Intermittent Claudication: Clinical Effectiveness of Endovascular Revascularization versus Supervised Hospital-based Exercise Training—Randomized Controlled Trial[1]

Sandra Spronk, PhD
Johanna L. Bosch, PhD
Pieter T. den Hoed, MD, PhD
Hermanus F. Veen, MD, PhD
Peter M. T. Pattynama, MD, PhD
M. G. Myriam Hunink, MD, PhD

Purpose: To compare clinical success, functional capacity, and quality of life during 12 months after revascularization or supervised exercise training in patients with intermittent claudication.

Materials and Methods: This study had institutional review board approval, and all patients gave written informed consent. Between September 2002 and September 2005, 151 consecutive patients who presented with symptoms of intermittent claudication were randomly assigned to undergo either endovascular revascularization (angioplasty-first approach) ($n = 76$) or hospital-based supervised exercise ($n = 75$). The outcome measures were clinical success, functional capacity, and quality of life after 6 and 12 months. Clinical success was defined as improvement in at least one category in the Rutherford scale above the pretreatment level. Significance of differences between the groups was assessed with the unpaired t test, χ^2 test, or Mann-Whitney U test. To adjust outcomes for imbalances of baseline values, multivariable regression analysis was performed.

Results: Immediately after the start of treatment, patients who underwent revascularization improved more than patients who performed exercise in terms of clinical success (adjusted odds ratio [OR], 39; 99% confidence interval [CI]: 11, 131; $P < .001$), but this advantage was lost after 6 (adjusted OR, 0.9; 99% CI: 0.3, 2.3; $P = .70$) and 12 (adjusted OR, 1.1; 99% CI: 0.5, 2.8; $P = .73$) months. After revascularization, fewer patients showed signs of ipsilateral symptoms at 6 months compared with patients in the exercise group (adjusted OR, 0.4; 99% CI: 0.2, 0.9; $P < .001$), but no significant differences were demonstrated at 12 months. After both treatments, functional capacity and quality of life scores increased after 6 and 12 months, but no significant differences between the groups were demonstrated.

Conclusion: After 6 and 12 months, patients with intermittent claudication benefited equally from either endovascular revascularization or supervised exercise. Improvement was, however, more immediate after revascularization.

[1] From the Vascular Laboratory (S.S.) and Department of Surgery (P.T.d.H., H.F.V.), Ikazia Hospital, Rotterdam, the Netherlands; Department of Epidemiology and Biostatistics (S.S., J.L.B., M.G.M.H.) and Department of Radiology (S.S., J.L.B., P.M.T.P., M.G.M.H.), Erasmus MC–University Medical Center Rotterdam, Room Ee 2140b, Postbus 2040, 3000 CA Rotterdam, the Netherlands; and Department of Health Policy and Management, Harvard School of Public Health, Boston, Mass (M.G.M.H.). Received April 10, 2008; revision requested June 8; revision received June 26; accepted July 14; final version accepted July 23. **Address correspondence to** S.S. (e-mail: *s.spronk@erasmusmc.nl*).

Intermittent claudication (Rutherford category 1, 2, or 3) is a lifestyle-limiting manifestation of peripheral arterial disease (1,2). The prevalence varies from 3% to 6% in patients aged 40 to 60 years (3). As individuals in Western society age, the incidence of intermittent claudication is expected to increase, making questions related to its treatment pertinent (4).

Exercise training is recommended as an initial treatment for intermittent claudication by the TransAtlantic Inter-Society Consensus (TASC) (3). Endovascular revascularization, however, is becoming more common, presumably because its immediate benefit may prevent unnecessary disability (3).

In a randomized controlled trial, we compared clinical success, functional capacity, and quality of life during 12 months of follow-up after endovascular revascularization or supervised hospital-based exercise training in patients with intermittent claudication.

Advances in Knowledge

- To our knowledge, prior to the current randomized controlled trial, there was no level I evidence with respect to the combined outcome measures clinical success, quality of life, and functional capacity of endovascular revascularization versus hospital-based exercise for intermittent claudication.
- Although the efficacy of supervised exercise programs compared with unsupervised exercise programs remains controversial, this randomized controlled trial shows the benefit of a hospital-based exercise program.
- The results from the current randomized controlled trial demonstrate that after 6 and 12 months, patients with intermittent claudication benefited equally from either endovascular revascularization or supervised exercise; this may lead to further research with revascularization plus supervised exercise training as a treatment arm.

Materials and Methods

In a single-center (Ikazia Hospital) randomized controlled trial (5) in a large community (Rotterdam, the Netherlands), the clinical effectiveness of primary endovascular revascularization was compared with supervised hospital-based exercise training as the initial treatment for patients with intermittent claudication (Rutherford category 1, 2, or 3). We adhered to the guidelines of Good Clinical Practice and the Consolidated Standards of Reporting Trials (6). The institutional review board approved the study, and all patients gave written informed consent for participation in the trial and for endovascular revascularization (if randomly assigned to this treatment arm).

Patients

From September 2002 to September 2005, all new patients with symptoms of intermittent claudication who were referred to the Department of Vascular Surgery were considered for recruitment (Figure). Inclusion criteria were as follows: *(a)* Rutherford category 1, 2, or 3 claudication with a duration of 3 months or longer, *(b)* a maximum pain-free walking distance of less than 350 m (almost 2 miles) (7), *(c)* an ankle-brachial index (ABI) of less than 0.9 at rest or an ABI that decreased by more than 0.15 after the treadmill test, *(d)* one or more vascular stenoses of greater than 50% diameter reduction at the iliac or femoropopliteal level at magnetic resonance angiography, *(e)* all criteria having been met for inclusion, and *(f)* informed consent. Exclusion criteria were as follows: *(a)* abdominal aortic aneurysm, *(b)* life-incapacitating cardiac disease (New York Heart Association class III and higher [8]), *(c)* multilevel disease (ie, same-side stenoses at both the iliac and femoral levels, requiring multiple revascularization procedures), *(d)* isolated tibial artery disease, *(e)* lesions deemed unsuitable for revascularization (iliac or femoropopliteal TASC type D and some TASC type B and/or C lesions, such as a unilateral external iliac occlusion that involved the origins of the internal iliac and/or common femoral artery or single or multiple femoral popliteal lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass procedure [9]), and *(f)* prior treatment for the lesion (including exercise training). Multiple stenoses localized in one iliac arterial segment (ie, the common iliac or external iliac artery) were classified as a single lesion in the analyses. Vascular surgeons and interventional radiologists decided by consensus to include patients at the multidisciplinary vascular conference.

