The SRGS Recommended Reading List is a carefully selected summary of current, classic, and seminal articles for further study. All of the articles below are cited in the order they appear in the literature review; they also appear in the reference list (53-57).

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1. Sex-based differences in the inflammatory profile of peripheral artery disease and the association with primary patency of lower extremity vein bypass grafts...64-72
   Hiramoto JS, Owens CD, Kim JM, Boscardin J, Belkin M, Creager MA, Conte MS
   The authors provide data supporting the role of persistent inflammation and adverse events following vein bypass revascularization.

2. Critical limb ischemia...73-96
   Blecha MJ
   This is a useful review article that summarizes important features of the diagnosis and management of critical limb ischemia.

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   Conte MS
   Conte provides data comparing open and endovascular approaches for managing patients with severe ischemic disease of the lower extremity region.

4. Acute limb ischemia...103-111
   Creager MA, Kaufman JA, Conte MS
   This review article provides valuable guidance relevant to managing acute ischemic events involving the lower extremity region.

5. Surgical intervention for peripheral arterial disease...112-127
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   This is a valuable review article dealing with managing symptomatic peripheral arterial disease.

6. Emerging national trends in the management and outcomes of lower extremity peripheral arterial disease...128-138
   Hong MS, Beck AW, Nelson PR
   The authors review data showing increasing use of endovascular interventions for managing ischemic disease of the lower extremity region.
Sex-based differences in the inflammatory profile of peripheral artery disease and the association with primary patency of lower extremity vein bypass grafts

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Objective: This study was conducted to determine if there are sex-based differences in the inflammatory phenotype of patients undergoing lower extremity bypass (LEB) and if they correlate with clinical outcomes.

Methods: This was a retrospective analysis of a prospective cohort of 225 patients (161 men and 64 women) who underwent autogenous vein LEB between February 2004 and May 2008. Fasting baseline blood samples were obtained before LEB, and the inflammatory biomarkers high-sensitivity C-reactive protein (CRP) and fibrinogen were assessed. All patients underwent ultrasound graft surveillance. CRP levels were dichotomized at 5 mg/L and fibrinogen levels at 600 mg/dL.

Results: There were no significant differences in age, race, history of hypertension or diabetes mellitus, body mass index, or coronary artery disease between men and women. Men were more likely to be current smokers (P = .02), have a history of hypercholesterolemia (P = .02), and be taking statins (P = .02). Women were more likely to present with critical limb ischemia (P = .03) and had higher median baseline CRP levels (5.15 mg/L; interquartile range [IQR], 1.51-18.62 mg/L) than men (2.70; IQR, 1.24-6.98 mg/L; P = .02). Median follow-up was 893 days (IQR, 539-1315 days). A multivariable Cox proportional hazards model for primary vein graft patency showed a significant interaction between sex and CRP (P = .03) and fibrinogen (P = .02). After adjustment for key covariates, primary vein graft patency was significantly less in women with CRP >5 mg/L compared with women with CRP <5 mg/L (P = .02). No such difference was seen in men (P = .95). Primary graft patency was also decreased in women with fibrinogen >600 mg/dL vs women with fibrinogen <600 mg/dL (P = .002); again, this pattern was not evident in men (P = .19).

Conclusions: Women undergoing LEB for advanced peripheral artery disease have a different inflammatory phenotype than men. Elevated baseline levels of CRP and fibrinogen are associated with inferior vein graft patency in women but not in men. These findings indicate an important interaction between sex and inflammation in the healing response of vein grafts for LEB. Women with elevated preoperative CRP and fibrinogen levels may benefit from more intensive postoperative graft surveillance protocols. (J Vasc Surg 2012;56:387-95.)

Although women have lower overall rates of cardiovascular disease (CVD) than men until the seventh decade of life,1 several population studies have demonstrated higher age-adjusted rates of peripheral artery disease (PAD) in women.2-4 Also, women who undergo lower extremity bypass (LEB) procedures appear to have increased rates of wound complications and lower rates of graft patency than men.5-7 The potential reasons for these poorer outcomes in women include smaller conduit and target vessels, more advanced disease, older age at presentation, and a difference in the underlying state of inflammation in women than in men.

Clinical studies have established that chronic inflammation is a strong risk factor for future atherothrombotic disease. C-reactive protein (CRP) is an acute-phase protein that is elevated in individuals at high risk for myocardial infarction,8-10 stroke,9,11 and cardiovascular death.9 CRP levels are also elevated in individuals with PAD,12,13 and higher CRP levels have been associated with the risk and progression of PAD.14,15 Recent studies have also suggested that preoperative CRP levels are predictive of adverse outcomes after vascular procedures, including LEB surgery.16-18

Fibrinogen, like CRP, is an acute-phase reactant.19 In addition, fibrinogen has important hemostatic properties, as it affects platelet and red cell aggregation as well as endothelial function.19 As a result, high levels of fibrinogen
in plasma might reduce blood flow, predispose to thrombosis, and enhance atherogenesis. Fibrinogen is also critical in inflammation; in an ex-vivo study, fibrinogen was important in mediating leukocyte adhesion to human vein grafts. Fibrinogen predicts the severity of PAD and serves as a marker for the future development of PAD. Moreover, some studies have demonstrated a positive association between plasma fibrinogen levels and subsequent graft stenosis and occlusion. Several population studies have demonstrated higher levels of CRP and fibrinogen in women compared with men, but the clinical significance of this is not known. Although many studies have evaluated the association between inflammatory markers and CVD outcomes, fewer have investigated the role of inflammation and graft patency after LEB procedures. Moreover, it is unclear whether the differences in the underlying inflammatory profiles between men and women are important in the outcome after LEB. To address this gap in research, our current study investigated whether sex-based differences exist in the baseline inflammatory markers of patients undergoing LEB and if these biomarker levels are associated with primary vein graft patency.

**METHODS**

**Study design.** This was a prospective cohort study sponsored by the National Institutes of Health and conducted at three Boston academic medical centers. The study sought to determine the relationship between inflammation and outcomes after LEB using autogenous vein grafts. Enrollment began in February 2004 and ended in May 2008 and included 225 patients. Details of patient selection, inclusion and exclusion criteria, and operative procedure have been previously described. Patients were excluded if they were treated with a prosthetic or nonautologous vein graft, had a history of a hypercoagulable state, or had a concurrent significant event ≤30 days before the index bypass operation (ie, myocardial infarction, stroke, or major surgical procedure). The study excluded patients with deep space infections of the foot or active infection. Although patients with small ulcers or those with dry gangrene were included in the study, those with ulceration or gangrene requiring operative debridement were excluded.

**Blood collection and biomarker measurement.** Blood was collected from the fasting patient on the morning of the LEB procedure. All samples were immediately centrifuged at 3000 rpm and stored at −80°C until analysis. All samples were analyzed in batches at a core laboratory to minimize variability. CRP levels were determined by a high-sensitivity immunoturbidimetric assay on a Hitachi 917 analyzer (Roche-Diagnostics, Indianapolis, Ind) using reagents and calibrators from Denka Seiken (Niigata, Japan), with a sensitivity of 0.03 mg/L. Day-to-day variations of the assay at differing concentrations were <3%. Fibrinogen was measured using an immunonephelometric technique on the Behring BNII analyzer (Dade Behring, Newark, Del). Other inflammatory and metabolic biomarkers were measured in the parent study and have been previously reported.

**Covariates.** Race and sex were assessed by self-report. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or if the patient was taking prescription medications for hypertension. Hypercholesterolemia and diabetes mellitus were present if the patient was taking prescribed medications or if the diagnosis was self-reported. Active smoking was defined by a positive answer to the question “Do you now smoke cigarettes?” A former smoker was defined as one who had smoked >100 cigarettes in his or her life but had not smoked in 30 days. Chronic kidney disease was defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² using the Modification of Diet in Renal Disease Study equation. Body mass index (BMI) was calculated as kg/m².

CRP levels were dichotomized at 5 mg/L and fibrinogen levels at 600 mg/dL. Although the American Heart Association and Centers for Disease Control and Prevention guidelines support measurement of CRP for risk stratification and consider CRP >3 mg/L to be a high cardiovascular risk, the median value in our overall cohort was nearly 3 mg/L, and the median value in women was >5 mg/L. We dichotomized at CRP >5 mg/L because this value has previously been shown to represent a high-risk subgroup in a stroke cohort, and patients with CRP >5 mg/L have impaired early vein graft luminal remodeling. CRP >5 mg/L also represented the upper limit of our core laboratory’s reference range. The standard reference values for fibrinogen range from 150 to 450 mg/dL. The median value in our cohort was 480 mg/dL (interquartile range [IQR], 401-585 mg/dL). We chose to dichotomize at 600 mg/dL because this represented the top quartile of values.

