between January 1993 and August 2000 were screened. Of these, 118 articles were retrieved, of which 19 articles met the inclusion criteria. The abstracts of 415 articles provided sufficient information to conclude that the authors did not report results following femoropopliteal percutaneous transluminal angioplasty or stent placement. These articles were excluded on the basis of the abstract. Of the 118 articles that were retrieved, 99 were excluded for the following reasons: a) combined analysis of treatment of multiple arterial segments (n = 18), (b) missing data on lesion type or clinical indication (n = 6), (c) overlap of study population (n = 5), (d) insufficient data to extract the patency rates or standard errors (n = 25), (e) missing data on initial failures (n = 6), (f) study sample of fewer than 20 patients (n = 7), (g) study follow-up of less than 1 year (n = 5), (h) focus on other percutaneous transluminal treatments such as laser-assisted percutaneous transluminal angoplasty or atherectomy (n = 23) or on the natural history of femoropopliteal arterial disease (n = 1), (i) not in the English language (n = 2), and (h) letter to the editor (n = 1).
Of the 19 studies included, three involved the same authors [9, 10, 22]. Overlap could be excluded in one article because the recruitment period

did not overlap [22]. In the other two articles, the authors reported overlap in inclusion period [9, 10]. In one of the articles, however, the authors analyzed only patients with a femoropopliteal occlusion (62 patients), whereas in the other, the authors analyzed patients with stenoses, with the exception of two cases out of 35, implying that the maximum overlap, if any, was two cases.

Review

The extracted data from the articles analyzed [9, 10, 18-34) ordered by publication year, are outlined in Tables 1 and 2. We identified one randomized trial [10] in which stent implantation was compared with balloon dilation and 18 non-comparative studies, including nine focused on balloon dilation, seven focused on stent implantation, and two in which both balloon dilation and stent implantation procedures were analyzed together in a single cohort [29, 30].

Follow-up periods and baseline characteristics of the study populations differed markedly across the 19 studies. Follow-up varied from 1 to 5 years. Overall, the follow-up after stent implantation was shorter than the follow-up after balloon dilation. The percentage of cases with an occlusion varied from 6% to 100%, and the percentage of cases with critical ischemia from 0 to 56%. Primary stent implantation was performed in two studies [10, 18] (Table 2). In the remaining studies, the majority of stent implantations were performed after a failed balloon dilation. In the balloon dilation studies, the authors of one article reported specifically that only patients undergoing repeat balloon dilation were included, whereas in the other balloon dilation studies, this criterion was not selected [23]. In one study, the authors included only patients with a lesion length larger than 10 cm [25]. All other studies included mainly patients with lesions smaller than 10 cm.

The published standard for evaluating results of interventional therapy for peripheral arterial disease as proposed by the SVS/ISCVS [15] was used as a reference in 17 of 19 articles. The authors classified the results extracted from these articles by using the SVS/ISCVS criteria for a marked change in clinical status in 11 articles [9, 10, 18, 21-24, 27, 31, 33, 34], and for patency in six articles [20, 25, 26, 28, 30, 32]. The authors of the remaining two articles did not refer to these standards but used a classification system that met the SVS/ISVCS criteria for a marked change in clinical status [29] or for patency [19].

Long-term oral anticoagulant treatment after the intervention was given to patients for 3 months in both arms of the randomized clinical trial [10], and for 6 months in one stent study [31]. The authors of another stent study reported use of oral anticoagulant treatment during the first half of the study period with a gradually reducing dose but replaced this with treatment by means of platelet inhibitors [34]. Platelet inhibitors, such as aspirin, ticlopidine, or dypidamole, were prescribed to patients after the intervention in all but two studies. The authors of these two studies did not report data on medication following the intervention [24, 27].

Overall, the results in 923 patients undergoing balloon dilation and 473 patients undergoing stent implantation were included in the analyses.

Funnel Plot

To detect publication bias, we constructed two funnel plots (Fig 1), one for balloon dilation studies and one for stent implantation studies. The distribution of data points for the balloon dilation studies seems fairly symmetric and funnel shaped and does not raise any suspicion of the presence of publication bias. The distribution of data points of the funnel plot for stent implantation studies, however, is asymmetric, indicating that publication bias may be present.

TABLE 1. Review of Study Population Characteristics and Patency

Study*	Year	No. of Patients	Age (y)†	Sex (%)‡	Critical ischemia (%)	Occlusion (%)
Treiman et al (23)	1994	35	69	57/43	20	17
Becquemin at al (19)	1994	95	67	64/36	31	45
Jeans et al (24)	1994	137	65	72/28	44	65
Vroegindeweij et al (22)	1995	62	64	73/27	2	100
Murray et al (25)	1995	42	74	50/50	11	59
Tielbeek et al (9)	1996	35	64	77/23	0	6
Stanley et al (26)	1996	176	69	55/45	26	41
Vroegindeweij et al (10) ||	1997	27	64	70/30	0	19
Martin et al (27)	1999	88	NA	52/48	26	6
Golledge et al (28)	1999	74	73	62/38	42	26
O'Donohoe et al (29)#	1999	96	69	57/43	56	46
Karch et al (30)**	2000	85	56	48/52	36	7

Note:
NA = not available.
* = Number in parentheses is the reference number.
† = Mean or median age, depending on what authors reported.
‡ = Data are percentage of male/female.
§ = Standard error of last available patency rate only.
|| = Balloon dilation arm of randomized clinical trial to compare femoropopliteal stent placement with balloon dilation
= Analyzed 70 balloon dilations and 30 stent placements together in one cohort.
** = Analyzed five stent deployments after failed balloon dilations and 108 balloon dilations together.