Each patient was assigned to a specific treatment arm by using a computer-generated block-randomized list (block

Implications for Patient Care

- The general consensus is that all patients presenting with symptoms of intermittent claudication should initially be treated with exercise training and that only if symptoms fail to improve should invasive procedures be considered.
- This randomized controlled trial showed that endovascular revascularization provides immediate benefit and therefore may prevent a patient's unnecessary disability.

Published online
10.1148/radiol.2501080607

Radiology 2009; 250:586–595

Abbreviations:
ABI = ankle-brachial index
CI = confidence interval
OR = odds ratio
SF-36 = 36-Item Short-Form Health Survey
TASC = TransAtlantic InterSociety Consensus

Author contributions:
Guarantors of integrity of entire study, S.S., P.T.d.H., H.F.V., M.G.M.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, S.S., P.T.d.H., H.F.V.; clinical studies, S.S., P.T.d.H., H.F.V., M.G.M.H.; statistical analysis, all authors; and manuscript editing, all authors

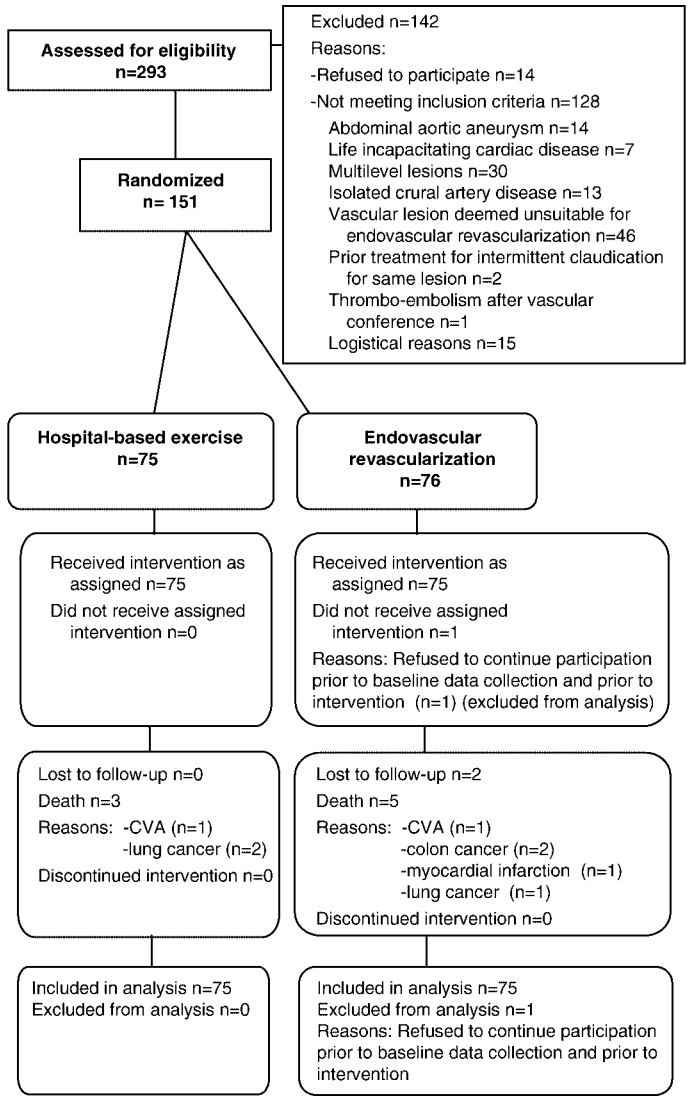
Authors stated no financial relationship to disclose.

size, 16) that had been prepared in advance by an independent statistician, was sealed for every particular patient, and was not accessible to the local trial coordinator (S.S.).

Interventions

Endovascular revascularization was performed by one of three interventional radiologists, each with more than 10 years of experience. Revascularization was performed by using a 10% oversized balloon (Powerflex or Opta-Pro; Cordis Johnson & Johnson, Miami, Fla). For iliac revascularization, the initial balloon angioplasty was considered technically successful if the mean residual pressure gradient across the treated arterial segment was less than 10 mm Hg at rest. If the balloon angioplasty failed, a self-expanding nitinol stent (Luminexx; Bard, Tempe, Ariz) was placed. For femoral revascularization, the decision to place an additional self-expanding nitinol stent (Luminexx) was based on results of angiography performed after balloon angioplasty (residual lumen diameter, <50%) rather than on a persistent pressure gradient. In all cases in which a stent was required, stent diameters were chosen with the aim of 1-mm oversizing and on the basis of the vessel diameter proximal and distal to the area of the stenosis. Iliac or femoral occlusions were treated with conventional guidewire recanalizations.

Supervised exercise was performed over 24 weeks on a walking treadmill (30 minutes per session, twice weekly) and was supervised by a vascular technologist (including S.S., with 10 years of experience). This is consistent with the practice in many previous clinical trials of supervised exercise in patients with intermittent claudication (10) and was considered the maximum attainable number of sessions in our setting. Treadmill exercise was initiated at a workload of 3.5 km/h without a graded incline. Patients decreased the workload to 1 km/h when, in their perception, maximum claudication pain occurred and continued exercising at this reduced workload until the pain subsided (1–3 minutes), after which the workload was increased again. If a patient's maximum pain-free walking distance increased, the workload was increased by modifying the treadmill grade and/or speed to ensure the stimulus of claudication pain during the workout. In addition, all patients were instructed to walk for at least 30 minutes three times a week outside the hospital setting. After the 24-week supervised exercise program, patients were instructed to continue their walking exercise daily in their own environment without supervision and with claudication pain as a guide. Patients received tips for keeping their exercise motivation strong, such as scheduling structured exercise on a "to-do" list, trying to get an exercise buddy, or visiting a fitness center with



Flow diagram of study (according to Consolidated Standards of Reporting Trials statement) shows reasons for exclusion, random assignment to endovascular revascularization or supervised hospital-based exercise training, and treatment actually received, including 6- and 12-month follow-up. *CVA* = cerebrovascular accident.

a treadmill. Between 6 and 12 months, we did not evaluate daily exercise until the follow-up visit at 12 months.