**Operative procedure and surveillance.** All patients underwent LEB using autogenous vein, with ipsilateral great saphenous vein (GSV) as the conduit of first choice. In the absence of suitable ipsilateral vein, the contralateral GSV or arm vein was used. Routine postoperative follow-up included a complete vascular examination by the attending surgeon and a standard duplex ultrasound examination of the bypass graft in an accredited vascular laboratory at 1, 3, 6, 9, and 12 months. After 12 months, follow-up visits occurred every 6 months. All clinical and graft-related events were recorded prospectively. Although the decision to intervene on a failing graft was not standardized across all surgeons, as a general rule, all patients underwent graft intervention for all hemodynamically significant stenoses detected on surveillance ultrasound imaging. The type of graft reintervention was left to the discretion of the operating surgeon.

**Definition of primary patency.** Loss of primary patency included any type of graft revision (balloon angioplasty, patch angioplasty, or interposition graft) when a graft stenosis was detected by duplex ultrasound imaging or
other imaging modality. Loss of primary patency was also noted if there was documentation of occlusion of the vein graft without revision.

Statistical analysis. All statistical analyses were performed using Stata/SE 10.1 software (StataCorp, College Station, Tex). The clinical characteristics and biomarker values of the cohort were compared for men and women and are presented as proportions for categoric characteristics and as mean ± standard deviation (SD) or median and IQR for continuous characteristics. Continuous variables between groups were compared with the Student t-test; if the distribution was not approximately normal, the Wilcoxon rank-sum test was used. Proportions between groups were compared with the Pearson \( \chi^2 \) test. A value of \( P \leq .05 \) was considered statistically significant.

Variable selection for multivariable models. The bivariate associations between clinical variables, graft characteristics, and biomarker levels with primary graft patency were assessed for the overall cohort using a Cox proportional hazards model. Variable selection was based on this primary analysis. Any variable with a value of \( P < .30 \) was included in the subsequent multivariable models. Interactions between sex and biomarker levels, race and biomarker levels, sex and race, and sex and critical ischemia were also assessed and further analyzed if the \( P \) value for interaction was <.30. A multivariable Cox proportional hazards model was used to evaluate primary patency in men and women. We did not include CRP and fibrinogen in the same multivariable models because it is scientifically plausible that CRP and fibrinogen are potential mediators for one another in the pathway to graft failure; hence, including both biomarkers in the same model would result in overadjustment. Indeed, CRP and fibrinogen were highly correlated in our cohort (Pearson correlation coefficient, 0.56; \( P < .001 \)).

### RESULTS

The 225 patients (28% women) were a mean age of 68 ± 11 years and 8% were black. There were no significant differences in age, race, diabetes mellitus, BMI, eGFR, history of hypertension, and coronary artery disease between men and women (Table I). Men were more likely to be current smokers (\( P = .02 \)), have a history of hypercholesterolemia (\( P = .02 \)), and be on statin therapy (\( P = .02 \)) compared with women (Table I). Women were more likely to present with critical limb ischemia (\( P = .03 \)) and had significantly higher baseline CRP levels (\( P = .02 \)) than men (Table I).

The indication for LEB surgery in 133 patients (59%) was critical limb ischemia, and 73 patients (32%) had evidence of distal tissue loss. Bypass graft placement in 190 patients (84%) was with a single-segment GSV, whereas the remainder underwent construction of bypass graft using composite GSV or arm vein. A previous ipsilateral bypass graft had failed in 22 patients (10%). There were no differences in the type of conduit used, primary vs redo bypass, or type of outflow vessel (popliteal, tibial, or pedal artery) in women compared with men.

The median CRP level in the entire cohort was 2.98 mg/L (IQR, 1.28-12.25). The median CRP level was higher in women (5.15; IQR, 1.51-18.62 mg/L) compared with men (2.70; IQR, 1.24-6.98 mg/L; \( P = .02 \); Table I). The mean fibrinogen level in the cohort was 509 ± 176 mg/dL and was not significantly different in women (536 ± 211 mg/dL) compared with men (498 ± 159 mg/dL; \( P = .16 \); Table I). In a multivariable analysis that included sex, race, age, BMI, coronary artery disease, diabetes, statin use, critical ischemia, current smoking, and eGFR, sex (\( P = .04 \)) and critical ischemia (\( P < .001 \)) were both independently associated with baseline CRP level >5 mg/L. In a similar model for fibrinogen, diabetes (\( P = .02 \)) was included in the subsequent multivariable models. Variable selection was based on this primary analysis. Any variable with a value of \( P < .30 \) was included in the subsequent multivariable models. Interactions between sex and biomarker levels, race and biomarker levels, sex and race, and sex and critical ischemia were also assessed and further analyzed if the \( P \) value for interaction was <.30. A multivariable Cox proportional hazards model was used to evaluate primary patency in men and women. We did not include CRP and fibrinogen in the same multivariable models because it is scientifically plausible that CRP and fibrinogen are potential mediators for one another in the pathway to graft failure; hence, including both biomarkers in the same model would result in overadjustment. Indeed, CRP and fibrinogen were highly correlated in our cohort (Pearson correlation coefficient, 0.56; \( P < .001 \)).

### Table I. Demographic characteristics of the cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 161)</th>
<th>Women (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.0 ± 10.4</td>
<td>69.3 ± 12.0</td>
<td>.14</td>
</tr>
<tr>
<td>Black race</td>
<td>9 (5.6)</td>
<td>8 (12.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Current smoker</td>
<td>67 (41.6)</td>
<td>16 (25.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>88 (54.7)</td>
<td>29 (45.3)</td>
<td>.21</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.9 ± 5.4</td>
<td>29.6 ± 8.6</td>
<td>.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>133 (82.6)</td>
<td>57 (89.1)</td>
<td>.23</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>90 (55.9)</td>
<td>28 (43.8)</td>
<td>.10</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>78.2 ± 32.9</td>
<td>70.8 ± 39.3</td>
<td>.15</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>123 (76.4)</td>
<td>39 (60.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>135 (83.9)</td>
<td>45 (70.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Critical ischemia</td>
<td>88 (54.7)</td>
<td>45 (70.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Composite vein</td>
<td>21 (13.0)</td>
<td>14 (21.9)</td>
<td>.10</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>2.70 (1.24-6.98)</td>
<td>5.15 (1.51-18.62)</td>
<td>.02</td>
</tr>
<tr>
<td>CRP &gt;5 mg/L</td>
<td>56 (34.8)</td>
<td>34 (53.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>498 ± 159</td>
<td>536 ± 211</td>
<td>.16</td>
</tr>
<tr>
<td>Fibrinogen &gt;600 mg/dL</td>
<td>38 (23.6)</td>
<td>21 (32.8)</td>
<td>.16</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

*Continuous data are shown as the mean ± standard deviation and median (IQR) and categoric data as number (%).
.008) and critical ischemia (P = .03) were associated with baseline fibrinogen levels > 600 mg/dL.

The median follow-up was 893 days (IQR, 539-1315 days). There were 78 (35%) primary graft failures; this occurred in 27 of 64 women (42%) and in 51 of 161 men (32%; P = .14). Of the 78 primary patency events, 26 (33%) were graft thromboses and 52 (67%) were revisions for graft stenosis. Men and women had similar profiles for loss of primary patency, with 10 of 27 thrombotic events (37%) in women and 16 of 51 thrombotic events (31%) in men (P = .61). There was no significant difference in the type of primary patency event (stenosis vs thrombosis) by CRP levels (P = .20) or fibrinogen values (P = .48) in the overall cohort or when analyzed separately by sex. There were 35 secondary graft failures in this cohort, 11 of 64 in women (17%) and 24 of 161 in men (15%; P = .67).

The bivariate associations between all of the variables listed in Table I and primary graft patency were evaluated in the entire cohort and then separately for men and women (Table II). In the overall cohort, black race (P = .002), diabetes mellitus (P = .007), critical ischemia (P = .009), composite vein graft (P = .06), CRP > 5 mg/L (P = .02), and fibrinogen > 600 mg/dL (P = .17) met the criteria (P < .30) for inclusion into the multivariable models. When these bivariate associations between predictors and primary graft failure were stratified by sex, the presence of diabetes mellitus (P = .05) and critical ischemia (P = .02) were significantly associated with primary graft failure in men. In women, black race (P = .03), CRP > 5 mg/L (P = .02), and fibrinogen > 600 mg/dL (P = .01) were associated with primary graft failure (Table II).

In a multivariable Cox proportional hazards model for primary graft patency for the entire cohort, there was no significant difference in primary vein graft patency in those individuals with CRP > 5 mg/L compared with those with CRP < 5 mg/L (P = .11; Fig 1, A). However, there was a statistically significant interaction between sex and CRP levels (P = .03). Women with CRP > 5 mg/L were significantly more likely to lose primary vein graft patency compared with women with CRP < 5 mg/L (hazard ratio [HR], 2.63; 95% confidence interval [CI], 1.15-6.02; P = .02), but no such difference was seen in men (HR, 0.98; 95% CI, 0.52-1.85; P = .95; Fig 1, B and C). The findings were similar with respect to secondary graft patency. Women with CRP > 5 mg/L were significantly more likely to lose secondary graft patency than women with CRP < 5 mg/L (P = .05), but no such difference was seen in men (P = .78).