Results of Studies that included Femoropopliteal Balloon Dilation

Poor Runoff (%)	Popliteal Location (%)	Patency Rate (%)						Standard Error §
		0-year	1-year	2-year	3-year	4-year	5-year	
46	49	94	41	24	11	11	11	10
52	16	79	60	51	NA	NA	NA	6
NA	NA	90	60	53	52	51	50	6
23	NA	82	63	56	46	46	46	9
33	NA	93	86	53	NA	NA	NA	26
0	NA	100	80	67	62	62	62	10
31	16	73	58	46	38	30	26	8
11	NA	89	85	NA	NA	NA	NA	7
NA	14	NA	62	57	57	44	37	7
28	NA	90	58	NA	NA	NA	NA	6
NA	NA	84	53	NA	NA	NA	NA	5
38	25	97	74	62	56	52	52	13

TABLE 2. Review of Study Population Characteristics and Patency

Study*	Year	No. of Patients	Age (y)†	Sex (%)‡	Critical ischemia (%)	Occlusion (%)
Martin et al (31)	1995	90	64	64/36	23	35
White et al (32)	1995	32	65	72/28	6	47
Henry et al (20)	1995	116 ||	62	87/13	7#	33
Bergeron et al (33)	1995	39	64	85/15	21	57
Chatelard et al (34)	1996	35	70	54/46	37	29
Vroegindeweij et al (10)**	1997	24	65	71/29	0	17
Strecker et al (21)	1997	80	64	73/27	16	59
Cheng et al (18)††	1999	28	70	67/33	42#	39

Note:

NA = not available.

* = Number in parentheses is the reference number.

† = Mean or median age, depending on what authors reported.

‡ = Data are percentage of male/female.

§ = Standard error of last available patency rate only.

|| = Number of patients not reported: authors reported data as number of limbs or number of procedures.

\# = Percentage of patients with critical ischemia was based on larger population that also included patients who underwent iliac intervention.

** = Stent implantation arm of randomized clinical trial to compare femoropopliteal stent implantation with balloon dilatation. Includes primary stent implantations.

†† = Includes primary stent implantations. Number of patients who underwent femoropopliteal intervention was derived from the number of femoropopliteal lesions and the ratio of total number of patients to total number of lesions.

Results of Studies that included Femoropopliteal Stent Implantation

Poor Runoff (%)	Popliteal Location (%)	Patency Rate (%)						Standard Error§
		0-year	1-year	2-year	3-year	4-year	5-year	
0	0	99	61	49	NA	NA	NA	5
47	31	97	72	63	63	NA	NA	38
9	0	100	81	73	72	65	NA	8
33	0	95	81	77	77	NA	NA	10
46	26	100	80	76	76	NA	NA	8
8	NA	100	74	NA	NA	NA	NA	9
38	24	100	59	48	48	NA	NA	11
NA	0	90	60	54	27	NA	NA	22

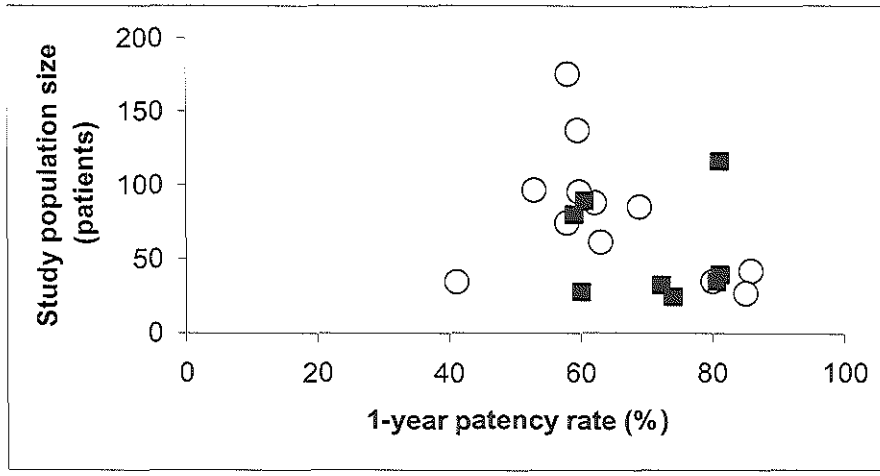


Figure 1. Funnel plot shows cumulative 1-year primary patency rates versus the number of patients included in the study. The distribution of the data points associated with balloon dilation (○) appears fairly funnel-shaped and symmetric, indicating that the presence of publication bias is unlikely. The distribution of the data points associated with stent implantation (■) is asymmetric indicating that publication bias cannot be excluded.

Pooled Results

The initial model incorporated main effects for time, treatment type, clinical indication, and type of lesion, as well as interaction terms to account for treatment-specific patency over time and treatment-specific effects for clinical indication and type of lesion. In a multivariate analysis, all of these effects were statistically significant.

Tables 3 and 4 and Figure 2 present estimates of the patency rates for subgroups of patients. Clinical indication and lesion type were statistically significant variables in explaining the observed heterogeneity in reported patency rates ($P < .001$ and $P = .001$, respectively). The 3-year patency rate following balloon dilation ranged from 61% to 30%, depending on clinical indication and lesion type. The 3-year patency rates following stent implantation ranged from 66% in patients with claudication and a stenosis to 63% in patients with critical ischemia and an occlusion; these rates were not substantially affected by clinical indication and lesion type (Fig 2).

TABLE 3. Estimated Pooled Primary Patency Rates after Balloon Dilation and Stent Implantation in Patients with Claudication

Lesion type and Year after Treatment	Balloon Dilation		Stent Implantation	
	Patency (%)*	Range (%)	Patency (%)*	Range (%)
Stenosis				
0	100 (1.0)	98-100	100 (1.2)	99-100
1	77 (1.7)	74-80	75 (2.2)	73-79
2	66 (2.0)	63-71	67 (2.4)	65-71
3	61 (2.2)	55-68	66 (2.7)	64-70
4	57 (2.5)	54-63	NA	NA
5	55 (2.8)	52-62	NA	NA
Occlusion				
0	88 (2.9)	81-94	99 (2.3)	92-100
1	65 (3.0)	55-71	73 (2.8)	69-75
2	54 (3.1)	45-61	66 (3.0)	61-68
3	48 (3.3)	40-55	64 (3.2)	59-67
4	44 (3.5)	36-53	NA	NA
5	42 (3.7)	33-51	NA	NA

Note:
Ranges are derived from sensitivity analyses.
NA = not available.
* = Number in parentheses is the standard error.

Balloon dilation and stent implantation yielded similar patency rates in the treatment of claudication and a femoropopliteal stenosis (respective 3-year patency rates, 61% [standard error, 2%] and 66% [standard error, 3%]; Fig 2, A), but significantly different patency rates in the treatment of occlusions (P = .02; Fig 2, B), and critical ischemia, (P = 0.01; Fig 2, C, D).