Patients in the revascularization group did not perform a similar exercise program but were given general recommendations concerning lifestyle changes according to the guidelines for cardiovascular disease prevention (11,12). In addition to revascularization or exercise training, all patients underwent atherosclerotic risk factor treatment performed by a designated study internist that included hypertension, serum glucose, cholesterol, lipid profile, and homocysteinemia (in patients <50 years of age) management, and all patients were prescribed aspirin therapy (100 mg/d). All smokers were advised of the health hazards of smoking, were strongly and repeatedly advised to quit smoking, and were offered a smoking-cessation program. Although risk factor management continued during follow-up, we did not evaluate the effect as part of our study.

Clinical Effectiveness

Clinical effectiveness included clinical success, functional capacity, and quality of life. We defined clinical success as an improvement in at least one category in the Rutherford scale (7) above the pretreatment level, measured after treadmill walking (3.5 km/h, no graded incline). Clinical success was measured 1 week after revascularization or after the first two exercise sessions (ie, 1 week) and at 6- and 12-month follow-up. Furthermore, we determined whether clinical success at follow-up was impaired by recurring symptoms of intermittent claudication in the initial symptomatic leg (ipsilateral) or by new symptoms in the contralateral leg by using the presence of symptoms in either extremity as a binary outcome (yes or no). We defined contralateral symptoms as the first occurrence of any contralateral symptoms in the limb, including claudication and rest pain that were not the indication for the initial treatment.

Functional capacity was expressed in terms of ABI, maximum pain-free walking distance, and maximum walking distance. The ABI was measured at rest and after treadmill walking (3.5 km/h, no graded incline), and maximum and pain-free walking distances were reported. Clinical success and functional capacity were both evaluated by an independent observer who was blinded to the specific treatment that had been assigned, and patients were instructed not to discuss their assigned treatment.

Quality of life was assessed by using the generic Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (13) and the disease-specific Vascular Quality of Life Questionnaire (14). The SF-36 helps evaluate the physical, social, and physical-role functioning of patients and elicits their perceptions of their general health and well-being in eight health dimensions (13). On the basis of the results of a previous study (15), we determined that four of these dimensions were relevant to intermittent claudication (physical functioning, role limitations due to physical problems, bodily pain, and general health perceptions), whereas the other four were not (social functioning, role limitations due to emotional problems, mental health, and change in health during the past year). The scoring per dimension was valued on a 100-point scale, from 0 (worst outcome) to 100 (best outcome). The Vascular Quality of Life Questionnaire was developed especially for patients with peripheral arterial disease and is responsive to subtle treatment effects (14). The questionnaire contains 35 questions subdivided into five dimensions (activity, symptom, pain, emotion, and social functioning). Each question has a seven-point response option. Patients' responses were converted to a scale ranging from 1 (worst outcome) to 7 (best outcome).

In addition, the EuroQol-5D rating scale and costs were assessed. The EuroQol-5D is a multiattribute utility instrument that assesses quality of life values from the societal perspective and helps classify patients into a health state (16). For each health state, a value was calculated by using the Dutch scoring algorithm, which was derived from the general population (17): 0 equates to death, and 1 equates to maximum health. The rating scale required the respondent to rate his or her overall health on a scale from 0 to 100, where 0 represents death and 100 represents perfect health (18). These results are reported separately in an article focusing on cost-effectiveness (19).

Statistical Analysis

The required sample size was estimated on the basis of the primary outcome: mean improvement in quality of life. Approximately 40%–50% of patients were expected to have a substantial reduction in their symptoms, as measured with the physical functioning dimension of the SF-36, after 6 months (15,20). A difference of 20%–25% between the treatment groups was considered to be clinically relevant on the basis of a difference of approximately 25% in the physical functioning dimension between the general population and patients with symptoms of intermittent claudication (21). To demonstrate a difference of 25% with $\alpha = .05$, a power of .80, and a two-sided test of differences in unpaired proportions with an estimated 45% improvement in the control group required 68 patients in each trial arm (total, 136). To compensate for some loss to follow-up, we recruited 15 extra patients; this was based on our prior experience with clinical studies.

Results were analyzed according to the intention-to-treat principle: Once a patient was randomly allocated, the patient remained in the allocated group for analysis regardless of whether crossover occurred or whether follow-up was completed. Only patients who withdrew immediately after randomization—thus, prior to data collection and intervention—were excluded from analysis. In a sensitivity analysis, we performed a per-protocol (on-treatment) analysis in which only data in patients who completed the entire trial in the allocated treatment arm (60 in the revascularization group and 61 in the exercise therapy group) (22) were analyzed.

A small number of variable values (96 of 2400) were missing, namely for patients who died or who refused follow-up. Because no patients died of peripheral arterial disease, and because no relationship was found between missing values and treatment arm, follow-up period, or variable, we assumed

the values were missing at random. In the analyses, mean values for clinical success, functional capacity, and quality of life at 6- and 12-month follow-up were imputed singly and unconditionally (23,24). As relatively few values were missing, we did not use more sophisticated methods. Significance of differences between group means was assessed by using the unpaired *t* test or the Mann-Whitney *U* test, as appropriate, whereas dichotomous outcomes were assessed with the χ^2 test.

In a Cox proportional hazards analysis, an event was defined as death, crossover, additional treatment, or clinical failure. To assess differences in clinical success rate between treatment groups, we calculated the actual numbers of the success rate for each treatment group and used logistic regression to determine the adjusted odds ratios (ORs) of revascularization versus exercise at 1-week and 6- and 12-month follow-up. To assess interactions between treatment strategy and disease level (iliac vs femoral disease) and between treatment strategy and smoking (fewer than six or six or more cigarettes per day) on clinical success, we added an interaction term to the adjusted model for "treatment group and disease level" or "treatment group and smoking." To avoid overfitting, no other interactions were tested. To assess the effect of stent placement on clinical success in the revascularization group, we performed a χ^2 test. Furthermore, we calculated adjusted ORs to determine if clinical success at follow-up became impaired by recurring ipsilateral symptoms or by new contralateral symptoms.