There was also a significant interaction between sex and fibrinogen (P = .02). In a multivariable Cox proportional hazards model for primary graft patency, there was no significant difference in primary vein graft patency in those with fibrinogen > 600 mg/dL compared with those with fibrinogen < 600 mg/dL in the overall cohort (P = .48; Fig 2, A). However, women with fibrinogen > 600 mg/dL were significantly more likely to lose primary vein graft patency than women with fibrinogen < 600 mg/dL (HR, 4.09; 95% CI, 1.66-10.05; P = .002; Fig 2, B), but again, no such difference was demonstrated in men (HR 0.62; 95% CI, 0.30-1.27; P = .19; Fig 2, C). These findings were similar when secondary graft patency was evaluated. Women with fibrinogen > 600 mg/dL were significantly more likely to lose secondary vein graft patency than women with fibrinogen < 600 mg/dL (P = .03), but no difference was demonstrated in men (P = .45).

The HRs for loss of primary graft patency, stratified by sex and in separate multivariable models of CRP and fibrinogen, are reported in Tables III and IV, respectively. In the CRP multivariable model for primary graft patency, black race was significantly associated with primary graft loss in men (HR, 2.68; 95% CI, 1.04-6.86; P = .04), whereas black race (HR, 3.04; 95% CI, 1.14-8.10; P = .03) and CRP > 5 mg/L (HR, 2.63; 95% CI, 1.15-6.02; P = .02) were significantly associated with primary graft loss in women (Table III). In the multivariable model with fibrinogen, black race (HR, 2.80; 95% CI, 1.09-7.22; P = .03) and critical ischemia (HR, 1.87; 95% CI, 1.00-3.50; P = .05) were significantly associated with primary graft loss in women (Table IV).
men, whereas in women, black race (HR, 4.22; 95% CI, 1.53-11.64; \( P = .005 \)) and fibrinogen >600 mg/dL (HR, 4.09; 95% CI, 1.66-10.05; \( P = .002 \)) were significantly associated with primary graft loss (Table IV).

**DISCUSSION**

This prospective study of patients with advanced PAD undergoing LEB with autogenous vein demonstrated that elevated baseline levels of CRP and fibrinogen were each associated with graft failure in women but not in men. We found a significant interaction between sex and both CRP and fibrinogen in the primary patency rate of LEB grafts, suggesting a different underlying inflammatory profile in men and women who present with severe PAD.

In our study, women had significantly higher baseline levels of CRP compared with men. This is not surprising, as several large cohort studies have demonstrated differences in CRP levels by both sex and race. The Multiethnic Study of Atherosclerosis (MESA) cohort of 6814 men and women aged 45 to 84 years found substantially higher median CRP levels in women than in men, despite accounting for estrogen use, BMI, and other confounding variables. This sex difference was maintained across all ethnic subgroups. In the Dallas Heart Study, women had significantly higher CRP levels than men, and black patients had significantly higher levels than white patients. These findings remained significant after adjustment for BMI and traditional cardiovascular risk factors, as well as after exclusion of individuals taking statins and estrogens. Our study population is limited with regards to racial diversity; therefore, we were unable to examine the potential synergies between sex, race, and inflammation. Although men and women differed in several baseline factors, it is noteworthy that female sex was independently correlated with CRP level even after adjustment for multiple covariates.

Previous studies have demonstrated CRP to independently predict future CVD events in both men and women. However, subgroup observations from both the Cardiovascular Health Study (CHS) and the Rural Health Promotion Project demonstrated the risks of vascular disease associated with CRP were greater for women than for men. Similarly, in the Women’s Health Study, the adjusted relative risk for either myocardial infarction or stroke in women with the highest quartile of CRP was 5.5 compared with 2.8 in men participating in the Physicians’
Although CRP is a strong and independent risk factor for adverse cardiovascular outcomes in men and women, these findings suggest that women with elevated CRP may be at a relatively higher risk for a cardiovascular event compared with men. Few studies have been performed examining the association between CRP and LEB graft patency, and none of these examined results by sex.

Recent work suggests there may be an important relationship between systemic inflammation and the early remodeling changes in LEB grafts; specifically, the early (1-month) venous dilation response to arterialization appears to be impaired in patients with elevated baseline CRP levels. This suggests a possible uncoupling between hemodynamic stress and vessel remodeling. If true, such impaired early remodeling may likely have greater clinical impact in the setting of smaller conduit vessels. In this study, we found that the divergence of loss of primary patency, by preoperative biomarker level, primarily occurred within the first year, further supporting this idea. This hypothesis will need to be formally examined in future and ongoing studies.

**Fig 2.** Multivariable Cox regression curves for primary graft patency for (A) all patients, (B) for women, and (C) for men undergoing lower extremity bypass surgery with autogenous vein, based on fibrinogen levels.

**Table III.** Multivariable Cox proportional hazards model for primary graft patency, including C-reactive protein (CRP), stratified by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>P</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>2.68 (1.04-6.86)</td>
<td>.04</td>
<td>3.04 (1.14-8.10)</td>
<td>.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64 (0.88-3.04)</td>
<td>0.12</td>
<td>1.10 (0.47-2.57)</td>
<td>0.82</td>
</tr>
<tr>
<td>Composite vein</td>
<td>1.21 (0.56-2.64)</td>
<td>0.63</td>
<td>1.85 (0.78-4.39)</td>
<td>0.16</td>
</tr>
<tr>
<td>Critical ischemia</td>
<td>1.72 (0.88-3.34)</td>
<td>0.11</td>
<td>1.16 (0.48-2.83)</td>
<td>0.74</td>
</tr>
<tr>
<td>CRP &gt;5 mg/L</td>
<td>0.98 (0.52-1.85)</td>
<td>0.95</td>
<td>2.63 (1.15-6.02)</td>
<td>.02</td>
</tr>
</tbody>
</table>

CI, Confidence interval; HR, hazard ratio.
Fibrinogen levels also differ by sex and race and have been reported to be higher in women than in men \textsuperscript{28-30} and in blacks than in whites.\textsuperscript{28-30} Fibrinogen levels increase with age, smoking, body size, diabetes, fasting serum insulin, low-density lipoprotein cholesterol, and menopause.\textsuperscript{28-30} A meta-analysis of fibrinogen as a CVD risk factor identified six prospective epidemiologic studies, all of which demonstrated that fibrinogen was associated with subsequent myocardial infarction or stroke.\textsuperscript{28} Although fibrinogen appears to be a strong CVD risk factor in both men and women, it is unclear from any of these previous studies whether there is a differential association in women compared with men.

We found a strong interaction between sex and fibrinogen with regards to vein graft patency in our cohort. A high fibrinogen level was significantly associated with graft failure in women but not in men. Fibrinogen plays an important role in patients with PAD. In the CHS cohort, ankle-brachial index levels were inversely correlated with fibrinogen levels.\textsuperscript{27} Plasma fibrinogen has also been shown to be a predictor of the development\textsuperscript{22,23} and severity of PAD.\textsuperscript{17,21} In studies in PAD patients, fibrinogen levels were found to be the strongest independent predictor of death from coronary disease\textsuperscript{28} and all-cause cardiovascular mortality.\textsuperscript{39} There are fewer data reporting the association between fibrinogen level and outcomes after lower extremity revascularization. Two reports evaluating patients with lower extremity vein grafts demonstrated elevated fibrinogen levels were associated with vein graft stenoses\textsuperscript{24} and graft occlusion.\textsuperscript{25} In contrast, a study that evaluated 57 patients undergoing infrainguinal arterial reconstruction with saphenous vein narrowly failed to demonstrate a statistically significant association between fibrinogen levels and graft failure.\textsuperscript{40} It is possible that a type II error occurred or, perhaps, that an unidentified interaction contributed to the overall negative results of the study. To our knowledge, no studies have evaluated the association between fibrinogen and LEB graft patency separately for women and men.

There are several studies that suggest that women have higher rates of graft failure and increased rates of wound complications after LEB graft procedures, but clear predisposing factors have not been identified.\textsuperscript{5-7} It is possible that women who present with advanced PAD have an underlying inflammatory phenotype that puts them at a disproportionately higher risk for subsequent graft failure compared with men. Measurement of both CRP and plasma fibrinogen in women before revascularization may identify those who are at highest risk for graft failure and could potentially improve results either by aggressive risk factor modification or a more intensive graft surveillance schedule. Prospective studies are needed to validate the use of these biomarkers for risk prediction in this population.