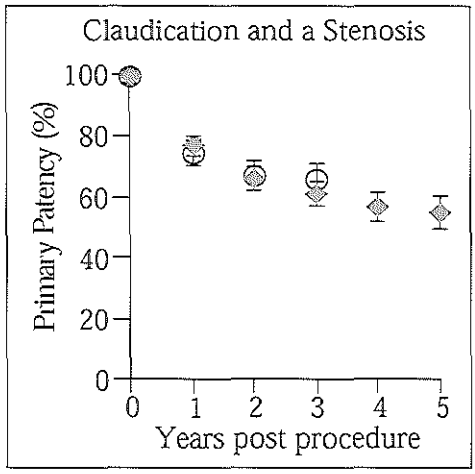


Figure 2a.

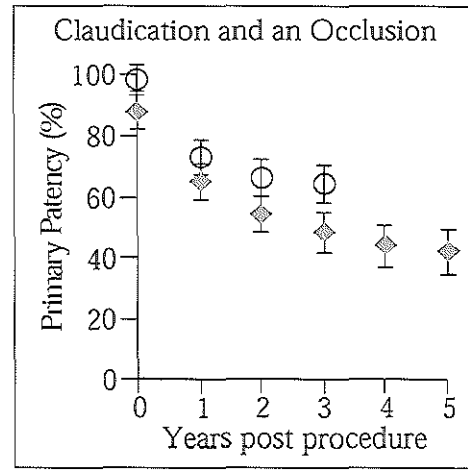


Figure 2b.

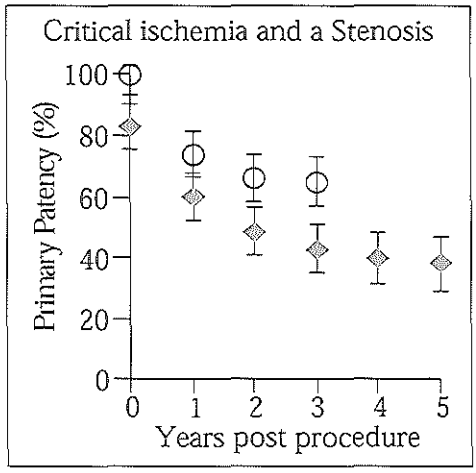


Figure 2c.

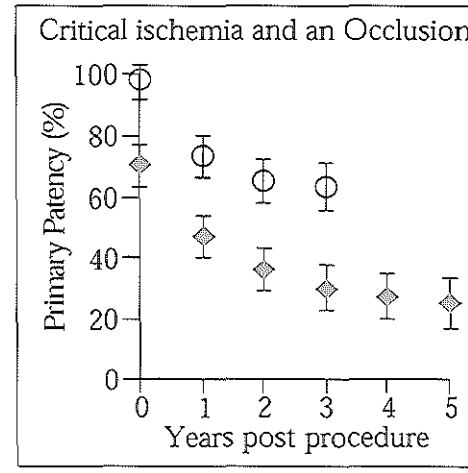


Figure 2d.

Figure 2. Cumulative primary patency rates and 95% CIs (error bars) for femoropopliteal balloon dilation (◈)and femoropopliteal stent implantation (O), depending on lesion type (stenosis vs occlusion) and clinical indication (claudication vs critical ischemia). A, Graph shows that the estimates for the primary patency following percutaneous transluminal angioplasty and stent placement are similar in patients with claudication and a femoro-popliteal stenosis. B-D, Graphs show that the the estimates for the primary patency following percutaneous transluminal angioplasty and stent placement are different in patients with critical ischemia and in patients with a femoropopliteal occlusion.

Table 4. Estimated Pooled Primary Patency Rates after Balloon Dilation and Stent Implantation in Patients with Critical Ischemia

Lesion type and Year after Treatment	Balloon Dilation		Stent Implantation	
	Patency (%)*	Range (%)	Patency (%)*	Range (%)
Stenosis				
0	83 (3.7)	69-88	100 (3.3)	94-100
1	60 (4.0)	46-63	74 (3.8)	68-80
2	49 (4.0)	35-54	66 (3.9)	59-72
3	43 (4.1)	30-51	65 (4.1)	58-71
4	40 (4.3)	26-46	NA	NA
5	38 (4.5)	24-44	NA	NA
Occlusion				
0	70 (3.5)	62-75	98 (3.2)	94-100
1	47 (3.5)	41-51	73 (3.6)	68-75
2	36 (3.6)	28-41	65 (3.7)	60-68
3	30 (3.7)	20-37	63 (3.9)	58-68
4	27 (3.9)	16-34	NA	NA
5	25 (4.1)	13-32	NA	NA

Note:
Ranges are derived from sensitivity analyses.
NA = not available.
* = Number in parentheses is the standard error.

The estimated 5-year patency rates associated with balloon dilation were 55% in patients with claudication and a stenosis, 42% in those with claudication and an occlusion, 38% in those with critical ischemia and a stenosis, and 25% in those with critical ischemia and an occlusion. The 5-year patency results for stent implantation were not reported.

Heterogeneity

To test for residual heterogeneity, a term representing study-specific effects within the two treatment groups was added to the model. This term was statistically significant in the multivariate analysis (P = .04), indicating that residual heterogeneity was present and that part of the variability between studies in reported patency rates could be explained by differences between studies other than differences in the percentages of occlusions, critical ischemia, and treatment type.

To identify variables that may help explain some of the residual heterogeneity, additional covariables representing baseline characteristics of the study populations-namely, age (data available in 18 of 19 studies), gender (data available in all studies), arterial runoff (data available in 15 studies), use of long-term anti-coagulant treatment versus platelet inhibitors (data available in 17 studies), and popliteal versus femoral localization of the lesion (data available in12 studies)-were tested in a multivariate model. Furthermore, to determine whether the differences in classification of outcome may have significantly contributed to the observed heterogeneity, an additional variable representing SCS/ISCVS patency versus SCS/ISCVS symptomatic outcome was added to the model. This variable was not associated with a statistically significant regression parameter (P= .5). Only the variable "age" had a statistically significant contribution in explaining the reported variation in patency rates (P = .04). A 10-year increase in age was associated with a 3.3% decrease in primary patency.