Significance of differences in mean score improvement between the treatment groups was assessed by using the unpaired *t* test or the χ^2 test. We used multivariate regression analysis. The variables included were baseline scores, age, sex, diabetes mellitus, smoking, hypertension, hyperlipidemia, and disease severity (mild or moderate claudication vs severe claudication). These variables were selected on the basis of the TASC II report (3) and clinical judgment. To adjust for multiple comparisons, a significance level of .01 (two tailed) was used because approximately five (range, two to eight) comparisons were made for each type of outcome. Calculations were performed by using software (SPSS, version 14.0 for Windows; SPSS, Chicago, Ill).

Results

Patients and Treatments

During the inclusion period, 293 potentially eligible patients were seen at the Department of Vascular Surgery (Figure). Fourteen patients refused to participate, and 128 did not meet the criteria. Thus, 151 patients were enrolled. Of these patients, 76 were randomly assigned to undergo revascularization and 75 were randomly assigned to receive exercise training. One patient refused further participation immediately after randomization and prior to baseline data collection and was therefore excluded from the analysis, leaving 150 patients for analysis (Figure).

Table 1

Baseline Patient Characteristics and Disease Severity

Characteristic	Endovascular Revascularization ($n = 75$)	Hospital-based Exercise ($n = 75$)	*P* Value*
Age (y)	65 ± 11.4	66 ± 9.1	.34
Male sex†	44 (59)	39 (52)	.62
Arterial hypertension†‡	32 (43)	28 (37)	.87
Diabetes mellitus†	11 (15)	15 (20)	.83
Hyperlipidemia†§	40 (53)	38 (51)	.87
History of ischemic heart disease†	14 (19)	21 (28)	.19
Pulmonary disease†	7 (9)	9 (12)	.50
Osteoarthritis of lower limb†	7 (9)	5 (7)	.66
Renal insufficiency†	1 (1)	3 (4)	.35
History of cerebrovascular disease†	8 (11)	4 (5)	.32
Smoking†			.87
Current	12 (16)	17 (23)	
Ever	40 (53)	32 (43)	
Never	23 (31)	25 (33)	
Body mass index (kg/m^2)	26 ± 4.3	25 ± 4.9	.88
ABI‖			
At rest	0.62 ± 0.18	0.63 ± 0.17	.62
After exercise	0.41 ± 0.22	0.42 ± 0.21	.60
Maximum pain-free walking distance (m)	82 ± 48	104 ± 65	.04
Maximum walking distance (m)	174 ± 76	186 ± 97	.62
Rutherford classification†#			.87
1 Or 2	57 (76)	57 (76)	
3	18 (24)	18 (24)	
SF-36 quality of life score**			
Physical functioning	42 ± 26	49 ± 20	.11
Physical-role functioning	37 ± 52	49 ± 45	.18
Pain	50 ± 21	55 ± 23	.18
General health	53 ± 23	54 ± 20	.91
Total Vascular Quality of Life Questionnaire score††	4.2 ± 1.1	4.3 ± 1.1	.79

Note.—Unless otherwise indicated, data are means ± standard deviations.

* Considering multiple statistical tests, $P \leq .01$ was considered to indicate a statistically significant difference.

† Data are numbers of patients, with percentages in parentheses.

‡ Diastolic pressure of more than 95 mm Hg.

§ Cholesterol level of 5.0 mmol/L or greater.

‖ Minimum value of those for right and left legs.

Most severe classification per person.

** On a scale from 0 (worst) to 100 (best).

†† On a scale from 1 (worst) to 7 (best).

The two treatment groups had similar demographic data and comorbidities, and there were no significant differences at baseline in functional capacity or quality of life scores (Table 1). Table 2 shows lesion characteristics. In four patients, revascularization failed technically for the following reasons: failure to enter the vessel ($n = 2$), failure to cross the lesion ($n = 1$), or failure to improve arterial blood flow ($n = 1$). Two of these patients were advised to practice home-based exercise, one received an aortobifurcation graft, and one underwent patch plasty of the common femoral artery. Stents were used in 46 of 71 iliac lesions (34 patients) and in 20 of 40 femoral lesions (16 patients). Asymptomatic iliac and femoral lesions on the contralateral side remained untreated. The two groups had a similar distribution of lesion characteristics and a similar distribution of contralateral symptoms (Table 2).

Table 2

Baseline Lesion Characteristics

Variable	Endovascular Revascularization ($n = 75$)	Hospital-based Exercise ($n = 75$)	*P* Value
Iliac disease	55 (73)	51 (68)	.47
Bilateral	13 (17)	12 (16)	.88
Unilateral in both common and external iliac arteries	3 (4)	5 (7)	.77
Total no. of iliac lesions	71	68	
Stenosis*	62 (87)	61 (90)	.90
Occlusion	9 (13)	7 (10)	.96
Femoral disease	20 (27)	24 (32)	.47
Bilateral	8 (11)	12 (16)	.32
Unilateral with multiple (>1) femoral lesions	5 (7)	6 (8)	.17
Total no. of femoral lesions	40	45	
Stenosis*	23 (58)	29 (64)	.18
Occlusion	17 (42)	16 (36)	.67

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Diameter reduction of 51%–99%.

Table 3

Additional Treatment during Follow-up

Additional Treatment	Endovascular Revascularization ($n = 75$)		Supervised Hospital-based Exercise ($n = 75$)	
	0–6 Months	6–12 Months	0–6 Months	6–12 Months
Home-based exercise	3	0	0	0
Endovascular revascularization with or without stent placement				
Common iliac artery	0	1	2	3
Femoral artery	0	1	2	1
Surgical intervention				
Aortic bifurcation graft	2	0	1	0
Femoral-femoral crossover graft	1	0	0	0
Femoropopliteal bypass	0	0	2	0
Patch plasty of common femoral artery	2	0	0	0

Note.—Data are numbers of patients.