This study has several limitations. Our series of patients had advanced PAD, including a large proportion with critical limb ischemia. Also, all patients were treated with a vein conduit. Therefore, our results may not be generalizable to those with more mild disease or in those who undergo LEB with a prosthetic graft. We dichotomized CRP at 5 mg/L and fibrinogen at 600 mg/dL, either or both of which may not be the ideal cut points. CRP and fibrinogen were not included together in the same multivariable Cox model, and hence we could not assess whether each biomarker was independently associated with graft failure. In addition, only preoperative levels of inflammatory markers were available in this study, and hence we could not evaluate whether changes in CRP and fibrinogen levels after LEB were associated with graft failure. The modest size and diversity of the study population also limit its generalizability. The findings should be considered hypothesis-generating and provide impetus for further studies examining the interaction of gender and inflammation in peripheral revascularization.

**CONCLUSIONS**

Women undergoing LEB for advanced PAD have a different inflammatory phenotype than men. Elevated baseline levels of CRP and fibrinogen are associated with inferior vein graft patency in women but not in men. These findings indicate an important interaction between sex and inflammation in the healing response of vein grafts for LEB. Women with elevated preoperative CRP and fibrinogen levels may benefit from more intensive postoperative graft surveillance protocols.

**AUTHOR CONTRIBUTIONS**

Conception and design: JH, CO, MB, MAC, MSC
Analysis and interpretation: JH, CO, JB, MB, MAC, MSC
Data collection: CO, JK, MB, MAC, MSC
Writing the article: JH, MSC

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**Table IV.** Multivariable Cox proportional hazards model for primary graft patency, including fibrinogen, stratified by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>P</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>2.80 (1.09-7.22)</td>
<td>.03</td>
<td>4.22 (1.53-11.64)</td>
<td>.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.85 (0.98-3.50)</td>
<td>.06</td>
<td>0.92 (0.40-2.10)</td>
<td>.84</td>
</tr>
<tr>
<td>Composite vein</td>
<td>1.13 (0.51-2.46)</td>
<td>.77</td>
<td>2.11 (0.92-4.83)</td>
<td>.08</td>
</tr>
<tr>
<td>Critical ischemia</td>
<td>1.87 (1.00-3.50)</td>
<td>.05</td>
<td>0.84 (0.33-2.14)</td>
<td>.71</td>
</tr>
<tr>
<td>Fibrinogen &gt;600 mg/dL</td>
<td>0.62 (0.30-1.27)</td>
<td>.19</td>
<td>4.09 (1.66-10.05)</td>
<td>.002</td>
</tr>
</tbody>
</table>

CI, Confidence interval; HR, hazard ratio.
Critical revision of the article: JH, CO, JK, JB, MB, MAC, MSC
Final approval of the article: JH, CO, JK, JB, MB, MAC, MSC
Statistical analysis: JH, JB
Obtained funding: MSC
Overall responsibility: JH

REFERENCES
DISCUSSION

Dr Michelle Mueller (Salt Lake City, Utah). I would like to thank the program committee for inviting me to be a discussant. Congratulations to Dr Hiramoto on a very nice presentation and the authors on an excellent study and paper.

Many of us have the impression that women with peripheral artery disease do more poorly than men. The question is why, and can we do anything to improve their surgical outcomes. In this prospective study, the authors show us that high-sensitivity C-reactive protein (CRP) and fibrinogen are not only elevated in women at baseline when compared to men, but those women with elevated CRP or fibrinogen have decreased primary graft patency.

A few questions and comments:

In the paper you state there are no differences in the outflow vessels (popliteal versus tibial versus pedal). However, there were significantly more women with critical limb ischemia than men. Is there a trend towards more infrapopliteal bypasses in women in general, and more specifically in those with elevated inflammatory markers?

Dr Jade S. Hiramoto. Thank you for reviewing our manuscript and for your kind comments. Indeed, there were significantly more women with critical limb ischemia in this cohort compared to men. However, there were no significant differences in the target outflow vessels by sex. In both men and women, about half underwent a bypass graft to the popliteal artery, and the other half underwent a bypass graft to either a tibial or pedal vessel. There was no statistically significant difference, nor was there a trend toward more infrapopliteal bypasses in women. Patients with CRP >5 mg/L or fibrinogen >600 mg/dL were more likely to undergo an infrapopliteal bypass compared to those with CRP <5 mg/L or fibrinogen <600 mg/dL, but this was true for both the men and women in this cohort.

Dr Mueller. Does the decreased primary graft patency in women with elevated CRP or fibrinogen correlate with graft thrombosis or limb loss, or are there just more interventions on grafts in these groups?

Dr Hiramoto. The discussant raises an important question. Of the 78 primary patency events, 26 (33%) were due to graft thrombosis and 52 (67%) were revisions for graft stenosis. Both men and women had similar profiles for loss of primary patency—37% of the primary patency events were graft thrombosis in women, and 31% were graft thrombosis events in men. There was no significant difference in the type of primary patency event (thrombosis or stenosis) based on CRP or fibrinogen values. This was true when analyzed in the overall cohort and when separately analyzed by sex.

We also analyzed secondary graft patency in this cohort and the findings were similar to those for primary graft patency. Women with CRP >5 mg/L were significantly more likely to lose secondary graft patency compared to women with CRP <5 mg/L, and women with fibrinogen >600 mg/dL were significantly more likely to lose secondary graft patency compared to women with fibrinogen <600 mg/dL. These findings were not seen in the men in this cohort.

Dr Mueller. Would a more intensive graft surveillance program decrease graft thrombosis and improve limb salvage?

Dr Hiramoto. It is difficult to know whether a more intensive graft surveillance program would decrease the graft thrombosis rate. Most of the losses of primary graft patency occurred within the first year, and we performed duplex ultrasound examination of the bypass grafts at 1, 3, 6, 9, and 12 months postoperatively. Based on the findings in this study, one might consider increasing the frequency of this surveillance in a higher risk patient, for instance, a woman with CRP >5 mg/L or fibrinogen >600 mg/dL. However, it is unclear whether this would change the overall outcome.

Dr Mueller. Finally, you recommend aggressive risk factor modification. Would you delay bypass in women with critical limb ischemia and elevated inflammatory markers for risk factor modification, and what modifications would you recommend? With our current knowledge regarding these inflammatory markers, are we not already encouraging smoking cessation and aggressively treating patients with statins? Perhaps we are failing to recognize peripheral artery disease early in women and also failing to aggressively medically manage them.

Dr Hiramoto. Because of the overall size of the cohort and relatively small numbers of women, I think that one should consider the findings from our study hypothesis-generating. I think it provides important background information for future studies to further evaluate this interaction between sex and inflammation. We believe that all at-risk individuals should stop smoking and be treated with statins, yet 37% of our cohort were still smoking, and 30% of the women in this cohort were not on statin therapy. So, there is still room for improvement. At this point in time, I would not recommend delaying bypass grafting in women with critical limb ischemia and elevated inflammatory markers for risk factor modification without further confirmatory data. Finally, I agree with Dr. Mueller—epidemiologic studies have demonstrated that peripheral artery disease prevalence is equal (if not higher) in women compared to men. We are not doing a good enough job at recognizing peripheral artery disease early in women, and hence, we are failing to provide the appropriate aggressive medical management.
Critical Limb Ischemia

Matthew J. Blecha, MD

KEYWORDS
- Acute limb ischemia
- Critical limb ischemia
- Lower extremity revascularization
- Arterial occlusive disease
- Lower extremity angioplasty
- PAD

KEY POINTS
- Acute limb ischemia should be suspected in patients with new-onset limb pain and a cool, pulseless extremity on physical examination.
- Acute limb ischemia is a surgical emergency, necessitating emergent heparinization and revascularization to prevent limb loss.
- Critical limb ischemia is defined clinically by ischemic rest pain or tissue loss in conjunction with either ankle-brachial index less than 0.4 or toe pressure less than 30 mm Hg.
- Management of critical limb ischemia includes optimization of medical therapy, arterial imaging, and revascularization, with the goal of achieving in-line flow to the affected limb when tissue loss is present.
- As a guiding principle, short-segment arterial stenosis or occlusions are treated with angioplasty and long-segment arterial occlusions are treated with surgical bypass in patients with critical limb ischemia.

INTRODUCTION

Critical limb ischemia refers to the clinical state of advanced arterial occlusive disease, placing an extremity at risk for gangrene and limb loss. This article reviews the etiologies, diagnosis, and treatment of critical limb ischemia. Critical limb ischemia has 2 broad clinical subcategories that are vital to differentiate:

1. Acute limb ischemia
2. Chronic arterial occlusive disease

Acute limb ischemia refers to the acute arterial thrombosis of an extremity, resulting in an abrupt cessation of flow to the extremity. Acute limb ischemia is a surgical emergency mandating urgent extremity revascularization to avoid the need for amputation. The potential sources of acute limb ischemia are arterial embolus, in situ arterial
thrombosis in the setting of advanced chronic arterial occlusive disease, and major arterial trauma.