Sensitivity Analyses

The jackknife sensitivity analysis, in which all articles were excluded one by one from the baseline group, did not show a large effect on long-term outcome. The ranges found are shown in Table 3 and 4. When a report of repeat balloon dilation results [23] was excluded, the 3-year patency rate after balloon dilation for claudication and stenosis increased from 61% to 68% (standard error, 2.2%). Exclusion of the one study that focused on treatment of long lesions [25] did not improve long-term patency rates

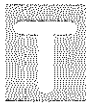
associated with balloon dilation (maximum absolute increase in long-term patency, 3%).

In a second sensitivity analysis, we extended the baseline group of studies by including those from the previous meta-analysis (all balloon dilation studies published between 1985 and 1993 [2]) that met our inclusion criteria. The results fell within the ranges of patency rates that are shown in Tables 3 and 4. To test whether the time period during which the studies were performed may help explain the influence on our results, we extended the model with a variable that represented the year of publication of the articles. This variable, however, showed no statistically significant explanatory value.

In an additional sensitivity analysis, we excluded the primary stent studies [10, 18] from the analysis. This resulted in slightly lower patency rates for stent implantation (absolute difference in 3-year patency rates, 1%-3%).

Finally, we explored the effect on our results of including patency reported for separate subgroups [19-21] instead of overall patency rates. This did not change the results substantially (all absolute differences were smaller than 3%) .

DISCUSSION



he current study represents a meta-analysis that combined the reported long-term results associated with balloon dilation and stent implantation for treatment of femoropopliteal arterial disease by using a weighted multiple linear regression model. We found similar long-term patency rates for stent implantation and balloon dilation in the treatment of claudication caused by a femoropopliteal stenosis, but when the clinical indication was critical ischemia or the lesion type was an occlusion, long-term patency results were better with stent placement. The results of sensitivity analyses, for example, in which studies were excluded one by one from the pooled sample, showed that our results were relatively independent of any one particular study. The robustness of our estimates

of long-term outcome after balloon dilation was also demonstrated in the sensitivity analysis that included studies identified in both the current study and in a previous meta-analysis [2].

Caution must be exercised, however, when interpreting the results. This study was limited by several factors. First, our results may have been affected by publication bias; that is, the greater likelihood of publication of results based on large sample sizes or of positive results. We constructed funnel plots to evaluate the presence of publication bias. These plots were based on the number of patients entering the cohort and the reported 1-year patency rates. These patency rates were not adjusted for differences in study populations. Nevertheless, the plot associated with balloon dilation was symmetric and funnel shaped and did not reveal the presence of publication bias. The funnel plot for stent implantation studies was asymmetric, which implies that we cannot exclude the possibility of publication bias among these studies. The distribution of data points was not, however, characteristic of the presence of publication bias and may be caused by the low number of stent implantation studies available for the current analysis.

Second, the results reported in articles may be difficult to compare because the study populations, study design, and reporting methods often differ. The meta-analytical technique used in the current study for aggregating patency data allows the incorporation of covariables, which makes it possible to correct for some of the differences in baseline characteristics between the studies. Adjustment for these differences was limited, however, because not all articles reported relevant information or they used different reporting methods, precluding a meaningful classification. In the current study, we adjusted for clinical indication, lesion type, and treatment type. The results of the heterogeneity analysis demonstrated that there was variability between studies within the same treatment group in reported patency rates that was explained neither by the percentage of subjects with critical ischemia nor by the percentage of subjects with an occlusion. A possible explanation for this may be related to study differences that were not explored in the current analysis, such as

differences in lesion length, diabetic status, surveillance program, materials used, type of stent, and skill of the radiologists performing the intervention. Although we extracted information on lesion length, we were unable to classify these in meaningful groups because of the different reporting methods used. For example, some authors reported the lesion length as the proportion of lesions larger than 3 cm or some other arbitrarily chosen cutoff length, whereas others reported the range of lesion length or the mean or median lesion length with or without standard deviation, making comparison of studies with regard to lesion length difficult. The influence of distal arterial runoff status and differences in definition of patency were explored in the current study. In the multivariate analysis, these influences were not statistically significant. An explanation for this may be related to the fact that only a limited number of studies were included in the analyses, and, therefore, the power may have been too low to enable detection of the influences associated with these factors. The lack of a statistically significant contribution associated with runoff status may also be explained by the other determinants that were incorporated in the multivariate regression model. Clinical indication and lesion type are probably stronger prognostic factors than runoff status and may, therefore, capture the prognostic information associated with runoff status.

Third, the meta-analytical technique that we used in the current study has advantages and disadvantages (17]. The main advantage is that it allows adjustment for differences in case mix of the study populations. A disadvantage is that it does not incorporate a random component in treatment effect, which may yield pooled patency data that seem more precise than if a meta-analytical technique had been used that does incorporate a random effect. However, the large differences in the study populations analyzed and the possibility that this method offers to explain observed differences in treatment effect outweigh the lack of a random-effects component.

Fourth, the majority of studies analyzed were nonexperimental cohort studies, and in only one study were patients randomly assigned to

treatment groups. This implies that the population undergoing stent implantation may differ from the population undergoing balloon dilation. Although we corrected for some of the differences in case-mix, it should be noted that the treatment indication in a large proportion of patients undergoing stent implantation was to salvage a failed balloon dilation procedure, which suggests that the lesions in those who underwent stent implantation were probably more difficult to treat, and this may lead to an underestimation of the stent-implantation results. To explore the possible influence of this selection bias on our results, we performed a sensitivity analysis in which we excluded the studies that reported primary stent implantation results. In other words, we excluded studies that were unlikely to be affected by selection bias and we assessed the influence on our results. The estimated patency rates associated with stent implantation did not differ substantially from our baseline results, suggesting that selection probably did not lead to an underestimation of patency results associated with stent implantation. Furthermore, despite possible underestimation, we still found stent implantation to yield higher patency results than balloon dilation. Thus, correcting for selection bias would support our conclusions.