The mean number of sessions in the supervised exercise program was 33 ± 10 (standard deviation) (median, 32). The mean time spent on home-based walking exercise was 4.2 hours per week ± 4.7 (median, 3.5 hours per week) during the first 6 months and 3.4 hours per week ± 3.5 (median, 3.5 hours per week) during the second 6 months. Sixty-nine (92%) of the 75 patients who underwent revascularization responded to the questionnaires at 6 months, and 67 (89%) responded at 12 months. Among the 75 patients in the exercise program, 74 (99%) responded at 6 months, and 72 (96%) responded at 12 months.

During follow-up, 10 patients who underwent revascularization and 11 patients in the exercise program underwent additional treatment (Table 3). Of these patients, eight in the exercise program crossed over to the endovascular revascularization arm, whereas no patient crossed over in the opposite direction. Additional treatment of patients who underwent revascularization was indicated by *(a)* technical failure ($n = 4$ [one iliac occlusion, two femoral occlusions, and one instance of multiple femoral stenoses]) and *(b)* symptomatic and hemodynamic failure ($n = 6$ [two iliac occlusions and four femoral occlusions]). Additional treatment of patients in the exercise program was related to symptomatic failures (three patients with iliac occlusions, five patients with bilateral iliac lesions, and three patients with multiple femoral lesions). Seven patients in the revascularization group experienced minor complications: six hematomas and one small dissection, for which a second stent placement was needed. The patients in the exercise group had no complications. Two patients in the revascularization group, but no patients in the exercise group, were lost to follow-up, while five patients in the revascularization group and three patients in the exercise group died during follow-up (Figure) (unadjusted death rate OR = 1.7; 99% confidence interval [CI]: 0.4, 7.4; $P = .47$). The causes of death were not related to either peripheral arterial disease or the intervention. Adjusted Cox regression

analysis demonstrated that the risk of treatment failure was not significantly different after revascularization versus after exercise (hazard rate ratio, 1.2; 99% CI: 0.6, 2.2; $P = .59$).

Clinical Outcomes

After revascularization, the clinical success rate was 88% at 1 week (66 of 75 patients; 99% CI: 78%, 98%), decreasing to 75% at 6 months (56 of 75 patients; 99% CI: 61%, 88%) and 68% at 12 months (51 of 75 patients; 99% CI: 54%, 82%). After initiation of exercise, the clinical success rate was 16% at 1 week (12 of 75 patients; 99% CI: 5%, 27%), increasing to 77% at 6 months (58 of 75 patients; 99% CI: 64%, 90%) and then decreasing to 65% at 12 months (49 of 75 patients; 99% CI: 51%, 80%). Although clinical success at 1 week was significantly higher with revascularization than with exercise (adjusted OR, 39; 99% CI: 11, 131; $P < .001$), there was no significant difference at 6-month (adjusted OR, 0.9; 99% CI: 0.3, 2.3; $P = .70$) or 12-month (adjusted OR, 1.1; 99% CI: 0.5, 2.8; $P = .73$) follow-up. Clinical success was not significantly associated with the interaction term "treatment group and level of disease" after 6 months (adjusted OR, 3.7; 99% CI: 0.7, 18; $P = .03$) or 12 months (adjusted OR, 0.8; 99% CI: 0.2, 3.3; $P = .71$) or with the interaction term "treatment group and smoking fewer than six cigarettes" after 6 months (adjusted OR, 0.52; 99% CI: 0.1, 4.4; $P = .43$) or 12 months (adjusted OR, 1.5; 99% CI: 0.3, 6.9; $P = .46$). Furthermore, clinical success after endovascularization was not significantly associated with stent placement after 6 months (adjusted OR, 0.8; 99% CI: 0.2, 4.1; $P = .78$) or 12 months (adjusted OR, 0.74; 99% CI: 0.2, 3.2; $P = .59$).

At 6 months, significantly fewer patients in the revascularization group than in the exercise group had symptoms of intermittent claudication on the ipsilateral side on the binary yes-or-no scale (37% vs 69%; adjusted OR, 0.4; 99% CI: 0.2, 0.9; $P < .001$). However, this difference disappeared at 12 months (41% vs 58%; adjusted OR, 0.7; 99% CI: 0.4, 1.3; $P = .25$). More patients in the revascularization group than in the exercise group had new intermittent claudication symptoms on the contralateral side after 6 and 12 months, although the difference was not significant (17% vs 8% [adjusted OR, 2.4; 99% CI: 0.9, 6.7; $P = .09$] and 21% vs 17% [adjusted OR, 1.6; 99% CI: 0.6, 4.2; $P = .34$], respectively).

At 6 and 12 months, patients in both the revascularization and exercise groups showed improvement in mean ABI at rest and after exercise, maximum pain-free walking distance, and maximum walking distance (Table 4). After adjustment for the baseline variables, there were no significant differences in functional capacity between the two groups at 6- or 12-month follow-up. Both revascularization and exercise improved the mean quality of life scores of the SF-36 dimensions and the total Vascular Quality of Life Questionnaire score (Table 5). After adjustment for the baseline variables, there were no significant differences in the quality of life scores between the two groups at 6 or 12 months (Table 5).

The per-protocol analysis demonstrated no substantial differences compared with the results reported above.

Table 4

Mean Improvement in Measures of Functional Capacity during Follow-up Compared with Baseline and Differences between Groups

Measure of Functional Capacity	Mean Score Improvement Compared with Baseline		Adjusted Mean Difference*	Adjusted *P* Value†
	Endovascular Revascularization ($n = 75$)	Hospital-based Exercise ($n = 75$)		
ABI at rest‡				
6 Months	0.14 (0.08, 0.19)	0.03 (−0.01, 0.07)	0.00 (−0.05, 0.05)	.92
12 Months	0.16 (0.10, 0.21)	0.04 (0.00, 0.07)	0.00 (−0.04, 0.04)	.97
ABI after exercise‡				
6 Months	0.27 (0.20, 0.34)	0.14 (0.08, 0.20)	0.01 (−0.06, 0.08)	.69
12 Months	0.27 (0.24, 0.30)	0.20 (0.15, 0.26)	0.01 (−0.04, 0.06)	.58
Maximum pain-free walking distance (m)				
6 Months	679 (519, 837)	899 (743, 1054)	−16 (−32, 2)	.02
12 Months	806 (646, 960)	943 (786, 1099)	24 (−42, 91)	.34
Maximum walking distance				
6 Months	755 (600, 909)	1138 (1006, 1270)	16 (−60, 93)	.58
12 Months	826 (680, 970)	1034 (896, 1170)	24 (−42, 91)	.34

Note.—Data in parentheses are 99% CIs.