Chronic arterial occlusive disease with critical limb ischemia is the condition of progressive atherosclerosis, creating a state of extremity hypoperfusion with insufficient tissue oxygenation. Chronic arterial occlusive disease warrants prompt treatment but is not an emergent state, allowing for thorough imaging, patient risk stratification, and planning of revascularization. Pathologies other than atherosclerosis can result in chronic arterial occlusive disease and are briefly reviewed.

**ACUTE LIMB ISCHEMIA**

**Treatment Steps for Acute Limb Ischemia**

1. Confirm diagnosis with physical examination and arterial imaging
2. Initiate anticoagulation therapy
3. Perform revascularization
4. Monitor post procedure for compartment syndrome and rhabdomyolysis
5. Evaluate the patient for potential embolic sources and continue therapeutic anticoagulation

**Diagnosis of Acute Limb Ischemia**

The clinical hallmark of acute limb ischemia is the acute onset of extremity pain in conjunction with absent pulses in the affected extremity. The severity of pain symptoms can vary dramatically depending on the etiology of the acute arterial occlusion. Patients who experience acute limb ischemia secondary to an arterial embolism versus patients who experience in situ arterial thrombosis in the setting of chronic arterial occlusive disease can have dramatically different clinical presentations.

Occlusive arterial embolism to an otherwise normal arterial bed will nearly universally result in the abrupt onset of severe pain in the affected extremity. These patients lack collateral vessels around the flush occlusion, making the affected limb completely devoid of any arterial flow. The physical examination findings in this state are the presence of bounding “water hammer” pulses proximal to the occlusion and absent pulses distal to the occlusion. The distal extremity will be cool to touch, and after 3 to 4 hours may have neurologic abnormalities (sensory loss followed by motor loss). The limb is pale with poor capillary refill. The contralateral limb in this situation will typically have normal pulses, unless the patient has underlying peripheral artery occlusive disease (PAD). Revascularization within 6 hours is critical to avoid limb loss.

In situ arterial thrombosis secondary to worsening chronic occlusive disease may present in a more indolent fashion. These patients experience acute primary vessel thrombosis due to either plaque rupture and secondary to arterial thrombosis, or due to a critically low-velocity flow state resulting in intra-arterial thrombosis. Although the primary symptom is limb pain, the acuity may be more vague than in patients with embolism. Physical examination findings will still be a cool, pulseless foot, often with dependent rubor instead of pallor. The contralateral pulse and Doppler examination are typically abnormal, as atherosclerosis affects both limbs. The severity of pain symptoms is inversely proportional to the quality of collateral arterial flow around the occlusion.

Emergent arterial imaging is indicated for any patient presenting with acute-onset limb pain and absent pulses. Imaging options include duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and invasive diagnostic angiogram.
Duplex ultrasound is rapid, can be performed at the bedside, and has near 100% sensitivity for diagnosing complete arterial occlusion. Ankle-brachial index (ABI) will be near zero for patients with acute limb ischemia. Evaluating aorto-iliac inflow and tibial arterial outflow vessels may be suboptimal with duplex alone.

CTA has the benefit of rapid availability and high-quality imaging, which allows for precise planning of revascularization. CTA provides imaging of the entire arterial tree from the aortic inflow to the digital level. CTA typically requires 150 mL of iodinated contrast and therefore has to be used with caution in patients with baseline renal insufficiency (glomerular filtration rate <40). For patients with renal insufficiency, aggressive hydration before and after examination with sodium bicarbonate is recommended for CTA or invasive angiography. ¹

MRA has a limited role in acute limb ischemia, as the examination can be lengthy (45–60 minutes), is less often available outside regular work hours, and generally has poorer arterial imaging than 64 (or greater) slice CTA.

Invasive angiography has the advantage of allowing for simultaneous percutaneous revascularization with both mechanical thrombectomy and thrombolytic therapy.

After revascularization for embolism, patients should undergo echocardiography and aortic imaging after the limb is revascularized to investigate the proximal source of embolus.

**Treatment of Acute Limb Ischemia**

Before engaging in any revascularization for acute limb ischemia, the treating surgeon should perform a global patient evaluation with confirmation of ambulatory status, relative quality of life, and surgical risk. A 30-day amputation rate of 15% ²,³ is discussed with the patient and family.

Once quality arterial imaging has been obtained, urgent revascularization is undertaken with the goal of achieving uninterrupted in-line flow from the aorta to the affected extremity. The goal of lower extremity revascularization is to have at least one tibial artery patent with angiographic confirmation of outflow to the foot. In the upper extremity, outflow to the hand via the radial or ulnar artery (ideally both) with filling of the palmar arch is the treatment goal.

If no contraindication to anticoagulation exists, the patient should be given an intravenous (IV) heparin bolus of 100 U/kg followed by IV heparin infusion of 15 U/kg with a goal partial thromboplastin time (PTT) of 60 to 80. If a continuous thrombolytic therapy drip is initiated, then heparin dose should be reduced to prevent bleeding complications. This dosing, as well as contraindications to anticoagulation and thrombolytic therapy are discussed later in this article.

There are 2 primary treatment options for acute limb ischemia:

1. Percutaneous thrombolytic therapy with adjunctive mechanical thrombectomy
2. Surgical thrombectomy with as-needed adjunctive bypass or endarterectomy

**Option 1 for Acute Limb Ischemia: Endovascular Percutaneous Thrombectomy and Thrombolysis**

Arterial access should be achieved proximal to the arterial occlusion. Most commonly, contralateral retrograde common femoral arterial access is achieved followed by angiogram of the aorto-iliac system. The primary predictor of success for percutaneous revascularization of acute limb ischemia is successful guidewire crossing through the thrombus burden. If the thrombus burden extends proximally to the aortic bifurcation, then brachial artery access may be necessary to achieve guidewire and catheter passage into the thrombus.
This is followed by catheter and sheath selection of the affected limb’s iliac arterial system. Through this sheath, dedicated lower extremity angiography can then be performed. A hydrophilic glidewire with supporting 4-Fr supporting catheter can then be used to cross into the arterial thrombus. The guidewire should be passed as distally as possible, then the angiojet catheter (Medrad/Possis, Minneapolis, MN, USA) can be passed over the guidewire, activated through the thrombus burden, and the thrombus treated with both tissue plasminogen activator (TPA) bolus of 5 mg and mechanical pulse spray/suctioning with the catheter (Fig. 1). Fig. 2 illustrates an acute iliac artery embolus treated with percutaneous mechanical thrombectomy.

For mechanical thrombectomy of the iliac, common femoral, superficial femoral, and popliteal arteries, 0.035-inch glidewires and 6-Fr thrombectomy catheters can be used. When treating tibial thrombus, smaller caliber 0.018-inch guidewires with 3-Fr angiojet thrombectomy catheter are used. The mechanical thrombectomy catheters will typically create a flow channel of adequate diameter to reperfuse the limb. Residual thrombus can then be treated as needed with continuous TPA drip of 0.05 to 0.1 U/kg per hour. Thrombolytic drip is performed through “side-hole” infusion catheters invested into the region of thrombus (Fig. 3). Moderate-dose IV heparin drip is also administered while patients are receiving TPA infusion. Fibrinogen level, PTT, international normalized ratio, and hemoglobin should be checked every 6 hours while the TPA drip is ongoing. TPA should be held for fibrinogen level below 100 mg/dL and heparinized saline infused through the catheter until the next angiogram should this occur. PTT goal while the TPA drip is ongoing is 30 to 50 seconds. Higher levels are associated with increased bleeding risk.

Once follow-up angiography confirms successful lysis of the thrombus burden, any underlying arterial occlusive disease can be identified and treated percutaneously with angioplasty, or if necessary surgically with bypass or endarterectomy.

Unlike anticoagulants and antiplatelet medications (heparins, warfarin, thrombin inhibitors, factor Xa inhibitors, aspirin, clopidogrel), which serve to prevent thrombus formation, TPA directly induces lysis of a fibrin-based clot, creating significant bleeding risks for anyone with recent endothelial injury. Contraindications to thrombolytic therapy include the following5–7:

- Cerebrovascular accident (CVA) within 3 months
- Intracranial tumor or other gross pathology
- Intrathoracic, abdominal, pelvic, or thoracic surgery within 3 weeks

Fig. 2. Acute arterial embolus to the right distal common iliac artery seen on the image on the left. After a 5-mg TPA bolus and percutaneous mechanical thrombectomy with angiojet device, successful resolution of the occlusion is seen on the right. The underlying external iliac stenosis would be subsequently treated with angioplasty.

