View metadata, citation and similar papers at

brought to you by CORE

provided by Erasmus University Digital Repository

Balloon Dilation and Stent Implantation for Treatment of Femoropopliteal Arterial Disease: Meta-Analysis[1]

Galied S. R. Muradin, M
Johanna L. Bosch, PhD
Theo Stijnen, PhD
M. G. Myriam Hunink, M
PhD

Index terms:
Arteries, femoral
Arteries, grafts and prostheses, 921.1268, 924.1268
Arteries, popliteal
Arteries, stenosis or obstruction, 921.721, 924.721
Arteries, transluminal angioplast 921.1282, 921.1286, 924.12 924.1286
Radiology and radiologists, outc studies
Stents and prostheses, 921.1282, 921.1286, 924.1282, 924.1286

Published online: September 18, 2001
10.1148/radiol.2211010039
Radiology 2001; 221:137–145

Abbreviation:
SVS/ISCVS = Society for Vascular Surgery and International Society for Cardiovascular Surgery

[1] From the Program for the Assessment of Radiological Technology (ART Program) and the Departments of Radiology (G.S.R.M., M.G.M.H.) and Epidemiology and Biostatistics (G.S.R.M., J.L.B., T.S., M.G.M.H.), Erasmus University Medical Center Rotterdam, Dr Molewaterplein 50, Rm EE21-40a, 3015 GE Rotterdam, the Netherlands; Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Mass (J.L.B.); and Department of Health Policy and Management, Harvard School of Public Health, Boston, Mass (M.G.M.H.). From the 2000 RSNA scientific assembly. Received November 28, 2000; revision requested January 24, 2001; revision received April 4; accepted April 9. **Address correspondence to** M.G.M.H. (e-mail: *hunink@epib.fgg.eur.nl*).

© RSNA, 2001

Author contributions:
Guarantor of integrity of entire study, M.G.M.H.; study concepts and design, all authors; literature research, G.S.R.M.; data acquisition, G.S.R.M., J.L.B.; data analysis/interpretation, all authors; statistical analysis, G.S.R.M., T.S.; manuscript preparation, G.S.R.M.; manuscript definition of intellectual content, editing, and revision/review, all authors; manuscript final version approval, G.S.R.M., M.G.M.H.

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 by 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.

CONCLUSION: 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.

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

We 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 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 (ie, 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 percentages 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 with 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 percentages 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 intervention, definition of patency, and unit of observation used in reporting patency—were tested with 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 angioplasty or atherectomy ($n = 23$) or on the natural history of femoropopliteal arterial disease ($n = 1$), *(i)* not in the English language ($n = 2$), and *(j)* 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 noncomparative 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

TABLE 1
Review of Study Population Characteristics and Patency Results of Studies that Included Femoropopliteal Balloon Dilation

Study*	Year	No. of Patients	Age (y)†	Sex (%)‡	Critical Ischemia (%)	Occlusion (%)	Poor Runoff (%)	Popliteal Location (%)	Patency Rate (%)						
									0-year	1-year	2-year	3-year	4-year	5-year	Standard Error§
Treiman et al (23)	1994	35	69	57/43	20	17	46	49	94	41	24	11	11	11	10
Becquemin et al (19)	1994	95	67	64/36	31	45	52	16	79	60	51	NA	NA	NA	6
Jeans et al (24)	1994	137	65	72/28	44	65	NA	NA	90	60	53	52	51	50	6
Vroegindeweij et al (22)	1995	62	64	73/27	2	100	23	NA	82	63	56	46	46	46	9
Murray et al (25)	1995	42	74	50/50	11	59	33	NA	93	86	53	NA	NA	NA	26
Tielbeek et al (9)	1996	35	64	77/23	0	6	0	NA	100	80	67	62	62	62	10
Stanley et al (26)	1996	176	69	55/45	26	41	31	16	73	58	46	38	30	26	8
Vroegindeweij et al (10)‖	1997	27	64	70/30	0	19	11	NA	89	85	NA	NA	NA	NA	7
Martin et al (27)	1999	88	NA	52/48	26	6	NA	14	NA	62	57	57	44	37	7
Golledge et al (28)	1999	74	73	62/38	42	26	28	NA	90	58	NA	NA	NA	NA	6
O'Donohoe et al (29)#	1999	96	69	57/43	56	46	NA	NA	84	53	NA	NA	NA	NA	5
Karch et al (30)**	2000	85	56	48/52	36	7	38	25	97	74	62	56	52	52	13

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 dilation and 108 balloon dilations together.

