

Histologic atherosclerotic plaque characteristics are associated with restenosis rates after endarterectomy of the common and superficial femoral arteries

Wouter J.M. Derksen, MD,^{a,b} Jean-Paul P.M. de Vries, MD, PhD,^d Aryan Vink, MD, PhD,^c Evelyn Velema, MSc,^a Jan-Albert Vos, MD, PhD,^c Dominique de Kleijn, PhD,^f Frans L. Moll, MD, PhD,^b and Gerard Pasterkamp, MD, PhD,^a *Utrecht and Nieuwegein, The Netherlands*

Objectives: This study assessed the predictive value of histologic plaque characteristics for the occurrence of restenosis after femoral artery endarterectomy.

Background: It would be advantageous if patients at increased risk for restenosis after arterial endarterectomy could be identified by histologic characteristics of the dissected plaque. Differences in atherosclerotic plaque composition of the carotid artery have been associated with restenosis rates after surgical endarterectomy. However, whether atherosclerotic plaque characteristics are also predictive for restenosis in other vascular territories is unknown.

Methods: Atherosclerotic plaques of 217 patients who underwent a common femoral artery endarterectomy (CFAE; n = 124) or remote superficial femoral artery endarterectomy (RSFAE; n = 93) were examined and scored microscopically for the presence of collagen, macrophages, smooth muscle cells, lipid core, intraplaque hemorrhage, and calcifications. The 12-month restenosis rate was assessed using duplex ultrasound imaging (peak systolic velocity [PSV] ratio ≥ 2.5).

Results: The 1-year restenosis rate was 66% (61 of 93) after RSFAE compared to 21% (26 of 124) after CFAE. Plaque with characteristics of high collagen and smooth muscle cell content were positively associated with the occurrence of restenosis, with odds ratios (ORs) of 2.90 (95% confidence interval [CI], 1.82-4.68) and 2.20 (1.50-3.20) for superficial femoral artery (SFA) and common femoral artery (CFA), respectively. SFA plaques showed significantly heavier staining for collagen (69% vs 31% for CFA; $P < .001$) and smooth muscle cells (64% vs 36% for CFA; $P < .001$). After multivariate analysis, the operation type (CFAE or RSFAE), gender, and the presence of collagen were independent predictive variables for restenosis after endarterectomy of the CFA and SFA.

Conclusion: Plaque composition of the CFA and SFA differs. Furthermore, the dissection of a fibrous collagen-rich plaque is an independent predictive variable for restenosis after endarterectomy of the CFA and SFA. (*J Vasc Surg* 2010;52:592-9.)

Prevention and risk management of restenosis after endarterectomy of the peripheral arteries represents one of the major challenges in peripheral revascularization. Extent of the disease, number of run-off arteries, and diabetes mellitus are known risk factors after peripheral vascular intervention.^{1,2} In contrast with established risk factors, the relation between local atherosclerotic plaque characteristics and the development of restenosis after femoral artery

endarterectomy has never been studied. It would be advantageous if patients at risk for restenosis could be identified directly after surgery by examining the dissected plaque.

Atherosclerotic plaque composition of the carotid artery has been associated with restenosis after surgical endarterectomy. Macrophage infiltration and a large lipid core in the dissected carotid plaque were independent predictive parameters for lower restenosis rates after carotid endarterectomy.³ However, whether atherosclerotic plaque characteristics are also predictive for restenosis in other vascular territories is unknown.

This study was conducted to determine whether histologic plaque characteristics of the femoral artery are predictive for the occurrence of restenosis after endarterectomy.

METHODS

Patient population. The studied patient population was a subgroup of patients who were included in the Athero-Express Biobank. The subgroup consisted of all patients who underwent a sole common femoral artery endarterectomy (CFAE) or remote superficial femoral artery endarterectomy (RSFAE). The design of the Athero-Express Biobank has been described previously.⁴ Briefly,

From the Experimental Cardiology Laboratory,^a Department of Vascular Surgery,^b and the Department of Pathology,^c University Medical Center Utrecht; the Department of Vascular Surgery,^d and the Department of Interventional Radiology,^e St Antonius Hospital, Nieuwegein; and the Interuniversity Cardiology Institute of the Netherlands,^f Utrecht.

Competition of interest: Dr Moll has a shared royalty agreement in LeMaitre Vasutek and Dr de Vries is a consultant for LeMaitre Vasutek. Furthermore, Dr Moll and Dr Pasterkamp are consultants for CAVADIS.