Fig. 3. Thrombolytic infusion “sidehole” catheter. (Courtesy of Angiodynamics, Inc, Latham, NY.)
- Major trauma within 3 weeks
- Severe (systolic blood pressure >180 mm Hg) hypertension that cannot be controlled with medication
- Cirrhosis with coagulation abnormality

Patients with acute limb ischemia who are not candidates for thrombolytic therapy should undergo emergent surgical revascularization.

**Option 2 for Acute Limb Ischemia: Open Surgical Thrombectomy With As-Needed Adjunctive Revascularization or Thrombolytic Therapy**

**Treatment of acute arterial embolus**

For patients experiencing acute embolus to an otherwise normal arterial tree, surgical embolectomy provides rapid revascularization and is an outstanding treatment option. The recommended exposure sites for acute embolus are based on anatomic location and extent of thrombus burden. Recommended dissection sites are the following:

- Lower extremity embolus with patent iliac, common femoral, and profunda femoral arteries: Below-knee popliteal artery cutdown with retrograde and antegrade Fogarty balloon thrombectomy. This dissection site allows for selective Fogarty balloon catheter thrombectomy of both the anterior tibial artery and the tibio-peroneal trunk.
- Lower extremity embolus with occluded common femoral artery: Common femoral artery cutdown with Fogarty balloon thrombectomy of the iliac, profunda femoral, and distal arteries. Secondary cutdown at the below-knee popliteal artery to expose the origin of the tibial vessels may also be necessary after the inflow thrombectomy if remote thrombectomy does not result in at least one tibial artery being widely patent to the foot.
- Upper extremity embolus: Brachial artery cutdown at the antecubital level just above the bifurcation with control of the proximal radial and ulnar arteries.

Muscular fascia should never be closed after surgical thrombectomy because of the risk for compartment syndrome. Appropriate Fogarty balloon sizes are No. 5 for iliac and subclavian arteries; No. 4 for femoral, popliteal, and brachial arteries; and No. 3 for tibial, radial, and ulnar arteries (Fig. 4). All embolectomy and thrombectomy procedures should be followed by completion angiography with confirmation of in-line flow to the affected distal limb.

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**Fig. 4.** Treatment options for acute arterial embolus. (From Hoballah JJ. Technique: open surgical. In: Cronenwett JL, Johnston KW, editors. Rutherford’s Vascular Surgery. 7th Edition. Philadelphia: Elsevier; 2010; with permission.)
If thrombectomy is unsuccessful at the tibial artery level, intraoperative direct intra-arterial distal thrombolytic therapy can be performed. A sheath or catheter can be placed in an antegrade fashion down the proximal arterial system and 5 mg of TPA injected directly into the thrombosed tibial vessel. Ten minutes later, secondary angiogram is performed to evaluate the efficacy of the TPA.

**Surgical treatment of acute limb ischemia in setting of chronic arterial occlusive disease**

Surgical treatment of acute limb ischemia secondary to arterial thrombosis in the setting of coexisting chronic arterial occlusive disease is a far more challenging scenario than acute embolus. It can be difficult to discern, based on angiography or CTA, which vessels have been occluded for several months and which arteries are acutely occluded. These patients, as mentioned previously, may present with more subtle onset of pain. Essentially they are patients with chronic arterial occlusive disease (discussed later in this article) who have developed arterial thrombosis and reached a critical threshold of tissue ischemia.

Surgical treatment for these patients is “whatever it takes” to achieve in-line flow to affected extremity. The treatment armamentarium includes thrombectomy, bypass, endarterectomy, thrombolytic therapy, angioplasty, and stenting. Treatment is individualized to patient anatomy. Dissection should be performed at the level of the most distal inflow artery that has uninterrupted proximal in-line flow. From here, attempts at distal thrombectomy can be made with the understanding that distal outflow vessel exposure, further thrombectomy, and bypass may be necessary based on post-thrombectomy angiographic findings. Similarly, based on post-thrombectomy imaging, subsequent sheath insertion with angioplasty can be performed if anatomically feasible. Ensuring patency of the profunda femoral artery should always be attempted to potentially prevent limb loss in the event of revascularization failure.

**Percutaneous Versus Open Surgical Revascularization in Acute Limb Ischemia**

Limb salvage and mortality rates were equivalent in the 2 largest randomized trials (Surgery vs Thrombolysis for Ischemic Lower Extremity [STILE] and Thrombolysis or Peripheral Arterial Surgery [TOPAS] II trials) comparing surgical thrombectomy to percutaneous thrombolysis. The endovascular limb in these trials, however, relied on thrombolysis alone without initial percutaneous mechanical thrombectomy. Mechanical thrombectomy achieves rapid revascularization and typically removes more than 90% of the acute thrombus burden within minutes while avoiding the morbidity of open vascular surgery. The author’s strong preference is to treat all patients with acute limb ischemia (without contraindication to TPA) with percutaneous mechanical thrombectomy and as-needed continued percutaneous thrombolytic drip.

**Monitoring and Treatment for Post Revascularization Compartment Syndrome and Rhabdomyolysis**

**Compartment syndrome**

Patients undergoing revascularization for acute limb ischemia are at high risk for calf compartment syndrome. Reperfusion edema and the confined space of the anterior, lateral, and deep/superficial posterior compartments can result in venous compression, worsening edema, and ultimately neurologic ischemia. Risk for compartment syndrome is highest for patients with a lack of collateral vessels (embolus or trauma in a normal arterial tree) and for patients with prolonged ischemia before revascularization.

The anterior and lateral compartments are the most common first symptomatic distribution, presenting with peroneal nerve distribution sensory deficit on the dorsum of
the foot. The most reliable physical exam finding in compartment syndrome is pain with passive extension of the muscles of the involved compartment.

Any suspicion for compartment syndrome warrants either immediate 4-compartment fasciotomy (Fig. 5) or measuring of compartment pressures. Any post revascularization compartment pressure greater than 30 mm Hg warrants fasciotomy. To avoid permanent neurologic injury, error should always be made on the side of full 4-compartment fasciotomy when concerning symptoms or signs of compartment syndrome exist.

**Rhabdomyolysis**

Patients with prolonged (greater than 6 hours) acute limb ischemia are at risk for acute renal tubular necrosis due to recirculation of the necrotic muscle breakdown product myoglobin. Oliguria and discolored (pink or red) urine should raise suspicion for rhabdomyolysis. Diagnosis can be confirmed with urine myoglobin level. Urine microscopy will be negative for red blood cells but urine dip will be positive for blood. Treatment is IV hydration, diuresis with mannitol, and alkalization of urine with IV bicarbonate. Urine myoglobin levels may not be rapidly attainable in many hospitals. Similar to compartment syndrome, it is safest to empirically treat rhabdomyolysis if the diagnosis is in question.

**CRITICAL LIMB ISCHEMIA SECONDARY TO CHRONIC ARTERIAL OCCLUSIVE DISEASE**

**Definition and Epidemiology**

Chronic arterial occlusive disease can reach a critical threshold, placing patients at risk for major lower extremity amputation. Clinically, critical limb ischemia is defined by specified hemodynamic findings in conjunction with either of the following:

1. Ischemic rest pain
2. Lower extremity ulceration with hemodynamic findings incompatible with wound healing.

**Fig. 5.** Double-incision (anterolateral and medial) fasciotomy of the lower leg. A longitudinal incision lateral to the tibia and overlying the intermuscular septum is used to visualize the anterior and lateral compartments. Parallel fascial incisions are used to decompress these compartments. A medial incision immediately posterior to the tibia is used to access both posterior compartments. The soleus muscle must be detached from the tibia to decompress the deep posterior compartment. (From Janzing H, Broos P, Rommens P. Compartment syndrome as a complication of skin traction in children with femoral fractures. J Trauma 1996;41:156.)
Atherosclerosis is a multisystemic process placing patients with PAD at high risk for stroke, myocardial infarction, and renal failure. More than 90% of patients who are symptomatic from PAD have some degree of coronary artery disease (CAD), of which more than 60% is severe or advanced. Subsequently, patients with critical limb ischemia have a median 5-year survival of less than 5 years (Fig. 6). The prevalence of PAD after age 70 is 14.5% in the United States.

**Etiology**

More than 95% of chronic lower extremity arterial occlusive disease with limb threat is secondary to atherosclerotic stenosis or occlusions. Atherosclerotic risk factors with relative risk for symptomatic PAD are illustrated in (Fig. 7). Other leading potential sources of chronic arterial occlusive disease are history of prior embolization, popliteal artery aneurysm with chronic thrombosis or emboli, popliteal artery entrapment syndrome, popliteal adventitial cystic disease, thromboangitis obliterans (Buerger disease), fibromuscular dysplasia, aortic coarctation, Takayasu arteritis, endofibrosis of the external iliac artery, persistent sciatic artery, and radiation injury.