TABLE 2
Review of Study Population Characteristics and Patency Results of Studies that Included Femoropopliteal Stent Implantation

Study*	Year	No. of Patients	Age (y)†	Sex (%)‡	Critical Ischemia (%)	Occlusion (%)	Poor Runoff (%)	Popliteal Location (%)	Patency Rate (%)						
									0-year	1-year	2-year	3-year	4-year	5-year	Standard Error§
Martin et al (31)	1995	90	64	64/36	23	35	0	0	99	61	49	NA	NA	NA	5
White et al (32)	1995	32	65	72/28	6	47	47	31	97	72	63	63	NA	NA	38
Henry et al (20)	1995	116‖	62	87/13	7#	33	9	0	100	81	73	72	65	NA	8
Bergeron et al (33)	1995	39	64	85/15	21	57	33	0	95	81	77	77	NA	NA	10
Chatelard et al (34)	1996	35	70	54/46	37	29	46	26	100	80	76	76	NA	NA	8
Vroegindeweij et al (10)**	1997	24	65	71/29	0	17	8	NA	100	74	NA	NA	NA	NA	9
Strecker et al (21)	1997	80	64	73/27	16	59	38	24	100	59	48	48	NA	NA	11
Cheng et al (18)††	1999	28	70	67/33	42#	39	NA	0	90	60	54	27	NA	NA	22

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 dilation. 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.

with an occlusion varied from 6% to 100%, and the percentage of cases with critical ischemia varied 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 (20,25,26,38,30,32). The authors of the remaining two articles did not refer to these standards but used a classi-

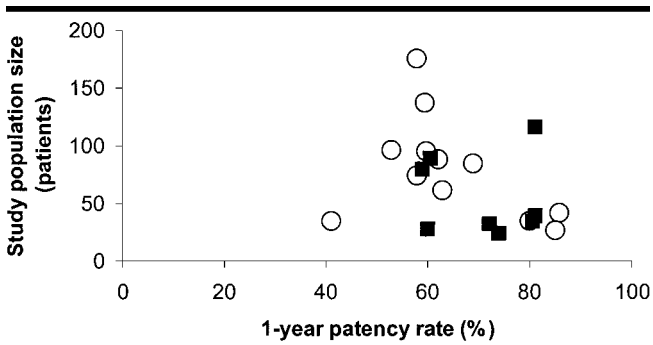

Figure 1. Funnel plot shows cumulative 1-year primary patency rates versus the number of patients included in the study. The distribution of data points associated with balloon dilation (○) appears fairly funnel shaped and symmetric, indicating that the presence of publication bias is unlikely. The distribution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

fication system that met the SVS/ISCVS 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.

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). 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*).

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 anticoagulant treatment versus platelet inhibitor treatment (data available in 17 studies), and popliteal versus femoral localization of the lesion (data available in 12 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. 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 (26) 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%).

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)	78–80	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.

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.