To our knowledge, only three randomized clinical trials comparing balloon dilation and stent implantation have been published so far [5, 10, 35]. Of these, only one met our inclusion criteria. In contrast to the results of the current study, no significant difference between femoropopliteal balloon dilation and stent implantation for the treatment of critical ischemia or occlusion was detected in these trials. A possible explanation may be that the trials were of limited sample size (range, 32-70 subjects) and had a maximum follow-up of only 1 year. Another explanation may be that the two larger randomized clinical trials included mainly patients with claudication (77%-100% of patients had claudication) and stenosis (61%-82% had a stenosis), which may result in a dilution of the difference between stent placement and balloon dilation that was observed only in the subgroup of patients with critical ischemia or occlusion.

None of the stent implantation studies included in the current analysis were stratified for clinical indication. In two studies, the authors reported a statistically significant lower patency rate after stent implantation for an occlusion, compared with the rate after stent implantation for a stenosis [20, 21]. It is possible that a meta-analysis that aggregates data at an overall group level fail to demonstrate findings relevant for specific patient groups. We did, however, detect the influence of critical ischemia and lesion type on the results after balloon dilation. Furthermore, in a sensitivity analysis, we explored the effect of including the patency rates reported for the subgroups of occlusion and stenosis (these were available in one balloon dilation study and in the two stent studies reporting a statistically significant difference), instead of the reported overall patency result. This did not change our results.

Our conclusions should be viewed in the light of study-design considerations and clinical implications for the patient. The results of this analysis of published articles on stent implantation and balloon dilation for femoropopliteal arterial disease suggest that stent implantation is a useful adjunct to balloon dilation and that in the treatment of occlusions and critical ischemia, stent implantation may be associated with more favorable long-term results, as compared with balloon dilation results. Publication bias, however, cannot be ruled out. A potential clinical concern associated with placement of a femoropopliteal stent is that among the failures following a technical successful stent placement, relatively more patients seem to develop thrombosis that may require more extensive treatment than among the failures following a technically successful balloon dilation [5, 6, 10, 35]. This higher risk for thrombosis, however, does not seem to result in lower primary 1-year patency rates, as compared with the balloon dilation results. Nevertheless, the potential risk may increase the inconvenience to the patient. The question remains whether the higher long-term patency rates after stent implantation for treatment of critical ischemia and occlusion, as compared with those after balloon dilation, counterbalance the higher risk of thrombosis after stent implantation, relative to the risk associated with balloon dilation.

In conclusion, stent placement is a useful bailout procedure to save a failed femoropopliteal balloon dilation procedure. More research seems necessary to compare the influence of disease severity on the outcomes of femoropopliteal balloon dilation and primary stent implantation and on the effects of successful treatment, treatment failure and thrombosis after these interventions on the patients well being.

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LETTERS TO THE EDITOR

Stent Placement in Femoropopliteal Arteries

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Editor:

The authors of the recent article in Radiology [1] are to be congratulated for their exhaustive review and meta-analysis of literature in which angioplasty was compared with stent placement in the treatment of femoropopliteal disease.

The authors confined their analysis to studies in which femoropopliteal disease was treated specifically in at least 20 patients, patients were followed up for 1 year, and estimates of primary patency were provided. To reduce the obvious potential for studies with selection bias, perhaps the most compelling criterion for inclusion should have been randomization. To date, four randomized controlled trials in which balloon angioplasty was compared with stent placement [2-5], albeit with relatively small sample sizes of 30-154 patients, have reached a concordant conclusion: Stent placement in the femoropopliteal artery produces no benefit in long-term patency.

A meta-analysis that involves multivariate models, sensitivity and jackknife analyses, and tests of residual heterogeneity, when applied to literature consisting largely of case series with inherent selection bias and no control group, will not surprisingly lead to uncertain results.

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Drs Muradin and Hunink respond:

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As Dr Clark correctly points out, randomized clinical trials provide the best evidence to determine whether therapies yield different results. However, the aim of our study [1] was not only to compare balloon dilation and stent deployment but also to determine the percentage of success over time associated with these procedures. As is generally known, randomized clinical trials are highly protocolized, which often limits generalization of the study results to daily practice.

At the time we started the study, we did not expect to find a difference between stent deployment and balloon dilation. However, after we performed a systematic review, the results of a meta-analysis demonstrated a significant difference between balloon dilation and stent placement in the subgroup of patients with occlusions (P = .02) or critical ischemia (P = .01). In the group of patients treated for claudication and femoropopliteal stenoses, which was the majority, the meta-analyses demonstrated

comparable results after balloon dilation and stent deployment. These findings proved to be robust in different types of sensitivity analyses.
One explanation for the finding that stent placement is more favorable than balloon angioplasty in a subgroup of patients, in contrast to the results of randomized clinical trials, may be that the results were affected by publication bias, as discussed in our article. However, an alternative explanation is that the randomized clinical trials were too small to demonstrate a significant difference in the subgroups. By pooling data from various studies, we increased the power to detect a difference.
With respect to the four randomized clinical trials [2-5] mentioned by Dr Clark, two [4,5] were not published at the time the meta-analysis was performed, one [3] was identified but did not meet our preset inclusion criteria, and one [2] was included in the meta-analysis. We recommend interpreting the results of our systematic review of the literature and meta-analysis together with any new evidence.

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CHAPTER 9

Summary and General Discussion

SUMMARY AND MAIN FINDINGS

This thesis presents 7 studies that examined the results of balloon dilation and stent placement performed for treatment of Peripheral Arterial Disease (PAD). The first 2 studies (chapter 2 and 3) explored the prognostic value of baseline characteristics on the outcome of the intervention. The outcome measures considered included occurrence of complications, improvement in ABI, and improvement in symptomatic status. The main results were that symptomatic status prior to intervention and renal function are important independent predictors of the occurrence of a systemic complication and that symptomatic status, diabetic status, lesion length, severity of stenosis, lesion localization, arterial runoff are important independent predictors for failure to improve symptomatic status and failure to improve the ABI. Furthermore the results showed that patients with lesions shorter than 10 cm had a better prognosis than patients with lesions longer than 10 cm. Within the group of patients with lesions shorter than 10 cm no difference in prognosis was detected. Patients treated for severe stenoses or even occlusions had a better prognosis on improvement of symptomatic status or ABI than patients treated with milder stenoses.