Reprint requests: Gerard Pasterkamp, MD, PhD, Experimental Cardiology Laboratory, University Medical Center Utrecht, G02.523, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands (e-mail: g.pasterkamp@umcutrecht.nl or <http://www.vascularbiology.org>).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/\$36.00

Copyright © 2010 by the Society for Vascular Surgery.

doi:10.1016/j.jvs.2010.03.063

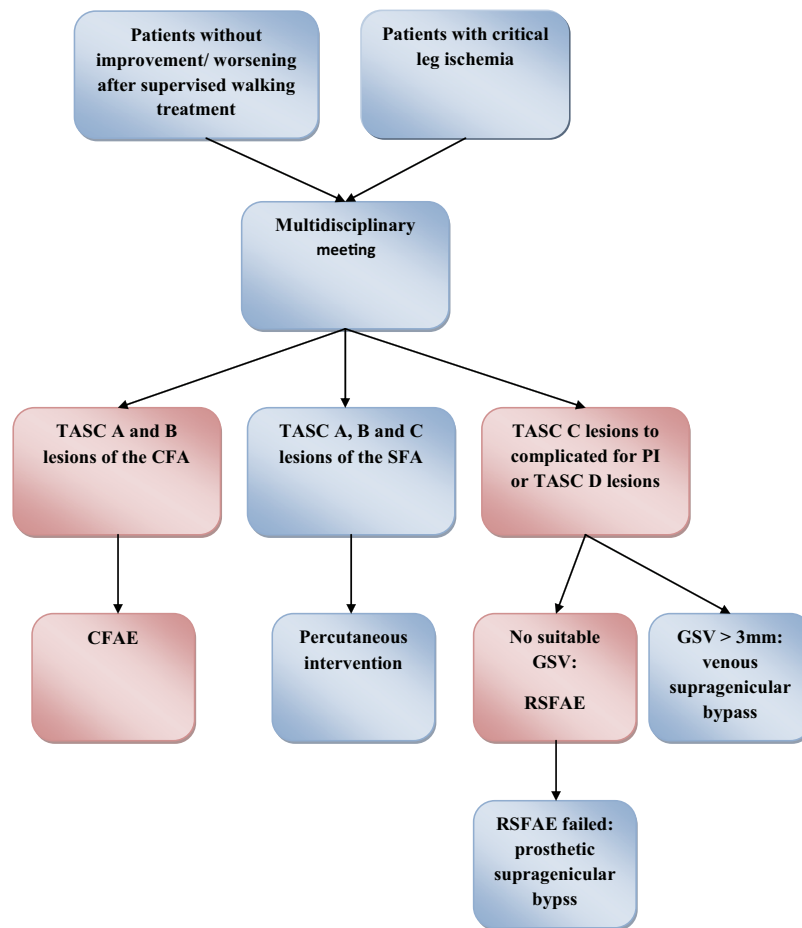


Fig 1. Treatment protocol of patients with peripheral leg ischemia when conservative treatment failed. In both hospitals, patients with peripheral leg ischemia are being treated according to the same protocol. The red boxes in the diagram are the studied patients. *CFA*, Common femoral artery; *CFAE*, common femoral artery endarterectomy; *GSV*, great saphenous vein; *PI*, percutaneous intervention; *RSFAE*, remote superficial femoral artery endarterectomy; *SFA*, superficial femoral artery; *TASC*, TransAtlantic Inter-Society Consensus.

Athero-Express is an ongoing vascular biobank study with a longitudinal study design. The main objective is to determine the predictive value of local atherosclerotic plaque characteristics for the occurrence of future local and systemic cardiovascular events. Dissected femoral plaques, freshly obtained during endarterectomy in two participating Dutch hospitals, were collected and underwent histologic examination. In addition, clinical follow-up was obtained 1 to 3 years after the surgical intervention.

In both hospitals, patients with peripheral leg ischemia are being treated by use of the same protocol (Fig 1). First, patients with intermittent claudication are treated conservatively with supervised walking exercise. Patients without improvement and disabling complaints, or whose complaints worsen after supervised exercise, and patients with critical ischemia primarily are discussed in a multidisciplinary meeting with interventional radiologists and vascular surgeons. Patients with a sole lesion (TransAtlantic Inter-Society Consensus [TASC] A and B lesions) of the

common femoral artery (CFA) are treated with endarterectomy and closed with patch plasty (Fig 1).

TASC C lesions of the superficial femoral artery (SFA), assessed as not treatable by percutaneous intervention, and TASC D lesions of the SFA are treated with a venous supragenicular bypass. A patient who does not have a suitable great saphenous vein will be treated primarily with RSFAE (Fig 1). If the RSFAE fails, patients undergo prosthetic supragenicular bypass.

The current study selected the 238 patients who underwent a CFAE (TASC A and B lesions) or RSFAE (TASC C and D lesions) to treat severe intermittent claudication, critical ischemia, or tissue loss (Rutherford classification II-VI) from June 2002 until October 2007. Surgical procedures were performed in a standardized way, as described previously.^{5,6} Clinical characteristics of all patients were prospectively recorded at baseline, their medical records were studied, and the patients completed a detailed validated questionnaire. The medical ethics boards of both

participating hospitals approved the study, and all patients provided written informed consent.⁴

Plaque characteristics. The procedures for processing and examination of the dissected atherosclerotic plaques have been described previously.⁴ Directly after excision, the atherosclerotic plaque was transferred to the laboratory. According to the literature, we chose the segment with the greatest plaque burden as the culprit lesion. When the femoral plaque was totally occluded, we chose the most voluminous and intact part of the plaque.⁴ The culprit lesion was fixed in 4% formaldehyde, decalcified in ethylenediaminetetraacetic acid, and embedded in paraffin. Segments adjacent to the culprit lesion were snap frozen in liquid nitrogen and stored at -80°C for future analysis.