DISCUSSION

The 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

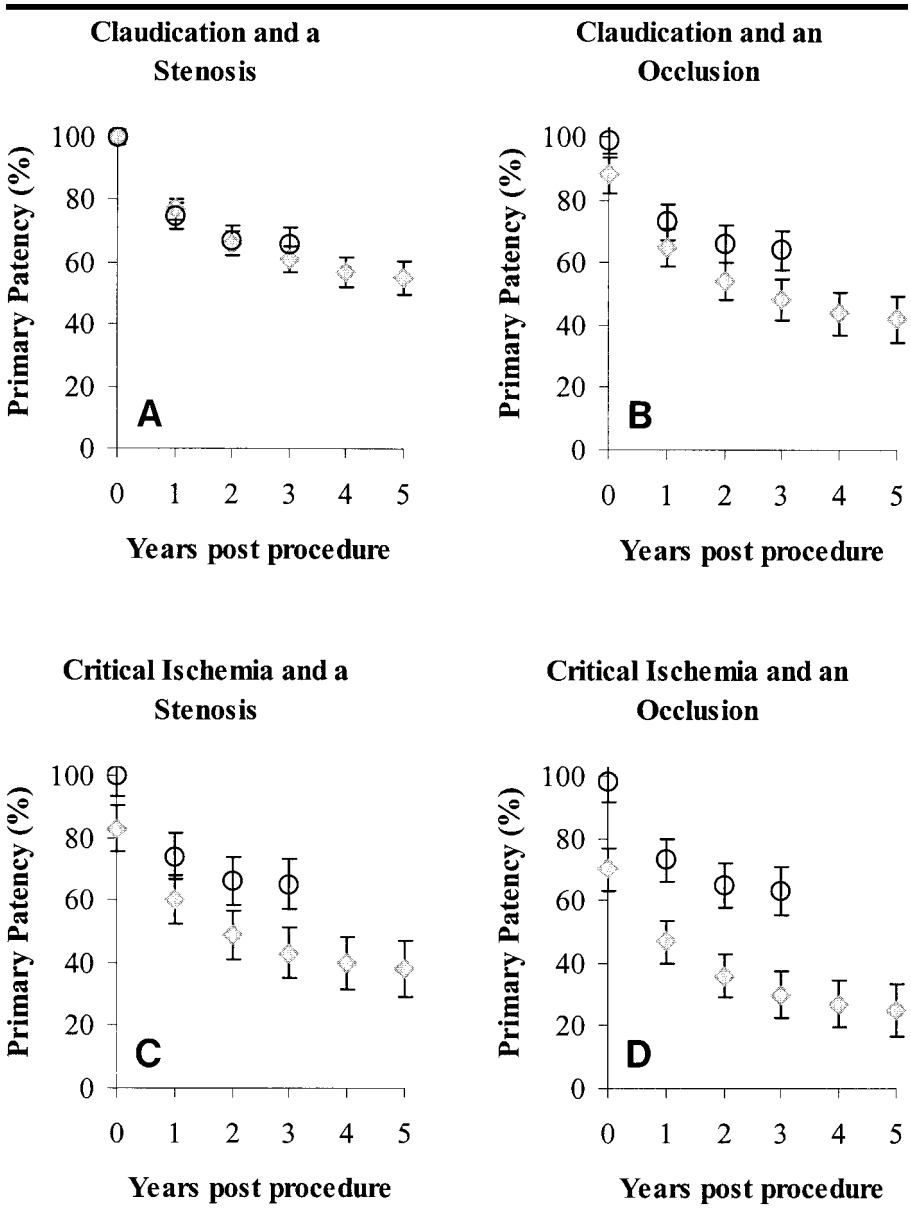

Figure 2. Cumulative primary patency rates and 95% CIs (error bars) for femoropopliteal balloon dilation (◆) and femoropopliteal stent implantation (○), depending on lesion type (stenosis vs occlusion) and clinical indication (claudication vs critical ischemia). *A,* Graph shows that the estimates for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

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 the 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-analytic 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-analytic 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 selec-

tion 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 clinical 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 would 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 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 the 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.

STATISTICAL CONSULTANT COMMENTARY

Any number of biases may arise in the synthesis of information from a wide range of studies purporting to address the same issue. Meta-analysis is one quantitative method to systematically pool all the available information regarding a medical technique. This statistical method combines measures of effect size—a single comparable index of the effectiveness of an intervention—across all the independent trials that have addressed the issue. In theory, this sounds good; we act "as if" we could perform a single multicenter experiment based on all the subject information gathered in multiple independent trials.

When performing a meta-analysis, one typically begins by locating all the studies in the area of interest. There are various ways to do this: for instance, a Web-based search of the literature. Mosteller and Chalmers (Stat Sci 1992; 7:227–236) report in their reviews of the meta-analysis literature that "We know that computer searches alone still find less than two-thirds of the relevant trials." As a result, one can never be sure that the authors of a review have located all the relevant studies. One potential source of bias in this process is publication bias. That is, it may be that all the relevant studies are not published in the literature. There are any number of reasons why a study was not published (JAMA 1990; 263: 1385–1389). Studies with "negative" findings may not be submitted to journals, or editors may not be enthusiastic about publishing contradictory studies. Statistically nonsignificant findings also may be less publishable. Justification for nonsubmission or nonacceptance may include a small sample size or the lack of randomization (Lancet 1991; 337:867–872). Even if such a study is publicly presented, it may be published in a format that is "below the radar" of the literature search (eg, symposium presentations, posters, meeting abstracts). In actuality, it is not necessary for all relevant studies to be included in a meta-analysis. A sample of results that represents the effect magnitude is all that is required. Any nonrandom selection process (as opposed to a random sampling process) will result in estimates that are debatable and sometimes false.