The fourth chapter presented a study that examined differences in performance between 6 hospitals. We compared the symptomatic and ABI outcome of percutaneous intervention for PAD across these hospitals. Cox regression analyses demonstrated a statistically significant difference in outcome across hospitals. In particular one hospital seemed to be associated with lower success rates. The baseline characteristics of the patient population treated in this hospital, however, showed that compared with the other hospitals a greater percentage of patients with severe PAD were treated. Although in the Cox regression analyses adjustments were made for differences in severity of disease the question

remains whether the Cox regression analyses could completely adjust for the differences in patient population and whether the results were affected by residual confounding. Exploration of the uncertainty in our estimates for the performance of the hospitals on the ranking of hospital performance showed substantial uncertainty in ranking. Taking this uncertainty and the posibility of residual confounding into account we concluded that the the restults did not demonstrate a difference across hospitals.

Chapter 5 presented a cost-effectiveness analysis that had as aim to determine the criteria that a new endovascular treatment for femoropopliteal arterial disease had to meet to become cost-effective compared with balloon dilation and bypass surgery. It yielded criteria for a hypothetical endovascular device with a slightly higher complication rate than a balloon dilation procedure, which seemed attainable. Furthermore the results indicated that the costs of such a new treatment are allowed to be substantial if counterbalanced by a moderate improvement in long-term results compared with the results following balloon dilation.

Chapter 6 presented a study that examined the influence of varying outcome criteria for classifying a procedural outcome as successful or failure on the reported success percentages. We applied 6 sets of outcome criteria and assessed the agreement between these sets of outcome criteria. Outcomes based on ABI measurements showed good agreement with each other. The set of outcomes based on ABI measurements and the set of outcomes based on symptomatic improvement showed only fair agreement indicating that ABI outcome and subjective symptomatic outcome may reflect different aspects of the result of treatment.

Combining subjective symptomatic outcome criteria with ABI measurements using the "OR" or "AND" showed good agreement with the set of outcomes based on, respectively, the subjective symptomatic improvement and the set of outcomes based on ABI measurements and did not yield substantially different success rates.

Interestingly the agreement between outcomes based on ABI measurement and subjective symptomatic outcomes was especially low in patients who had a relatively high pre-procedural ABI. This indicates that assessment of outcome in this group of patients using ABI measurements may not completely cover the impact of treatment and may therefore be inappropriate.
In chapter 7 we evaluated a method to limit the potential distorting effect of incomplete follow-up on estimates of procedural outcome in multi-center studies. The main results were that assessing the completeness of follow-up per medical center and including only the follow-up data that was considered relatively complete yielded less biased pooled estimates than pooling all available follow-up data.
In the last study (chapter 8) we performed a systematic review and meta-analysis of literature on the long-term results of balloon dilation and stent placement for femoropopliteal arterial disease. Comparison of published results of balloon dilation with published results of stent placement showed that both treatment modalities had similar results in the group of patients presenting with claudication and a stenosis but different results in the group of patients with occlusions or critical ischemia. These differences were in favor of stent placement in patients with occlusions or critical ischemia. Publication bias could not be demonstrated but could also not be ruled out.

DISCUSSION

The criteria for assigning patients to treatment proposed by the TASC Working Group are for a large extent based symptomatic status prior to treatment, lesion localization, and lesion type [1]. The results presented in this thesis support the view that balloon dilation and stent placement is a safe and effective treatment in patients with claudication.

In patients with ulceration or gangrene, however, percutaneous treatment is limited to that of a short-term rescue method. In the latter group of patients percutaneous treatment is associated with a relatively high systemic complication rate and poor long-term success rates. We did not find a difference in prognosis between patients with restpain and patients with claudication indicating that patients with restpain are appropriate candidates for percutaneous treatment.

With respect to lesion length the TASC Working Group proposed that patients with lesions shorter than 3 cm should be assigned to percutaneous treatment but that in patients with lesions longer than 3 cm but shorter than 5 cm insufficient evidence is available to make a recommendation. In multivariable analysis we did not detect a substantial difference in prognosis between subgroups of patients with lesions of less than 2 cm vs 2-5 cm indicating that all patients with lesions shorter than 5 cm are also appropriate candidates for percutaneous treatment. We also did not detect a difference in prognosis between patients with 5 to 10 cm lesions and patients with lesions shorter than 5 cm indicating that these patients may also be candidates for percutaneous treatment, but this group of patients was somewhat limited in size (n =117) indicating that small differences may have been missed. Besides lesion length, severity of the stenosis also had a statistically significant prognostic value. In multivariable analyses we found that treatment of severe stenoses or occlusions was associated with a higher chance of improvement in ABI or symptomatic status compared with the treatment of mild stenoses. A potential explanation may lie in the dynamic nature of the outcome measures applied namely change in ABI or change in symptomatic status. Revascularization of severe stenoses or occlusions has probably a greater impact on the vascularization of the leg compared with treatment of mild stenoses resulting in a greater change in patient status.

Besides symptomatic status and lesion characteristics other baseline characteristics were also found to be associated with prognostic value.

Diabetic status and impaired femoropopliteal runoff were predictors of failure to improve the symptomatic and ABI status. Impaired renal failure was a predictor for the occurrence of a systemic complication.
This thesis included a study in which the outcome of percutaneous treatment for PAD was compared across 6 hospitals. To adjust for differences in case-mix variables representing the differences in case-mix were entered in multi-variable Cox-regression analyses. Despite this adjustment in multi-variable analyses the hospital with the highest proportion of patients with critical ischemia, the lowest mean ABI, and the highest proportion of patients with diabetes was associated with the poorest performance. This raises the question whether the Cox regression method could completely adjust for the differences in case-mix and whether the results provide sufficient evidence to conclude that a hospital performed poorly. In our view the limitations of the methods applied should be acknowledged. The finding that one hospital was associated with a statistically significant higher hazard ratio compared with the overall performance could be explained by differences in case mix and by the limitations of adjustment methods. After evaluating the uncertainty in rank order and after considering the possibilty of residual confounding we concluded that the performance across hospitals was comparable.
The cost-effectiveness analysis and meta-analysis examining the results of current therapies for femoropopliteal arterial disease and estimating target criteria for a new endovascular treatment showed the limitations of current therapies and the room there is for a new treatment. An important finding was that even when very low estimates for the societal willingness to pay were used the costs of a new endovascular device are allowed to be considerable if counterbalanced by moderate long-term results. The role of stent placement in the treatment of femoropopliteal arterial disease is still unclear. The meta-analysis presented in chapter 8 showed that in patients with more severe disease, stent placement was associated with more favorable results than balloon dilation.