The paraffin segment of the culprit lesion was cut on a microtome into sections of $5\ \mu\text{m}$ for histologic and immunohistochemical staining and the following stainings were performed to characterize the plaque: picosirius red (collagen and lipid core), CD 68 (macrophages), α -actin (smooth muscle cells), hematoxylin and eosin (calcification, lipid core, and intraplaque hemorrhage), and fibrin (intraplaque hemorrhage). All stainings were examined microscopically, and plaque characteristics were scored semiquantitatively (no/minor vs moderate/heavy). The definitions of each staining category have been published previously.⁴ All scorings were based on visual estimates and were rated on ordinal scales. Two observers independently scored all stainings. A third independent observer was consulted when interpretations differed between the first two observers. Briefly, “no or minor” represent absent or minimal staining with a few clustered cells, whereas “moderate and heavy” represent larger areas of positive staining.⁴

Before determination of the different histologic characteristics, we differentiated between the intima and media in the hematoxylin and eosin and elastin von Gieson staining by deciding where the internal elastic lamina was located. The studied histologic characteristics are only scored in the intimal layer.^{4,7}

No or minor macrophage and smooth muscle cell infiltration is shown by absent or minimal staining with few clustered cells, whereas moderate and heavy infiltration is shown by moderate or heavy staining with larger areas of clustered cells. No or minor collagen content is shown by absent or minimal staining for collagen with a thin fibrous cap, whereas moderate or heavy collagen is shown by moderate staining or heavy staining for collagen, covering any lipid in the atherosclerotic lesion, as visualized with and without polarized light. No or minor calcifications are indicated by absent or nonconfluent speckled areas of plaque calcification, whereas moderate or heavy represent nodules of calcified plaque or confluent areas of calcified plaque, respectively.

Intraplaque hemorrhage was scored as present or absent. The size of the lipid core was estimated as a percentage of the total plaque area with a division in three categories: none, $<40\%$, and $\geq 40\%$. We have recently demonstrated that our semiquantitative analysis of atherosclerotic plaque histology is well reproducible, both intraobserver and in-

terobserver variability.⁷ CD-68 and α -actin stains were also analyzed quantitatively, and these values revealed excellent correlations with our semiquantitative analyses.⁷

Follow-up. Follow-up of the patients was scheduled at 3, 6, and 12 months, and annually thereafter, and included medical history, physical examination, and duplex ultrasound scanning. Duplex ultrasound scanning to detect restenotic lesions was performed according to protocol. The entire CFA, the proximal profunda femoral artery, the entire SFA (from origin to the popliteal artery, including the distal stent after RSFAE), and the entire popliteal artery were scanned in every patient. Obstructions were classified on the basis of the peak systolic velocity (PSV) within the obstruction (numerator of the PSV ratio) and proximally of the obstruction (denominator of the PSV ratio). A stenosis of 50% was considered if the PSV ratio was 2.5. The endpoint of this study was restenosis 12 months postoperatively, which was assessed by duplex ultrasound imaging. Lumen reduction of $\geq 50\%$ using duplex ultrasound imaging (PSV ratio ≥ 2.5) was considered as the presence of significant postoperative restenosis.

Data analysis. Statistical analysis was performed with SPSS 15.0 software (SPSS Inc, Chicago, Ill). Univariate analysis was used to test baseline characteristics for association with restenosis. Categorical variables were tested using cross tables (2×2), and the accompanying *P* value was calculated with the χ^2 statistic. Continuous variables were tested nonparametrically by using the Mann-Whitney *U* test. *P* values $< .05$ were considered statistically significant. To test independency of the univariate variables, multivariate binary logistic regression analysis (with backward exclusion of nonsignificant variables using likelihood ratio test) was performed. Variables showing a significant association with restenosis in univariate analysis were included in the multivariate analysis. Age, gender, and operation indication were always included in the multivariate analysis models.

RESULTS

A total of 238 patients underwent a CFAE or RSFAE. Excluded from the study were two patients who died in the first postoperative month of coronary artery disease and 19 patients whose atherosclerotic plaque material was insufficient for histologic analyses. Therefore, a total 217 patients were examined for the current study.

CFAE was done in 124 patients (57%) and RSFAE in 93 patients (43%). Of the 217 patients, 168 (77%) were operated on for intermittent claudication (Rutherford class III). The other patients had critical ischemia or tissue loss (Rutherford class IV-VI). Men comprised 73% of the patients who received surgery, and most patients were affected by risk factors for atherosclerotic disease, as summarized in Table I.