Levels of lower extremity arterial occlusive disease are anatomically categorized as follows:

- Inflow distribution: aortic, common iliac, external iliac arteries
- Femoral popliteal distribution: common femoral, superficial femoral, profunda femoral, and popliteal arteries
- Tibial distribution: anterior tibial, posterior tibial, peroneal, and pedal arteries

Most patients with critical limb ischemia have multisegment arterial occlusive disease. Tibial distribution disease confers the highest risk for major amputation. Tibial disease is most common in patients with diabetes and renal failure. Patients with diabetes and PAD have a ninefold higher amputation rate versus patients who are nondiabetic with PAD.

**Symptoms**

Ischemic rest pain is pain in the foot at rest, particularly when the patient is laying flat or elevates the affected limb. The loss of gravity’s supplemental effect on arterial flow to the foot creates a “tipping point” at which tissues in the foot become ischemic. Pain is
typically relieved with lowering of the affected extremity. Diabetic patients with coexisting neuropathy may not experience rest pain despite critically diminished arterial flow, because of chronic sensory loss.

Ulceration may be primarily ischemic or gangrenous. Other potential ulceration sources, such as neuropathy and venous stasis can be difficult to heal if inadequate perfusion exists.

**Diagnosis**

Multiple physical examination findings are associated with critical limb ischemia. Absent pedal pulses, dependent rubor of the foot, absent calf and pedal hair, cool sensation, and ulceration are all characteristic.

Noninvasive arterial Doppler examination with ankle and digital pressures have near 100% sensitivity in detecting chronic arterial occlusive disease. Arterial calcification, seen commonly in patients with diabetes or renal failure, may result in falsely elevated ankle pressure and ABI. However, Doppler waveforms and digital pressures are still reliable with vessel calcification and have excellent sensitivity for PAD. The hemodynamic criteria for critical limb ischemia are as follows:

1. ABI less than 0.4
2. Toe pressure less than 30 mm Hg

These findings are considered a threshold beneath which nonhealing of pedal ulceration can be expected. Simultaneous arterial duplex scanning can be performed in the vascular laboratory to evaluate the location and extent of infrainguinal stenosis or occlusion. Toe pressures of less than 30 mm Hg are predictive of nonhealing of pedal ulceration in diabetic and nondiabetic patients alike (Fig. 8).  

Once the diagnosis of critical limb ischemia is made, patients with adequate risk for revascularization should undergo further arterial imaging. All revascularization must be
based on quality arterial imaging from the abdominal aorta level to the foot of the affected extremity. Options include invasive diagnostic angiography with the potential for simultaneous endovascular intervention, CTA, MRA, and arterial duplex scanning. CTA and MRA provide adequate imaging on which inflow and femoral-popliteal artery revascularization can be planned. Tibial artery imaging with CTA and MRA is institutionally variable and can be difficult in CTA because of dense arterial calcification. The author’s strong preference before performing any tibial-level revascularization is a preoperative subtraction angiogram achieved through a catheter inserted as distally as possible within the affected arterial tree (Fig. 9).

Fig. 8. Toe pressures of less than 30 mm Hg consistently predict nonhealing of pedal ulceration for diabetic and nondiabetic patients alike. (Data from Ramsey DE, Manke DA, Summer DS. Toe blood pressure: a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. J Cardiovasc Surg 1983;24:43.)

Fig. 9. Selective popliteal artery catheterization for patient with digital gangrene reveals complete occlusion of the below-knee popliteal and proximal tibial arteries (right) with reconstitution of the distal posterior tibial and anterior tibial arteries (left) as potential bypass targets. Distal SFA to posterior tibial artery bypass was ultimately performed.
Treatment Goals

Medical therapy

Initial evaluation should include global health assessment, with particular attention paid to any recent symptoms of CAD if open surgery is planned. Although essentially all patients with PAD have some element of CAD, asymptomatic patients have not been found to benefit from preoperative coronary revascularization. Nevertheless, the prevalence of CAD in patients with PAD makes cardiac stress testing before major vascular surgery recommended.

Risk factor modification is critical in preventing limb loss, myocardial infarction, stroke, and death in patients with symptomatic PAD. Medical management with survival benefit for patients with symptomatic PAD includes the following:

1. Antiplatelet therapy with either aspirin or clopidogrel
2. Low-density lipoprotein cholesterol less than 100 mg/dL and HMG-CoA reductase inhibitor (statin) medication use
3. Tight blood sugar control for patients with diabetes, with HBA1C goal of lower than 7%
4. Blood pressure control with particular benefit of angiotensin-converting enzyme inhibitor therapy
5. Tobacco cessation

Revascularization goal

Lower extremity revascularization to prevent amputation is recommended for ambulatory patients with critical limb ischemia. In the setting of tissue loss, the goal of revascularization is to achieve uninterrupted in-line flow to the area of ulceration. Anatomic findings, as well patient operative risk, are the primary determinants of what endovascular and surgical interventions are performed. General guiding principles of revascularization are as follows:

1. Endovascular therapy: stenosis at all arterial levels; short-segment occlusions in the iliac or superficial femoral artery (SFA) distribution
2. Surgical bypass: long-segment arterial occlusions
3. Surgical endarterectomy: occlusion or high-grade stenosis at the common femoral artery bifurcation level to preserve flow to both the SFA and profunda femoral artery

These are not hard rules for revascularization, and treatment must be individualized with consideration given to patient operative risk, life expectancy, adequacy of autogenous venous conduit for potential bypass, and individual operator expertise and comfort level with given procedures.

For patients with rest pain in the absence of ulceration, correction of in-flow disease alone is often adequate to remove the patient from the limb threat category without the need for more morbid distal bypass procedures. If inflow alone is corrected, patients should be carefully monitored postoperatively for persistent rest pain or ulceration development. If either of these occur, more distal revascularization should be performed to achieve in-line flow to the foot.

Endovascular therapy

The following is a simplified summary of endovascular revascularization steps:

1. Obtain arterial access and perform angiography
2. Pass a guidewire beyond areas of stenosis or occlusion
3. Confirm that the guidewire is in the true lumen of the distal arterial tree
4. Perform angioplasty, stent placement, or atherectomy over the guidewire
5. Confirm success of results with completion angiography

The angioplasty concept is depicted in Fig. 10. The 2 primary indications for stent placement are residual stenosis after angioplasty or presence of dissection after angioplasty.

With respect to patency outcomes, stenosis fares better than occlusions and short-segment disease has improved patency to long-segment lesions. Iliac percutaneous revascularization has primary and secondary patency rates of 67% and 80% at 5 years.

An example of a short-segment SFA lesion well suited to angioplasty is seen in Fig. 11. Transluminal treatment patency rates for femoral-popliteal lesions are listed in Table 1. Within the superficial femoral artery long segment TransAtlantic Inter-Society Consensus (TASC) class C and D occlusive disease has improved patency with primary stenting versus angioplasty alone (Fig. 12).

Tibial-level angioplasty is also feasible, but has significantly poorer patency than iliac and SFA percutaneous interventions. Tibial angioplasty primary patency rates are less than 50% at 1 year. An example of a short-segment anterior tibial artery stenosis well suited to angioplasty in a patient with digital gangrene is illustrated in Fig. 13. Often patency is necessary only until pedal ulceration has healed, beyond which correction of above-knee disease may keep patients out of the limb threat category.

Access site complications represent the most frequent morbidity of endovascular procedures with bleeding, pseudoaneurysm, or arterial dissection and thrombosis inducing a complication that requires open surgical intervention after 1% to 2% of procedures. Pseudoaneurysms larger than 2 cm can be treated percutaneously with thrombin injection under duplex ultrasound guidance: 1000 units of thrombin diluted in 3 mL of normal saline is injected to the pseudoaneurysm through a 21-gauge needle (Fig. 14). Access site dissection resulting in arterial thrombosis is best treated with surgical thromboendarterectomy. Bleeding refractory to direct pressure and reversal of anticoagulation resulting in hemodynamic compromise, tense hematoma on the
skin, or transfusion requirement greater than 4 units of packed red blood cells should be treated with surgical arterial repair and hematoma drainage.

**Open surgical therapy**

Surgical bypass is performed for long-segment occlusive disease in acceptable risk patients with critical limb ischemia. All bypasses should be based on angiographic and hemodynamically confirmed normal inflow arteries. In the setting of tissue loss, the outflow target should provide in-line distal flow to the affected foot. The shortest-length bypass that provides in-line flow to the foot should be performed.

Aorto-iliac reconstructions are generally performed with prosthetic Dacron or polytetrafluoroethylene (PTFE) conduit. Open aorto-iliac reconstruction is preferred for

<table>
<thead>
<tr>
<th>Lesion and Treatment</th>
<th>1-Y Patency, %</th>
<th>3-Y Patency, %</th>
<th>5-Y Patency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis – PTA</td>
<td>77</td>
<td>61</td>
<td>55³</td>
</tr>
<tr>
<td>Stenosis – PTA + Stent</td>
<td>75</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Occlusion – PTA</td>
<td>65</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>Occlusion – PTA + Stent</td>
<td>73</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** PTA, percutaneous transluminal angioplasty.