Five randomized clinical trials (RCT) comparing these treatment modalities did not detect a difference between the results of balloon dilation and stent placement [2-6]. Of these 5 studies 2 were published after the meta-analysis was performed [5,6]. Of the remaining 3 only 1 met the inclusion criteria. Four studies were small and included only a small proportion of patients with severe disease. A real difference could therefore easily have gone undetected in these trials. One RCT randomized 141 patients (154 limbs) and did not detect a statistically significant difference [5]. The percentage of patients with critical ischemia, however, was 19 out of 77 limbs (25%) in the balloon dilation arm and 27 out of 77 limbs (35%) in the stent placement arm indicating that although the patients were randomized the study arms may not have been comparable with respect to severity of disease indicating that a difference may have been missed.

RECOMMENDATIONS FOR FUTURE RESEARCH

lthough there is a general agreement that evaluation of the quality of medical care must be instituted, to date only a limited number of studies comparing quality of radiological procedures have been published. In principal, all interventional radiologists collect and record data on patient characteristics, procedural details, and procedural outcome. Registries simply record the data that already are being collected enabling comparison of performance. Comparison of indicators of performance such as crude morbidity, mortality, and success rates may be misleading, as these do not take into account differences in patient population. As described in chapter 4 risk adjusted comparisons, however, are also associated with limitations and may not completely adjust for the differences in case-mix. This does not imply that registries do not have a role in the assessment of the quality of health care but that a spectrum of

statistical tests must be considered before conclusions can be drawn. Apart from registries, other tools are available to assess quality of care. These include, for example, vignettes (written case reports) and standardized patients (actors posing as patients). Using vignettes and standardized patients to assess quality of care focuses directly on the process of care. Furthermore, these methods are relatively inexpensive. Their limitation is that they do not measure the actual outcome.

Since considerable public attention has been directed to the quality of care steps must be taken to allow a valid comparison of performance. Assessment and comparison of quality of care, however, is not straightforward and may lead to false conclusions if not properly conducted. To ensure valid conclusions we feel that quality assessment programs should include multiple tools to assess the quality of care. This may provide sufficient data to assure and improve the quality of care.

As described in chapter 5 and 8 the current treatment options for femoropopliteal arterial disease have their limitations leaving room for new therapies. Currently new stent-grafts and coated stents are being developed. Preliminary results of treatment for coronary artery disease with coated stents seem promising and indicate that coated stents may also have a place in the treatment of femoropopliteal arterial disease. Studies evaluating the outcome of these new therapies for treatment of PAD may provide sufficient evidence to make an appropriate treatment decision.

With respect to currently available therapies, a decision analysis comparing the benefits and costs of bypass surgery and percutaneous treatment and considering all relevant baseline characteristics including symptomatic status, localization of lesion and lesion length, severity of stenosis, arterial runoff, diabetic status and renal function seems necessary to the determine the optimal treatment in subgroups of patients groups.

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CHAPTER 10

Samenvatting en Algemene Discussie

SAMENVATTING

Achtergrond

Perifeer vaatlijden is een ziekte waarbij de zuurstofrijke bloedaanvoer naar de benen belemmerd wordt door vernauwingen in de bloedvaten. Dit kan pijnklachten geven en in ernstige vormen van de ziekte zelfs tot weefselversterf leiden. Wanneer de patiënt ernstige klachten heeft en loopoefeningen niet genoeg effect hebben op de klachten van de patiënt, kan worden geprobeerd de vernauwing op te heffen. Dit kan door een open chirurgische benadering waarbij een bypass wordt aangelegd of door een percutane ingreep waarbij door middel van een ballon dilatatie of een stent plaatsing (een metalen buisje) de vernauwing wordt opgerekt. Zowel de bypass behandeling als de percutane behandeling hebben voordelen en nadelen. Elke invasieve behandeling heeft een bepaald risico op complicaties. De risico's van een bypass operatie zijn hoger dan die van een percutane ingreep, maar het aantal patiënten dat een verbetering van klachten heeft is hoger na een bypass operatie dan na een percutane ingreep.

Vraagstelling en methoden

Dit promotieonderzoek richtte zich voor een groot deel op de vraag welke patiëntengroepen een grote kans op klachtenverbetering na een percutane ingreep hebben, en welke patiëntengroepen een hoog risico op een complicatie tijdens of na een percutane ingreep hebben (Hoofstuk 2,3). De achterliggende gedachte is dat deze kennis zal leiden tot een betere behandelingskeuze. Dit hebben we onderzocht door gegevens van percutane interventies en hun uitkomst uitgevoerd in de dagelijkse medische praktijk, te registreren. Zes ziekenhuizen deden mee aan deze registratie.

In hoofdstuk 4 hebben we de ziekenhuizen onderling vergeleken en onderzocht of er verschillen in behandelingsresultaten na een percutane interventie bestaan. Indien er verschillen zijn, is bekeken of hier een oorzaak voor aan te wijzen is. In totaal werden de resultaten van 1346 percutane ingrepen voor perifeer vaatlijden in dit onderzoek geanalyseerd. Omdat in de medische literatuur verschillende criteria voor succes of falen van de behandeling worden gebruikt en niet duidelijk is wat het effect hiervan op de gerapporteerde succes percentages is, hebben we in onze dataset onderzocht hoe de succes percentages veranderen wanneer verschillende veel gebruikte succes criteria worden toegepast (hoofdstuk 6). Daarnaast hebben we op een systematische manier een literatuur studie verricht (hoofdstuk 8). In dit hoofdstuk geven we een overzicht van gepubliceerde lange termijn resultaten na een ballon dilatatie of stent plaatsing voor vaatlijden in de femoropopliteale bloedvaten. Met behulp van statistische methoden hebben we onderzocht of er een verschil in de resultaten na een ballon dilatatie of stent plaatsing kan worden aangetoond en of er verschillen bestaan tussen bepaalde patiëntengroepen. Verder hebben we door middel van een besliskundig model onderzocht aan welke eisen een nieuwe percutane behandeling moet voldoen om te kunnen concurreren met de huidige behandelingen (hoofdstuk 5).