Most of the atherosclerotic plaques were fibrotic, 85% contained moderate ($n = 114$) to heavy ($n = 74$) staining for collagen, 75% had moderate ($n = 90$) to heavy ($n = 73$) staining for smooth muscle cells, and 69% had moderate ($n = 46$) to heavy ($n = 104$) staining for calcifications. Macrophage staining was only moderate ($n = 36$) to heavy ($n = 7$) in 20%, and a lipid core was present in 25% of the

Table I. Patient characteristics*

	All patients N = 217	No restenosis n = 130	Restenosis n = 87	Odds ratio (95% CI)	P value
Age; mean (SD)	67 (9.0)	68 (9.3)	67 (8.5)	0.82 (0.62-1.10) [†]	.19
Gender					
Male	158/217 (73)	104/158 (66)	54/158 (34)	0.41 (0.22-0.75)	.004 [§]
Female	59/217 (27)	26/59 (44)	33/59 (56)	—	—
Operation Indication				Reference	
Rutherford class III	168/217 (77)	95/168 (57)	73/168 (44)		
Rutherford class IV	26/217 (12)	18/26 (69)	8/26 (31)	0.58 (0.24-1.40)	.23
Rutherford class V-VI	23/217 (11)	17/23 (74)	6/23 (26)	0.46 (0.17-1.22)	.12
Operation type/operated artery					
CFAE	124/217 (57)	98/124 (79)	26/124 (21)	0.14 (0.08-0.26)	<.001 [§]
RSFAE	93/217 (43)	32/93 (34)	61/93 (66)	—	—
Hypertension	158/217 (73)	98/158 (62)	60/158 (38)	0.73 (0.40-1.33)	.30
Hypercholesterolemia	154/217 (71)	91/154 (59)	63/154 (41)	1.13 (0.62-2.05)	.70
Diabetes mellitus	67/217 (31)	39/67 (58)	28/67 (42)	1.11 (0.62-1.99)	.73
Current smoker	83/217 (38)	42/83 (51)	41/83 (49)	1.87 (1.07-3.27)	.03 [§]
Serum creatinine; mean (SD)	99 (56)	99 (65)	99 (41)	1.04 (0.85-1.28) [‡]	.71
Myocardial infarction in past	70/217 (32)	43/70 (61)	27/70 (39)	0.91 (0.51-1.63)	.75
Cerebrovascular event in past	26/217 (12)	15/26 (58)	11/26 (42)	1.11 (0.48-2.55)	.81
Statin use	170/217 (78)	99/170 (58)	71/170 (42)	1.39 (0.71-2.73)	.34
Aspirin use	175/217 (81)	107/175 (61)	68/175 (39)	0.77 (0.39-1.52)	.45

CFAE, Common femoral artery endarterectomy; CI, confidence interval; n, number; RSFAE, remote superficial femoral artery endarterectomy.

*Data are presented as No. (%) unless otherwise indicated.

[†]Age per 10 years.

[‡]Creatinine per 20 mg/dL.

[§]P < .05.

plaques (n = 162). Intraplaque hemorrhage was present in 65% of all plaques (n = 141).

Duplex ultrasound examinations revealed a restenosis (≥50% lumen reduction) in 87 patients (40%) 12 months postoperatively. Restenosis was present in 56% of women (33 of 59) compared to 34% of men (54 of 158), which was significant. Current smoking was also significantly associated with restenosis (Table I). Restenosis rates were significantly higher in patients who underwent an RSFAE compared to CFAE (61 of 93 [66%] vs 26 of 124 [21%], respectively; Table I). Restenosis occurred after RSFAE in 61 patients. Of these, 38 patients (62%) were symptomatic and needed a reintervention, which consisted of percutaneous transluminal angioplasty in 25, a bypass graft in 11, and open repeat endarterectomy of the proximal SFA with proximal patch plasty in 2. Of the 26 patients with restenosis after CFAE, 4 (15%) needed reintervention, 3 were treated with a repeat endarterectomy of the CFA with proximal patch plasty, and 1 patient was treated with a renewed bypass graft.

In univariate analyses, the presence of collagen and smooth muscle cells were significantly (P < .001) associated with restenosis (Fig 2). The risk that stenosis would develop was higher in patients with moderate or heavy collagen or smooth muscle cell staining in their plaque with odds ratios (ORs) of 2.90 (95% confidence interval [CI], 1.82-4.68) and 2.20 (95% CI, 1.50-3.20), respectively, than in patients who showed no or minor staining of collagen or smooth muscle cells in their femoral plaque. In addition, heavy staining for calcification was inversely related (P = .001) with restenosis rates (OR, 0.67; 95% CI,

0.53-0.86). The presence of macrophages, lipid core, or intraplaque hemorrhage was not related with restenosis development (Fig 2).

Of the total 87 patients with restenosis (≥50% lumen reduction with duplex ultrasound scan) 12 months postoperatively, 5 patients were detected with a restenosis by ultrasound duplex scan at 3 months, another 36 patients at 6 months, and another 46 patients at their 12-month follow-up. We could not show a significant difference in plaque histology between patients suffering from early restenosis (<6 months) compared with patients suffering from late (>6 months) restenosis (data not shown).

When the histologic plaque characteristics between the CFA and SFA were compared, staining for calcification, collagen, and smooth muscle cells differed significantly between the two femoral arteries (Fig 3). Moderate to heavy staining for collagen was significantly more prevalent in the SFA (89 of 93 [96%]) compared to the CFA (99 of 124 [80%]; P < .001). Moderate to heavy staining for smooth muscle cells also seemed more prevalent in the SFA (83 of 93 [89%]) compared to the CFA (80 of 124 [65%]; P < .001). Moderate to heavy calcifications were significantly more present in the CFA (94/124 [76%]) than in the SFA (56 of 93 [60%]; P < .001). Intraplaque hemorrhage, lipid core, and macrophages did not differ significantly between the CFA and SFA plaques (Fig 3).