* Adjusted for baseline ABI, maximum pain-free walking distance or maximum walking distance, age, sex, severity of disease (mild or moderate versus severe), smoking, hypertension, hyperlipidemia, and diabetes mellitus. Positive difference indicates endovascular revascularization has a better outcome; negative difference indicates supervised hospital-based exercise has a better outcome.

† Considering multiple statistical tests, $P \leq .01$ was considered to indicate a statistically significant difference.

‡ Minimum value of those for right and left legs.

Discussion

This randomized controlled trial evaluated the effect of endovascular revascularization versus supervised hospital-based exercise training on clinical success, functional capacity, and quality of life after 6 and 12 months of follow-up in patients with intermittent claudication. While patients in the revascularization group scored better in clinical success shortly after the start of treatment, the benefit compared with exercise was lost over time. Revascularization reduced ipsilateral symptoms at 6 months, but

this did not translate into improved clinical success, functional capacity, or quality of life when compared with exercise training. After 6 and 12 months, the treatment groups did not differ significantly in functional capacity or quality of life scores.

In a small randomized controlled trial (25,26) evaluating functional capacity in patients with intermittent claudication, maximum walking distance at 6 years was better among patients treated with exercise than among patients treated with angioplasty; however, quality of life outcomes were not reported. A randomized controlled trial comparing angioplasty to conventional medical treatment (27,28) revealed that angioplasty improved neither walking nor quality of life after 2 years. Another randomized controlled trial (29) compared invasive treatment (eg, endovascular or open surgical procedures), exercise, and simple observation in patients with intermittent claudication. These researchers concluded that only invasive therapy improved walking ability; however, compliance with exercise programs was low. A systematic review (20) showed that quality of life at 6-month follow-up improved after either exercise training or angioplasty, whereas functional capacity improved only after angioplasty. That systematic review, however, was limited by the quality of the included studies—not randomized, with insufficient power, inconsistently reported data, and nonstandardized exercise programs.

Several studies (10) have evaluated the efficacy of exercise programs, but the value of supervision remains controversial. Some studies (30,31), particularly in Europe, have shown good results from a home-based program; however, other studies have demonstrated little benefit from home-based exercise (32). Supervised exercise, however, has induced clinical improvement in almost every study (32–35).

The most important limitation of our study was that it was a single-center study performed in the Netherlands with adherence to strict inclusion and exclusion criteria, which may affect the generalizability of the results to other countries. However, the patient population was homogeneous and representative of the typical patient with claudication, as baseline patient characteristics were similar to those of patients in a systematic review of revascularization versus exercise in patients with claudication (20). Our study may also have been limited by lack of power, as it was designed to demonstrate clinically relevant differences, rather than equivalences, in quality of life and because the sample size calculation did not take the multiple comparisons into account. The negligible effect size (indicating no clinically significant difference) was found for practically all outcomes.

Quality of life is a subjective outcome that may be influenced by the perception of individual subjects. Patients in an exercise program might underestimate quality of life because improvement occurs slowly and less noticeably during an exercise program. Conversely, patients who underwent revascularization might overestimate quality of life because improvement is immediate and therefore contrasts with the preintervention state. Furthermore, more patients in the exercise group than in the revascularization group in our study had ipsilateral symptoms at 6 months, even though the proportion of patients with clinical success was equal. This may be most likely related to the specific induction of claudication symptoms during exercise (3).

An additional limitation included lack of use of a graded incline, given that graded treadmill testing is superior to nongraded testing in patients with intermittent claudication (9). Our study was further limited by the revascularization technique used. While our technique reflected clinical practice at the time of the

Table 5

Mean Improvement in Measures of Health-related Quality of Life during Follow-up Compared with Baseline and Differences between Groups

Measure of Quality of Life	Mean Score Improvement Compared with Baseline		Adjusted Mean Difference*	Adjusted *P* Value†
	Endovascular Revascularization ($n = 75$)	Hospital-based Exercise ($n = 75$)		
SF-36 quality of life score‡				
Physical functioning				
6 Months	19 (14, 25)	12 (7, 18)	2 (−3, 8)	0.22
12 Months	17 (12, 22)	13 (8, 18)	2 (−1, 6)	0.10
Physical-role functioning				
6 Months	25 (14, 36)	14 (4, 24)	7 (−5, 19)	0.12
12 Months	21 (10, 32)	6 (−4, 16)	7 (−5, 19)	0.11
Bodily pain				
6 Months	14 (7, 21)	7 (2, 13)	4 (−4, 10)	0.11
12 Months	11 (5, 17)	10 (4, 16)	3 (−3, 8)	0.20
General health				
6 Months	1 (−4, 6)	5 (1, 9)	−1 (−6, 5)	0.74
12 Months	2 (−3, 7)	5 (1, 9)	−1 (−4, 4)	0.73
Vascular Quality of Life Questionnaire score§				
6 Months	0.6 (0.1, 1.1)	0.7 (0.4, 1.0)	0.1 (−0.3, 0.4)	0.08
12 Months	0.7 (0.3, 1.1)	0.6 (0.3, 0.9)	0.1 (−0.2, 0.3)	0.61

* Adjusted for baseline quality of life scores, age, sex, severity of disease (mild or moderate versus severe), smoking, hypertension, hyperlipidemia, and diabetes mellitus. Positive difference indicates endovascular revascularization has a better outcome; negative difference indicates supervised hospital-based exercise has a better outcome.

† Considering multiple statistical tests, $P \leq .01$ was considered indicate a statistically significant difference.