RESULTATEN

We vonden dat patiënten met slecht werkende nieren of met (dreigend) weefselversterf aan het been een veel hoger risico hebben op een zware complicatie, zoals een hartaanval of overlijden, dan patiënten met goed werkende nieren en alleen pijnklachten aan het been bij inspanning (hoofdstuk 3). Verder vonden we dat in de volgende patiëntengroepen behandeling relatief vaak niet het gewenste resultaat gaf vergeleken met patiëntengroepen zonder die kenmerken: patiënten met

weefselversterf aan het been, patiënten met diabetes mellitus, patiënten met een lange vernauwing (>10cm), patiënten met een slechte uitstroom traject en patiënten met een relatief milde vernauwing van het bloedvat (hoofdstuk 2). Vergelijking van de behandelingsresultaten van de 6 ziekenhuizen (hoofdstuk 4) liet zien dat één ziekenhuis het statistisch significant slechter deed dan de overige vijf ziekenhuizen. In dit ziekenhuis werden echter relatief meer patiënten met ernstige vormen van perifeer vaatlijden behandeld.
Verder hebben we de succes percentages die werden verkregen door verschillende criteria toe te passen met elkaar vergeleken. Dit liet zien dat de succes criteria gebaseerd op de ratio van de bloeddruk in de arm en die in de enkel (de enkel-arm index, hoe hoger de enkel arm index hoe beter) in succes percentages resulteerden welke weinig van elkaar verschilden.
Er werden wel verschillen gevonden tussen de succes percentages die werden verkregen door enkel-arm index criteria te hanteren en succes percentages die op basis van door de patiënt geraporteerde subjectieve klachtenverbetering werden verkregen. Opvallend was dat dit verschil het grootst was in de groep patiënten die voor de behandeling al een redelijk hoge enkel arm index waarde hadden (en dus een relatief milde vorm van perifeer vaatlijden hadden). Dit suggereert dat in deze groep de enkel-arm index mogelijk geen bruikbaar criterium is om te bepalen of de behandeling succesvol was.
Het literatuur-onderzoek liet zien dat in patiënten met (dreigend) weefselversterf in de benen de gepubliceerde succes percentages na een stent plaatsing in de femoropopliteale bloedvaten hoger waren dan die na een ballon dilatatie. Het kon niet worden uitgesloten dat dit resultaat het gevolg was van het verschijnsel dat hoge succes percentages vaker gepubliceerd worden dan lage succes percentages (publicatie bias), wat een vertekend beeld van de werkelijke resultaten na de interventie kan opleveren.

Overigens, in de grootste groep patiënten die een ballon dilatatie of stent plaatsing ondergaan, namelijk de patiënten zonder dreigend weefelversterf, waren de succes-percentages niet verschillend. Ook hebben we onderzocht wat de criteria zijn waaraan een nieuwe percutane behandeling voor vaatlijden in de femoropopliteale vaten moet voldoen om te kunnen concurreren met de ballon dilatatie en bypass chirurgie. Dit onderzoek liet zien dat de nieuwe behandeling zelfs als deze maar een gering hogere effectivieit heeft en zelfs een iets hogere complicatiekans heeft dan ballon dilatatie, de kosten van de nieuwe behandeling aanzienlijk hoger mogen zijn.

DISCUSSIE

Wat zijn nu de lessen die geleerd kunnen worden uit dit promotieonderzoek. Ten eerste geeft dit onderzoek een beeld van de resultaten die na een ballon dilatatie en stent plaatsing in Nederland in de dagelijkse praktijk worden behaald. Ten tweede, gezien een relatief hoge kans op een zware complicatie is het verstandig om patiënten met een relatief slechte nierfunctie goed voor te bereiden voor de ingreep en mogelijk intensiever te volgen na de ingreep. Verder is het bij deze patiënten waarschijnlijk beter langer door te gaan met de niet invasieve behandelingen alvorens een percutane ingreep te overwegen. Ten derde, patiënten met weefselversterf hebben een aanzienlijke kans op een zware complicatie en bovendien een kleine kans op verbetering van de klachten. Alleen als er geen ander behandelingsalternatief is valt een percutane ingreep bij deze patiënten te overwegen.
Ten vierde, de verschillen in behandelingsresultaten tussen ziekenhuizen lijken te kunnen worden verklaard door verschillen in patiëntenkarakteristieken, met name verschillen in de ernst van de ziekte.

Er zijn geen aanwijzingen dat het ene ziekenhuis beter of slechter presteerde dan een ander ziekenhuis. De studie liet zien dat vergelijking van behandelingsresultaten tussen ziekenhuizen minder eenvoudig is dan het op het eerste gezicht lijkt. Er zijn vele factoren die een vertekend beeld kunnen geven en die, indien ze niet in de analyse en interpretatie worden meegenomen, ten onrechte tot de conclusie kunnen leiden dat een ziekenhuis slecht of juist uitstekend heeft gepresteerd. Als de gegevens van een registratie zorgvuldig worden geanalyseerd is een registratie een bruikbaar middel voor de verbetering en handhaving van de kwaliteit van medisch handelen. Het geeft een beeld van hoeveel behandelingen worden uitgevoerd, bij welke patiënten, wat de resultaten in de dagelijkse praktijk zijn en of er verschillen tussen zorgverstrekkers zijn en kunnen een indicatie geven wat de oorzaak hiervoor is. Gegevens die niet beschikbaar zijn als er geen registratie is en die nodig zijn om te bepalen of er verdere stappen nodig zijn en in welke richting, om de kwaliteit van de zorg te garanderen.

CHAPTER 11

Dankwoord

DANKWOORD

Het is gelukt het boekje is klaar! Het gezegde "de laatste loodjes wegen het zwaarst" heeft voor mij weer een extra dimensie gekregen. Dit promotieonderzoek was niet mogelijk geweest zonder de hulp van anderen aan wie ik dan ook veel dank verschuldigd ben.

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GALIED

CHAPTER 12

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