Collagen, calcification, or smooth muscle cell content in the plaque did not correlate with the presence or absence of diabetes, use of statins, or use of aspirins (data not shown).

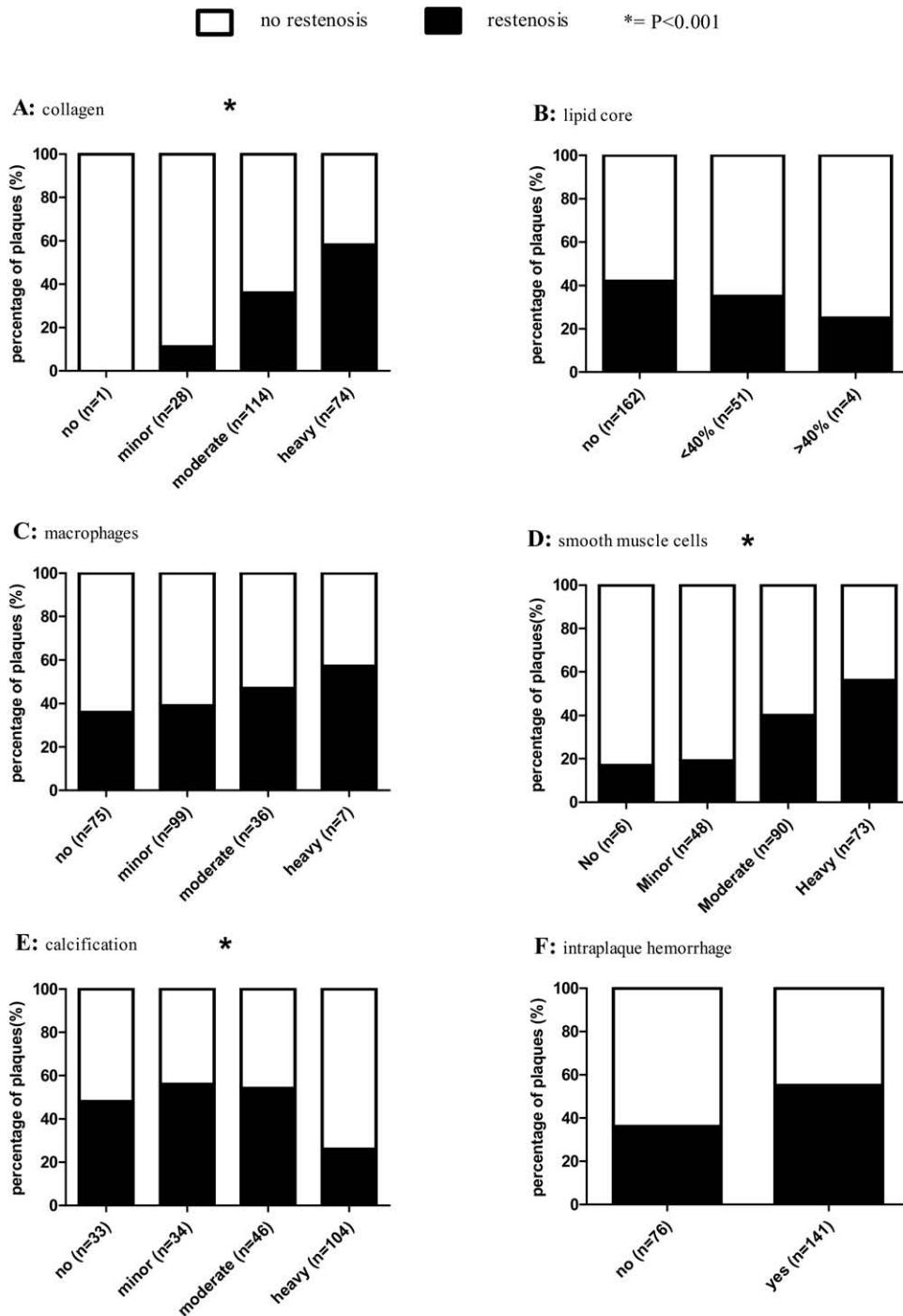


Fig 2. Plaque characteristics in relation to restenosis. Different plaque characteristics in relation to restenosis after endarterectomy of the femoral arteries. **A**, collagen; **B** lipid core; **C** macrophages; **D** smooth muscle cells; **E** calcification; **F** intraplaque hemorrhage. *P < .001.