Publication bias is probably impossible to eliminate, but one technique for detecting it is the inverted funnel plot, as described by Egger and colleagues (BMJ 1997; 315:629–634) and Light and Pillemer (*Summing Up: The Science of Reviewing Research.* Cambridge, Mass: Harvard University Press, 1984). With funnel plots, we begin by assuming that larger studies of the effect of an intervention are more precise and thus more likely to be published. The results of smaller studies will be less precise, and thus their estimated effect size will vary considerably. A funnel plot is a scatterplot of the results of all studies used in a meta-analysis. The effect size (usually a log odds ratio or standardized difference) is plotted on the horizontal axis, and the weight of the study (usually the reciprocal of the standard error or the sample size) is plotted on the vertical axis. If publication bias is absent, then the plot looks like an inverted funnel, with most of the smaller studies scattered symmetrically at the bottom of the graph. If there is bias, then the lack of negative small studies will result in an asymmetric plot. To some extent, it is possible to correct for publication bias, although it is best to make the effort to avoid it.

Publication bias is but one difficulty to be surmounted by those who wish to review

research findings. Ultimately, the best test of the question is a single, well-controlled trial. Egger et al (BMJ 1997; 315:629–634) reported that in eight cases where a published meta-analysis was compared to a subsequent clinical trial, the findings of the meta-analysis were concordant in half the cases. "In all cases discordance was due to meta-analysis showing larger effects. Funnel plot asymmetry was present in three out of four discordant pairs but in none of the concordant pairs."