‡ On a scale from 0 (worst) to 100 (best).

§ On a scale from 1 (worst) to 7 (best).

study, better results may be currently achievable with the use of improved stents and changes in practice. For example, we now know that primary stent placement in the femoral arteries results in better patency at 6 and 12 months than the balloon angioplasty–first approach followed here (36,37). In addition, new-generation stents combined with clopidogrel administration have improved patency compared with that of the stent type without clopidogrel used in this study (37).

Another limitation of our study was that exercise treats both limbs, which is an advantage compared with revascularization because one extremity is not discerned from the other and therefore symptoms of the contralateral extremity are treated as well. The severity of baseline ipsilateral symptoms may have disguised contralateral symptoms in some patients. Increased mobility after revascularization would encourage the discovery of the contralateral symptoms. Most patients with bilateral lesions, however, underwent bilateral treatment. Furthermore, as peripheral arterial disease is a two-limb problem, a patient-based analysis of treatment effects is the appropriate approach.

In a previous randomized study (38), albeit one with a small number of patients, the combination of revascularization and home-based exercise was better than either approach to treatment alone. To the best of our knowledge, early intervention plus supervised exercise has never been studied in a large randomized controlled trial, but this combination is certainly an interesting option. Revascularization plus exercise would presumably combine effective short-term relief of claudication symptoms with the added long-term benefits of exercise training. Furthermore, the cost-effectiveness of the combination would need to be evaluated.

In conclusion, our randomized controlled trial demonstrated that endovascular revascularization or supervised hospital-based exercise in patients with claudication yielded similar benefits in terms of clinical success, functional capacity, and quality of life after 6 and 12 months of follow-up, whereas the benefit was more immediate with revascularization.

Acknowledgments: We thank vascular technologists Willeke Dolman and Karin Goederaad for their contributions to data collection; outpatient assistants Miranda Stuijt, Ria Dijkstra, and Els Pors-van Veen for their contributions to follow-up; and the radiology personnel for their contributions to the Comparing Exercise Training and Angioplasty for Claudication study.

References

1. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–1324.
2. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA 2001;286:1599–1606.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(suppl S):S5–S67.
4. Rose G, McCartney P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. Br J Prev Soc Med 1977;31:42–48.
5. Nederlands Trial Register. Trial info: comparing exercise training and angioplasty for claudication—a randomized controlled trial. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=199. Accessed June 10, 2003.
6. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? J Clin Epidemiol 2000;53:964–972.
7. 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.
8. American Thoracic Society. Quality of life resource: New York Heart Association (NYHA) classification. http://www.atsqol.org/sections/instruments/ko/pages/nyhac.html. Accessed January 24, 2006.
9. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000;31(1 pt 2):S1–S296.
10. Wind J, Koelemay MJ. Exercise therapy and the additional effect of supervision on exercise therapy in patients with intermittent claudication: systematic review of randomised controlled trials. Eur J Vasc Endovasc Surg 2007;34:1–9.
11. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14(suppl 2):S1–S113.
12. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388–391.
13. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.
14. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. J Vasc Surg 2001;33:679–687.
15. Bosch JL, van der Graaf Y, Hunink MG. Health-related quality of life after angioplasty and stent placement in patients with iliac artery occlusive disease: results of a randomized controlled clinical trial. The Dutch Iliac Stent Trial Study Group. Circulation 1999;99:3155–3160.
16. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108.
17. Busschbach JJV (personal Web site). FAQ & tools. http://www.xs4all.nl/~jannetvb/busschbach/faq_qoL&euroqol.htm. Accessed March 10, 2005.
18. Froberg DG, Kane RL. Methodology for measuring health-state preferences. II. Scaling methods. J Clin Epidemiol 1989;42:459–471.
19. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. J Vasc Surg. 2008 Sep 3. [Epub ahead of print]
20. Spronk S, Bosch JL, Veen HF, den Hoed PT, Hunink MG. Intermittent claudication: functional capacity and quality of life after exercise training or percutaneous transluminal

angioplasty—systematic review. Radiology 2005;235:833–842.

21. Bosch JL, Hunink MG. The relationship between descriptive and valuational quality-of-life measures in patients with intermittent claudication. Med Decis Making 1996;16:217–225.
22. Schoenfeld PS. Evidence-based medicine in practice: applying intention-to-treat analysis and perprotocol analysis. Am J Gastroenterol 2005;100:3–4.
23. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006;59:1102–1109.
24. Kline R. Principles and practice of structural equation modeling. New York, NY: Guildford, 1998.
25. Creasy TS, Fletcher EW. Angioplasty for intermittent claudication. Clin Radiol 1991;43:81–83.
26. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication: long and medium term results of a prospective, randomised trial. Eur J Vasc Endovasc Surg 1996;11:409–413.
27. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. Eur J Vasc Endovasc Surg 1996;12:167–172.
28. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? a randomized controlled trial. J Vasc Surg 1997;26:551–557.
29. Gelin J, Jivegard L, Taft C, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients. I. 1 year results of functional and physiological improvements. Eur J Vasc Endovasc Surg 2001;22:107–113.
30. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease: implications for the mechanism of the training response. Circulation 1994;90:1866–1874.
31. Jonason T, Ringqvist I, Oman-Rydberg A. Home-training of patients with intermittent claudication. Scand J Rehabil Med 1981;13:137–141.
32. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. Angiology 1997;48:291–300.
33. Regensteiner JG, Hiatt WR. Exercise rehabilitation for patients with peripheral arterial disease. Exerc Sport Sci Rev 1995;23:1–24.
34. Savage P, Ricci MA, Lynn M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. J Cardiopulm Rehabil 2001;21:152–157.
35. Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. J Vasc Surg 1997;25:312–318; discussion 318–319.
36. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. Circulation 2007;115:2745–2749.
37. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol 2005;45:312–315.
38. Nylaende M, Abdelnoor M, Stranden E, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT): the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2007;33:3–12.

Radiology 2009

This is your reprint order form or pro forma invoice

(Please keep a copy of this document for your records.)

Reprint order forms and purchase orders or prepayments must be received 72 hours after receipt of form either by mail or by fax at 410-820-9765. It is the policy of Cadmus Reprints to issue one invoice per order. **Please print clearly**.