To determine whether histologic plaque characteristics were independent predictors for restenosis, we performed a multivariate analysis. The initial variable set consisted of gender, age, severity of ischemia, operation (CFAE or

RSFAE), collagen, smooth muscle cells, heavy staining for calcification, and current cigarette smoking. Type of operation (CFAE or RSFAE), collagen staining, and gender were independent predictive parameters for restenosis de-

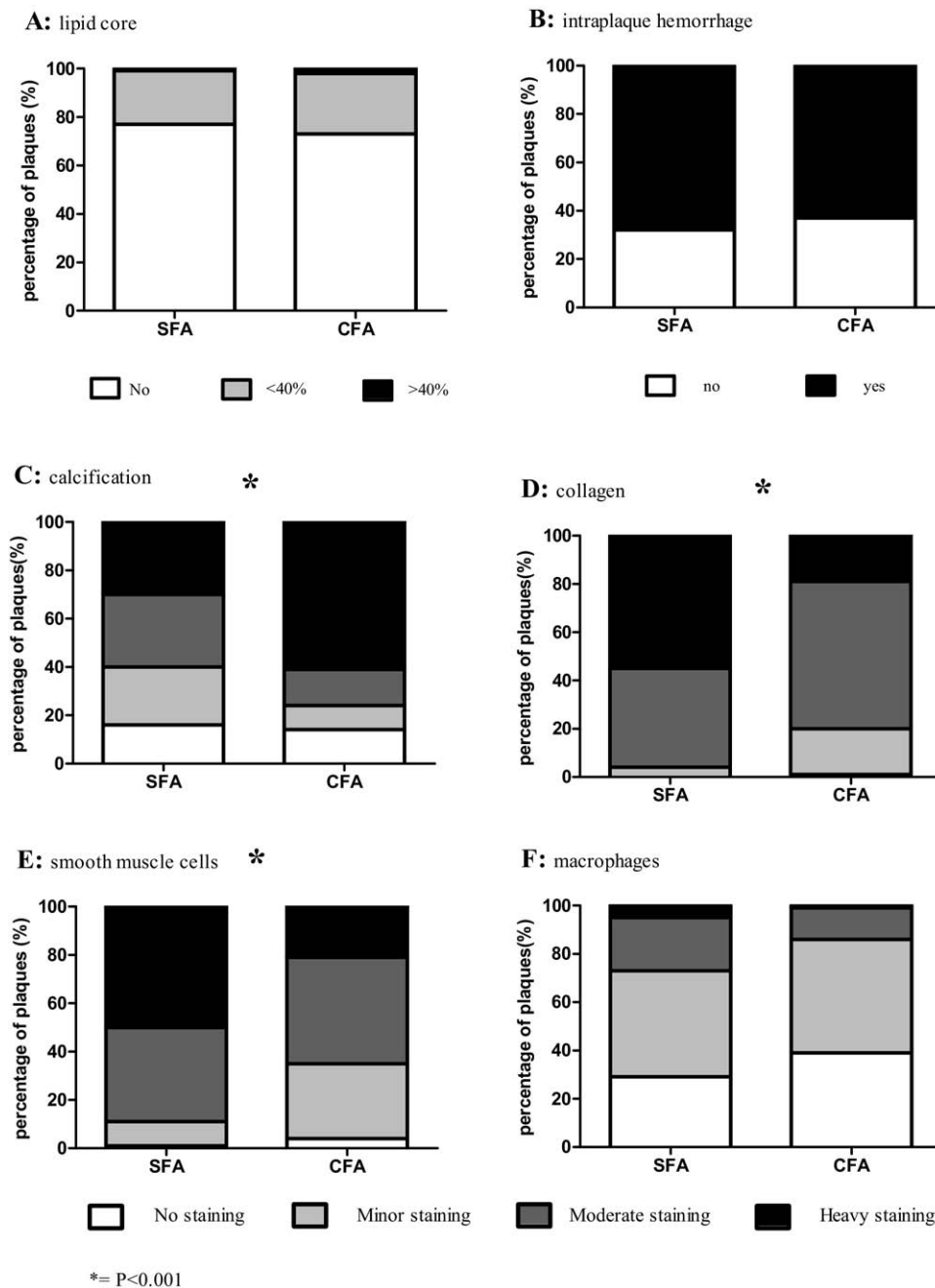


Fig 3. Plaque characteristics in relation to operation (common femoral artery endarterectomy [CFAE] or remote superficial femoral artery endarterectomy [RSFAE]). Different plaque characteristics for the common femoral artery (CFA) and the superficial femoral artery (SFA). **A**, lipid core; **B**) intraplaque hemorrhage; **C**) calcification; **D**) collagen; **E**) smooth muscle cells; and **F**) macrophages. * $P < .001$.

velopment after femoral endarterectomy (Table II). In our cohort, there was no interaction between collagen and type of artery or between collagen and gender.

DISCUSSION

This is the first study, to our knowledge, that provides evidence that histology of the dissected femoral plaque

hides predictive value for risk of restenosis after CFAE and RSFAE. Logically, the operation type is a strong independent predictor for restenosis: CFAE and RSFAE are different surgical techniques, and RSFAE is performed for TASC C/D lesions, while CFAE for TASC A/B. However, when we corrected for the operation type, and inherent to this for the different TASC lesions, moderate to heavy staining of

Table II. Multivariate logistic regression analysis*

	Odds ratio (95% CI)	P value
Gender		
Male	0.33 (0.15-0.69)	.003
Female	—	
Operation type/operated artery		
CFAE	0.02 (0.00-0.17)	<.001
RSFAE	—	
Collagen	1.87 (1.03-3.37)	.038
Smooth muscle cells	0.69 (0.34-1.38)	.29
Interaction smooth muscle cells - type of artery (CFA or SFA)	0.02 (1.16-7.20)	.02
Calcification (heavy staining)	0.53 (0.26-1.07)	.075

CFA, Common femoral artery; CFAE, common femoral artery endarterectomy; RSFAE, remote superficial femoral artery endarterectomy; SFA, superficial femoral artery.