References

1. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD): TASC Working Group. J Vasc Surg 2000; 31 (1 pt 2):S103–S106.
2. Hunink MGM, Wong JB, Donaldson MC, Meyerovitz MF, Harrington DP. Patency results of percutaneous and surgical revascularization for femoropopliteal arterial disease. Med Decis Making 1994; 14: 71–81.
3. Hunink MGM, Wong JB, Donaldson MC, Meyerovitz MF, de Vries JA, Harrington DP. Revascularization for femoropopliteal disease. A decision and cost-effectiveness analysis. JAMA 1995; 274:165–171.
4. Vroegindeweij D, Tielbeek AV, Buth J, Schol FP, Hop WC, Landman GH. Directional atherectomy versus balloon angioplasty in segmental femoropopliteal artery disease: two-year follow-up with color-flow duplex scanning. J Vasc Surg 1995; 21:255–269.
5. Cejna M, Schoder M, Lammer J. PTA versus stent in der femoropoplitealen strombahn. Radiologe 1999; 39:144–150.
6. Do-dai-Do, Triller J, Walpoth BH, Stirnemann P, Mahler F. A comparison study of self-expandable stents vs balloon angioplasty alone in femoropopliteal artery occlusions. Cardiovasc Intervent Radiol 1992; 15:306–312.
7. Fisher CM, Fletcher JP, May J, et al. No additional benefit from laser in balloon angioplasty of the superficial femoral artery. Eur J Vasc Endovasc Surg 1996; 11: 349–352.
8. Spoelstra H, Casselman F, Lesceu O. Balloon-expandable endobypass for femoropopliteal atherosclerotic occlusive disease. A preliminary evaluation of fifty-five patients. J Vasc Surg 1996; 24:647–654.
9. Tielbeek AV, Vroegindeweij D, Buth J, Landman GH. Comparison of balloon angioplasty and Simpson atherectomy for lesions in the femoropopliteal artery: angiographic and clinical results of a prospective randomized trial. J Vasc Interv Radiol 1996; 7:837–844.
10. Vroegindeweij D, Vos LD, Tielbeek AV, Buth J, van den Bosch HC. Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: A comparative randomized study. Cardiovasc Intervent Radiol 1997; 20:420–425.
11. Kessel DO, Wijesinghe LD, Robertson I, et al. Endovascular stent-grafts for superficial femoral artery disease: results of 1-year follow-up. J Vasc Interv Radiol 1999; 10:289–296.
12. Rodriguez-Lopez JA, Soler L, Werner A, Martinez E, Papazoglou K, Diethrich EB. Long-term follow-up of endoluminal grafting for aneurysmal and occlusive disease in the superficial femoral artery. J Endovasc Surg 1999; 6:270–277.
13. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD): TASC Working Group. J Vasc Surg 2000; 31 (1 pt 2):S107–S109.
14. Altman DG. Analysis of survival times. In: Practical statistics for medical research. London: Chapman & Hall, 1991; 365–395.
15. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997; 26:517–538.
16. Begg CB, Berlin JA. Publication bias: a problem in interpreting medical data. J R Statist Soc. 1988; 151:419–463.
17. Dear KB. Iterative generalized least squares for meta-analysis of survival data at multiple times. Biometrics 1994; 50: 989–1002.
18. Cheng SW, Ting AC, Lau H, Wong J. Immediate stenting of iliofemoral occlusive lesions: a surgeon's early experiences. J Endovasc Surg 1999; 6:256–263.
19. Becquemin JP, Cavillon A, Haiduc F. Surgical transluminal femoropopliteal angioplasty: multivariate analysis outcome. J Vasc Surg 1994; 19:495–502.
20. Henry M, Amor M, Ethevenot G, et al. Palmaz stent placement in iliac and femoropopliteal arteries: primary and secondary patency in 310 patients with 2–4-year follow-up. Radiology 1995; 197:167–174.
21. Strecker EP, Boos IB, Gottmann D. Femoropopliteal artery stent placement: evaluation of long-term success. Radiology 1997; 205:375–383.
22. Vroegindeweij D, Tielbeek AV, Buth J, van Kints MJ, Landman GH, Mali WP. Recanalization of femoropopliteal occlusive lesions: a comparison of long-term clinical, color duplex US, and arteriographic follow-up. J Vasc Interv Radiol 1995; 6:331–337.
23. Treiman GS, Ichikawa L, Treiman RL, et al. Treatment of recurrent femoral or popliteal artery stenosis after percutaneous transluminal angioplasty. J Vasc Surg 1994; 20:577–585; discussion 585–577.
24. Jeans WD, Cole SE, Horrocks M, Baird RN. Angioplasty gives good results in critical lower limb ischaemia. A 5-year follow-up in patients with known ankle pressure and diabetic status having femoropopliteal dilations. Br J Radiol 1994; 67:123–128.
25. Murray JG, Apthorp LA, Wilkins RA. Long-segment (≥10 cm) femoropopliteal angioplasty: improved technical success and long-term patency. Radiology 1995; 195:158–162.
26. Stanley B, Teague B, Raptis S, Taylor DJ, Berce M. Efficacy of balloon angioplasty of the superficial femoral artery and popliteal artery in the relief of leg ischemia. J Vasc Surg 1996; 23:679–685.
27. Martin DR, Katz SG, Kohl RD, Qian D. Percutaneous transluminal angioplasty of infrainguinal vessels. Ann Vasc Surg 1999; 13:184–187.
28. Golledge J, Ferguson K, Ellis M, et al. Outcome of femoropopliteal angioplasty. Ann Surg 1999; 229:146–153.
29. O'Donohoe MK, Sultan S, Colgan MP, Moore DJ, Shanik GD. Outcome of the first 100 femoropopliteal angioplasties performed in the operating theatre. Eur J Vasc Endovasc Surg 1999; 17:66–71.
30. Karch LA, Mattos MA, Henretta JP, McLafferty RB, Ramsey DE, Hodgson KJ. Clinical failure after percutaneous transluminal angioplasty of the superficial femoral and popliteal arteries. J Vasc Surg 2000; 31:880–887.
31. Martin EC, Katzen BT, Benenati JF, et al. Multicenter trial of the Wallstent in the iliac and femoral arteries. J Vasc Interv Radiol 1995; 6:843–849.
32. White GH, Liew SC, Waugh RC, et al. Early outcome and intermediate follow-up of vascular stents in the femoral and popliteal arteries without long-term anticoagulation. J Vasc Surg 1995; 21: 270–281.
33. Bergeron P, Pinot JJ, Poyen V, et al. Long-term results with the Palmaz stent in the superficial femoral artery. J Endovasc Surg 1995; 2:161–167.
34. Chatelard P, Guibourt C. Long-term results with a Palmaz stent in the femoropopliteal arteries. J Cardiovasc Surg (Torino) 1996; 37:67–72.
35. Zdanowski Z, Albrechtsson U, Lundin A, et al. Percutaneous transluminal angioplasty with or without stenting for femoropopliteal occlusions? a randomized controlled study. Int Angiol 1999; 18: 251–255.