Author Name _____
Title of Article _____
Issue of Journal_____ Reprint # _____ Publication Date _____
Number of Pages_____ KB # _____ Symbol Radiology
Color in Article? Yes / No (Please Circle)

Please include the journal name and reprint number or manuscript number on your purchase order or other correspondence.

Order and Shipping Information

Reprint Costs **(Please see page 2 of 2 for reprint costs/fees.)**

_____ Number of reprints ordered $_____
_____ Number of color reprints ordered $_____
_____ Number of covers ordered $_____
Subtotal $_____
Taxes $_____

(*Add appropriate sales tax for Virginia, Maryland, Pennsylvania, and the District of Columbia or Canadian GST to the reprints if your order is to be shipped to these locations*.)

First address included, add $32 for each additional shipping address $_____

TOTAL $_____

Shipping Address **(cannot ship to a P.O. Box) Please Print Clearly**

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity_____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

Additional Shipping Address* **(cannot ship to a P.O. Box)**

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

** Add $32 for each additional shipping address*

Payment and Credit Card Details

Enclosed: Personal Check _____
Credit Card Payment Details _____

Checks must be paid in U.S. dollars and drawn on a U.S. Bank.

Credit Card: __ VISA __ Am. Exp. __ MasterCard
Card Number _____
Expiration Date_____
Signature: _____

Please send your order form and prepayment made payable to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box.

FEIN #:541274108

Invoice or Credit Card Information

Invoice Address **Please Print Clearly**

Please complete Invoice address as it appears on credit card statement

Name _____
Institution _____
Department _____
Street _____
City _____ State _____ Zip _____
Country _____
Phone _____ Fax _____
E-mail Address _____

Cadmus will process credit cards and *Cadmus Journal Services* will appear on the credit card statement.

If you don't mail your order form, you may fax it to 410-820-9765 with your credit card information.

Signature _____ Date _____

Signature is required. By signing this form, the author agrees to accept the responsibility for the payment of reprints and/or all charges described in this document.

RB-1/01/09

Radiology 2009

Black and White Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	$239	$260	$285	$303	$323	$340
5-8	$379	$420	$455	$491	$534	$572
9-12	$507	$560	$651	$684	$748	$814
13-16	$627	$698	$784	$868	$954	$1,038
17-20	$755	$845	$947	$1,064	$1,166	$1,272
21-24	$878	$985	$1,115	$1,250	$1,377	$1,518
25-28	$1,003	$1,136	$1,294	$1,446	$1,607	$1,757
29-32	$1,128	$1,281	$1,459	$1,632	$1,819	$2,002
Covers	$149	$164	$219	$275	$335	$393

International (includes Canada and Mexico)						
# of Pages	50	100	200	300	400	500
1-4	$299	$314	$367	$429	$484	$546
5-8	$470	$502	$616	$722	$838	$949
9-12	$637	$687	$852	$1,031	$1,190	$1,369
13-16	$794	$861	$1,088	$1,313	$1,540	$1,765
17-20	$963	$1,051	$1,324	$1,619	$1,892	$2,168
21-24	$1,114	$1,222	$1,560	$1,906	$2,244	$2,588
25-28	$1,287	$1,412	$1,801	$2,198	$2,607	$2,998
29-32	$1,441	$1,586	$2,045	$2,499	$2,959	$3,418
Covers	$211	$224	$324	$444	$558	$672

Color Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	$247	$267	$385	$515	$650	$780
5-8	$297	$435	$655	$923	$1194	$1467
9-12	$445	$563	$926	$1,339	$1,748	$2,162
13-16	$587	$710	$1,201	$1,748	$2,297	$2,843
17-20	$738	$858	$1,474	$2,167	$2,846	$3,532
21-24	$888	$1,005	$1,750	$2,575	$3,400	$4,230
25-28	$1,035	$1,164	$2,034	$2,986	$3,957	$4,912
29-32	$1,186	$1,311	$2,302	$3,402	$4,509	$5,612
Covers	$149	$164	$219	$275	$335	$393

International (includes Canada and Mexico))						
# of Pages	50	100	200	300	400	500
1-4	$306	$321	$467	$642	$811	$986
5-8	$387	$517	$816	$1,154	$1,498	$1,844
9-12	$574	$689	$1,157	$1,686	$2,190	$2,717
13-16	$754	$874	$1,506	$2,193	$2,883	$3,570
17-20	$710	$1,063	$1,852	$2,722	$3,572	$4,428
21-24	$1,124	$1,242	$2,195	$3,231	$4,267	$5,300
25-28	$1,320	$1,440	$2,541	$3,738	$4,957	$6,153
29-32	$1,498	$1,616	$2,888	$4,269	$5,649	$7028
Covers	$211	$224	$324	$444	$558	$672

Minimum order is 50 copies. For orders larger than 500 copies, please consult Cadmus Reprints at 800-407-9190.

Reprint Cover

Cover prices are listed above. The cover will include the publication title, article title, and author name in black.

Shipping

Shipping costs are included in the reprint prices. Domestic orders are shipped via FedEx Ground service. Foreign orders are shipped via a proof of delivery air service.

Multiple Shipments

Orders can be shipped to more than one location. Please be aware that it will cost $32 for each additional location.

Delivery

Your order will be shipped within 2 weeks of the journal print date. Allow extra time for delivery.

Tax Due

Residents of Virginia, Maryland, Pennsylvania, and the District of Columbia are required to add the appropriate sales tax to each reprint order. For orders shipped to Canada, please add 7% Canadian GST unless exemption is claimed.

Ordering

Reprint order forms and purchase order or prepayment is required to process your order. Please reference journal name and reprint number or manuscript number on any correspondence. You may use the reverse side of this form as a proforma invoice. Please return your order form and prepayment to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box.
FEIN #:541274108

Please direct all inquiries to:

Rose A. Baynard
800-407-9190 (toll free number)
410-819-3966 (direct number)
410-820-9765 (FAX number)
baynardr@cadmus.com (e-mail)

Reprint Order Forms and purchase order or prepayments must be received 72 hours after receipt of form.