*With backward exclusion of nonsignificant variables using log-rank test.

collagen in the dissected plaque seemed to be an independent variable for restenosis. Furthermore, we observed that the histologic plaque characteristics differ between the CFA and SFA.

Reported restenosis rates seem high in this study compared to other literature.^{5,8} Published studies on CFAE or RSFAE reported primary patency rates, which is defined as uninterrupted patency without any procedures performed on the target lesion. We reported restenosis rates and scored all patients with a lumen reduction of 50% or more as restenotic lesion, although a substantial number of asymptomatic patients were treated conservatively.

A recent published article of our group showed that the inflammatory unstable carotid plaques with high content of macrophages and a large lipid core were associated with less restenosis, probably due to inflammatory activity in the vascular wall, which elicits expansive remodeling.³ In this study, we determined that the fibrotic (stable plaque) features of femoral artery plaques, like collagen and smooth muscle cells, were associated with a higher incidence of restenosis, whereas the inflammatory plaque characteristics were not. Although these results may suggest conflicting observations between the carotid and femoral artery with respect to restenosis prediction, the observation supports the underlying concept that stable plaques are associated with a higher restenosis rate. The different plaque characteristics (eg, low content of macrophages and absence of a lipid core vs high collagen and smooth muscle cell content) are considered determinants of the same plaque type: the stable fibrous plaque.

It has been demonstrated that inflammatory carotid plaque characteristics are less prevalent in patients with a longer time interval between the clinical onset of symptoms (eg, stroke) and carotid endarterectomy.⁹ Owing to the current treatment policy of supervised walking exercise after the start of intermittent claudication, patients are often operated on several years after the initiation of ischemic complaints, whereas carotid endarterectomy generally

occurs within 1 month after the first ischemic event. This may partly explain why inflammatory characteristics in the femoral plaque were much less prevalent than fibrous characteristics.

We can only hypothesize about the mechanism for the increased restenosis rates when fibrous, collagen-rich plaques have been dissected. Previously, fibrotic characteristics of the femoral plaque have been associated with constrictive remodeling (arterial shrinkage or negative remodeling). Postmortem studies have demonstrated that constrictive remodeling is an important determinant of lumen decrease in the femoral artery.¹⁰ In addition, femoral and coronary arteries with the smallest vessel area encompass plaques that show fewer inflammatory cells and are more fibrous.¹¹⁻¹³ Other studies described that collagen accumulation results in arterial shrinkage analogous to scar constriction.¹⁴ A likely assumption is that the occluded femoral artery will shrink over time due to fibrotic remodeling, subsequently resulting in a smaller lumen area after intervention and increased restenosis rates.

To our knowledge, this is the first study showing differences in plaque phenotype between the CFA and SFA. The SFA plaques contained significantly more collagen compared to the CFA plaques, and this characteristic was associated with different restenosis rates between these arteries. Our results may also have implications for other vascular territories. For instance, it is appreciated that the left anterior descending coronary artery is more prone for restenosis after intervention than the other coronary arteries.¹⁵ The reason for this remarkable difference is not clear. One hypothesis is that, like the femoral and carotid arteries, the difference in patency rates after intervention of other vascular territories may also be associated with differences in plaque characteristics.

It is known from literature that race is of influence on atherosclerotic disease. For example, blacks have larger coronary lumen and areas enclosed by internal elastic lamina compared with whites, and Indian Asians have less lower limb atherosclerosis than Europeans, unexplained by established risk factors.^{16,17} Because only white Europeans were included in this study, we can only speculate that race will be of influence on histologic femoral plaque findings.

Study limitations. This study had several limitations. First, we can only speculate about the possibility of arterial shrinkage (negative remodeling) as an explanation for the current observations. Future research has to confirm our hypothesis that constrictive remodeling and subsequently reduced vessel size and residual lumen are reasons for lower patency rates after endarterectomy. Second, we included patients operated on with two different techniques (CFAE and RSFAE), and inherent to these operations, the TASC lesions that were operated on were also different. However, this is intrinsic to the different arteries that were operated on, and besides, we corrected for this in the multivariate analysis.

Third, according to our study design, we defined the lesion with the greatest plaque burden as the culprit lesion.⁴ We assume that this is the most representative lesion of the

total plaque. We did not examine different lesions in a single patient. The assumption that the histology of the culprit lesion is consistent in the total plaque might be a study limitation.

This study has multiple clinical applications. To our knowledge, this is the first study to prove that femoral plaque histology could predict increased risk of restenosis after endarterectomy. Furthermore, it has been determined that plaque histology differs between the common and superficial femoral artery. This may point to new clues for the understanding of the mechanisms of predicting and preventing restenosis in both arterial territories.

Besides, individual risk assessment for restenosis is needed to improve patency rates after femoral endarterectomy. The new concept that plaque histology can predict restenosis rates, will likely contribute to this. Fourth, our results can be helpful for developing strategies for incorporating imaging of atherosclerotic plaques into clinical trials.

The authors are convinced that structural histologic analysis of the dissected femoral plaque could be an important factor for predicting restenosis after endarterectomy. Restenosis after femoral endarterectomy is still a major complication. Using histologic plaque characteristics for the prediction of restenosis is a new concept. Together with other risk factors, plaque histology could be of influence on the intensity of the follow-up scheme of the individual patient.

This study will certainly influence the indication for RSFAE. We may conclude that women with collagen-rich plaques should be considered as high-risk patients for restenosis post-RSFAE, and venous bypass grafting is the preferred operation for this subgroup. When venous material is lacking, we think that women can be treated by RSFAE, but they require more stringent follow-up to identify early restenosis.

CONCLUSION

Plaque composition of the CFA and SFA differs. Furthermore, the presence of a fibrous collagen-rich atherosclerotic plaque is an independent predictive variable for restenosis after CFAE and RSFAE.

The authors thank Dr C.L.J.J. Kruitwagen for his expert opinion and help with our statistical analysis.

AUTHOR CONTRIBUTIONS

Conception and design: WD, JV, AV, DK, FM, GP
Analysis and interpretation: WD, JV, AV, DK, FM, GP
Data collection: WD, EV, JV
Writing the article: WD, JV, FM, GP
Critical revision of the article: WD, JV, AV, EV, JV, DK, FM, GP
Final approval of the article: WD, JV, AV, EV, JV, DK, FM, GP
Statistical analysis: WD, DK, GP
Obtained funding: Not applicable
Overall responsibility: GP

REFERENCES

- Owens CD, Ho KJ, Conte MS. Risk factors for failure of lower-extremity revascularization procedures: are they different for bypass and percutaneous procedures? *Semin Vasc Surg* 2008;21:143-53.
- Sabeti S, Mlekusch W, Amighi J, Minar E, Schillinger M. Primary patency of long-segment self-expanding nitinol stents in the femoropopliteal arteries. *J Endovasc Ther* 2005;12:6-12.
- Hellings WE, Moll FL, De Vries JP, Ackerstaff RG, Seldenrijk CA, Met R, et al. Atherosclerotic plaque composition and occurrence of restenosis after carotid endarterectomy. *JAMA* 2008;299:547-54.
- Verhoeven BA, Velema E, Schoneveld AH, de Vries JP, de Bruin P, Seldenrijk CA, et al. Athero-express: differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. *Eur J Epidemiol* 2004;19:1127-33.
- Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP. Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. *J Vasc Surg* 2008;48:872-7.
- Rosenthal D, Martin JD, Smeets L, de Vries JP, Gisbertz SS, Wellons ED, et al. Remote superficial femoral artery endarterectomy and distal aSpire stenting: results of a multinational study at three-year follow-up. *J Cardiovasc Surg (Torino)* 2006;47:385-91.
- Hellings WE, Pasterkamp G, Vollebregt A, Seldenrijk CA, de Vries JP, Velema E, et al. Intraobserver and interobserver variability and spatial differences in histologic examination of carotid endarterectomy specimens. *J Vasc Surg* 2007;46:1147-54.
- Gisbertz SS, Ramzan M, Tutein Nolthenius RP, van der Laan L, Overtom TT, Moll FL, et al. Short-term results of a randomized trial comparing remote endarterectomy and supragenicular bypass surgery for long occlusions of the superficial femoral artery [the REVAS trial]. *Eur J Vasc Endovasc Surg* 2009;37:68-76.
- Peeters W, Hellings WE, de Kleijn DP, de Vries JP, Moll FL, Vink A, et al. Carotid atherosclerotic plaques stabilize after stroke: insights into the natural process of atherosclerotic plaque stabilization. *Arterioscler Thromb Vasc Biol* 2009;29:128-33.
- Pasterkamp G, Wensing PJ, Post MJ, Hillen B, Mali WP, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. *Circulation* 1995;91:1444-9.
- Pasterkamp G, Schoneveld AH, van der Wal AC, Haudenschild CC, Clarijs RJ, Becker AE, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. *J Am Coll Cardiol* 1998;32:655-62.
- Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 2000;101:598-603.
- Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002;105:939-43.
- Brasselet C, Durand E, Addad F, Al Haj Zen A, Smeets MB, Laurent-Maquin D, et al. Collagen and elastin cross-linking: a mechanism of constrictive remodeling after arterial injury. *Am J Physiol Heart Circ Physiol* 2005;289:H2228-33.
- Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710-7.
- Litovsky SH, Farb A, Burke AP, Rabin IY, Herderick EE, Cornhill JF, et al. Effect of age, race, body surface area, heart weight and atherosclerosis on coronary artery dimensions in young males. *Atherosclerosis* 1996;123:243-50.
- Chaturvedi N, Coady E, Mayet J, Wright AR, Shore AC, Byrd S, et al. Indian Asian men have less peripheral arterial disease than European men for equivalent levels of coronary disease. *Atherosclerosis* 2007;193:204-12.

Submitted Jan 31, 2010; accepted Mar 24, 2010.