³ Versus 75% for above-knee vein bypass; versus 60% for above-knee polytetrafluoroethylene bypass.

acceptable surgical risk patients with bilateral TASC C and D occlusive disease. An example of anatomy best treated with aorto-bifemoral artery bypass is depicted in Fig. 15. Primary patency for direct aorto-iliac reconstructions is excellent and approaches 90% in most series.35–39

Patients with high abdominal operative risk critical limb ischemia with advanced aorto-iliac occlusive disease that is not amenable to endovascular therapy can be treated with extra-anatomic bypass. Axillary bifemoral artery bypass (Fig. 16) can be performed with heavy sedation and local anesthesia and has 3-year patency rates


Fig. 13. Stenosis of the proximal anterior tibial artery in a patient with digital gangrene successfully treated with angioplasty. Pretreatment seen left and posttreatment on the right. Arrows pointing to occlusive disease segments.
in the 70% to 80% range.\textsuperscript{40–45} For unilateral iliac occlusion with patent contralateral iliac artery system, fem-fem bypass is an option (\textbf{Fig. 17}).

For infrainguinal long-segment arterial occlusions, surgical bypass with autogenous venous conduit provides the most durable revascularization. In addition to improved patency, autogenous vein does not have the graft infection potential of prosthetic conduit. A venous conduit of 3 mm or greater should be sought. Ipsilateral greater

\textbf{Fig. 14.} Pseudoaneurysm thrombin injection. Duplex ultrasound of a femoral pseudoaneurysm. (A) Color-flow image demonstrating typical swirling flow in the pseudoaneurysm cavity. (B) This image, taken 18 seconds later with color flow turned off, shows the tip of a 22-gauge needle in the left lower portion of the pseudoaneurysm (arrow). After placement of the needle, color flow is turned back on and thrombin is injected. (C) Color-flow image 21 seconds later demonstrating that the pseudoaneurysm cavity is completely filled with echogenic thrombus. (From Kang SS, Labropoulos N, Mansour MA, et al. Percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms. J Vasc Surg 1998;27:1032–8; with permission.)

\textbf{Fig. 15.} Patient with complete aorto-iliac occlusion previously treated with covered stents at outside hospital, subsequently treated with aorto-bifemoral artery bypass with good success. Arrows pointing to occlusive disease segments.
saphenous vein is the first preference. Other options include contralateral greater saphenous vein and upper extremity cephalic and basilic veins. In multiple randomized trials of infragenual bypass, autogenous venous conduit has demonstrated significantly better patency than PTFE and Dacron. It is the author’s practice to perform completion angiography in the operating room after all infragenual bypasses.

If no autogenous vein is available, then 6-mm-diameter PTFE or Dacron conduit is used for infragenual bypass. For bypasses to distal tibial arteries where wound breakdown is particularly common, cryopreserved cadaveric saphenous vein or composite sequential (proximal prosthetic and distal autogenous) conduit are useful to

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**Fig. 16.** Axillary bifemoral artery bypass. (From Schneider JR. Extra-anatomic bypass. In: Cronenwett JL, Johnston KW, editors. Rutherford’s vascular surgery. 7th edition. Philadelphia: Elsevier; 2010; with permission.)

**Fig. 17.** Femoral-femoral artery bypass. (From Schneider JR. Extra-anatomic bypass. In: Cronenwett JL, Johnston KW, editors. Rutherford’s vascular surgery. 7th edition. Philadelphia: Elsevier; 2010; with permission.)
reduce the incidence of exposed prosthetic bypass. Heparin-bonded PTFE conduit has illustrated modest improvement in prosthetic bypass patency relative to non-heparin-bonded historical patency for below-knee bypass in patients with critical limb ischemia.\(^4^8\)

Thromboendarterectomy with patch angioplasty remains the gold standard treatment for common femoral artery occlusive disease. When concomitant bypass is needed, a long proximal graft hood can be constructed to serve effectively as a patch angioplasty. Preserving and optimizing profunda femoral artery outflow, particularly for patients with SFA disease, is critical in the event the SFA revascularization fails in the future.

Open surgical lower extremity revascularization does carry fairly high morbidity. Wound complications (20%) and persistent edema (20%) are common. Within 1 year, 10% of patients who received bypass experience graft thrombosis and 10% experience major amputation. Graft infection occurs following 1% to 2% of prosthetic conduit bypasses.\(^1^1\)

**Hybrid surgical therapy**

Combinations of endovascular and open surgical therapies are frequently applicable to patients with critical limb ischemia with short-segment lesions in one anatomic distribution and more advanced lesions in another segment. The most frequent hybrid revascularization performed is iliac distribution angioplasty and stent placement in conjunction with infrainguinal bypass or common femoral endarterectomy. **Fig. 18** exhibits such anatomy and treatment. Similarly, outflow vessel angioplasty is an option when a short focal stenosis exists and the total bypass length can be significantly shortened by treating a distal lesion with endovascular therapy.

**Surgical versus endovascular therapy in critical limb ischemia**

The decreased morbidity associated with endovascular revascularization relative to open surgery has led many vascular specialists to adopt an endovascular first approach to treating critical limb ischemia. The primary advantage of surgical intervention over endovascular revascularization is durability of reconstruction, particularly for TASC C and D infrainguinal occlusions with vein graft 5-year patencies of more than 75%. Although 2-year primary patency for endovascular treatment of TASC D

![Fig. 18. Patient best treated with hybrid revascularization of common iliac angioplasty with above result followed by common femoral endarterectomy. The image on the left and center are pretreatment. Image on the right is post common iliac artery stent placement.](image-url)
SFA-popliteal lesions is just 28%, secondary patency with percutaneous reintervention is achieved in more than 80%, avoiding the need for major open surgery.⁴⁹

The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial represents the largest randomized trial comparing surgical bypass to endovascular therapy for lower extremity arterial occlusive disease. Limb salvage rates were found to be equivalent for endovascular versus open surgical bypass (Fig. 19).⁵⁰ Overall survival was similar between the 2 groups at 2 years, and there was a trend toward increased overall survival in the open surgical group after 2 years. Further, patients with failed angioplasty who crossed over into the surgical bypass cohort experienced a statistically significant higher amputation rate at all follow periods up to 6 years.⁵¹

**Postrevascularization surveillance**

Regardless of the type of revascularization performed, patients with critical limb ischemia should be followed with serial arterial duplex and ABI with digital pressures. Angioplasty and stenting sites are prone to re-stenosis. Lower extremity bypasses are vulnerable to neo-intimal hyperplasia-induced stenosis anywhere along the length of a vein bypass and near the anastomosis sites of prosthetic bypasses.⁵²–⁵⁴ Stenoses are detected as areas of increased peak systolic velocity on Doppler analysis. A velocity ratio of greater than 3:1 between an area of stenosis and the proximal normal arterial segment indicates a 50% or greater stenosis. Fig. 20 depicts a proximal

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**Fig. 19.** Limb salvage rates in the bypass first versus angioplasty limbs of the BASIL trial. *(Data from Adam DJ, Beard JD, Cleveland T, et al. Bypass vs angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925–34.)*

**Fig. 20.** Proximal femoral-popliteal artery bypass stenosis detected after drop in ABI treated with angioplasty. Preangioplasty seen on the left and post angioplasty images on the right. Arrows pointing to occlusive disease segments.
femoral-popliteal bypass graft stenosis treated with angioplasty after a drop in ABI was detected. An absolute velocity of less than 40 cm per second in a bypass distal to a stenosis represents a threatened graft that should be imaged with CTA or angiography. Significant in-graft stenosis should be treated with transluminal angioplasty, surgical patch angioplasty, or revision jump graft. In addition, new atherosclerotic lesions in the native arteries proximal or distal to lower extremity bypasses should be treated to assist bypass patency.

There is profound benefit to correction of significant stenosis in a threatened bypass to maintain primary assisted patency. Once a bypass becomes thrombosed, secondary patency is reduced threefold relative to assisted primary patency for bypasses intervened on before thrombosis occurs (Fig. 21). After revascularization, it is our practice to obtain arterial duplex scanning at 1, 3, 6, and 12 months after the procedure and every 6 months thereafter.

**Nonreconstructable tibial occlusive disease and critical limb ischemia**

Patients with nonreconstructable tibial distribution occlusive disease (no bypass targets) benefit from intermittent pneumatic compression treatment at the calf level. This can be used as a last measure for attempt at limb salvage before major amputation in patients with critical limb ischemia. Further ongoing research in treating such patients is directed at angiogenesis via stem cell and growth factor implantation in the calf, as well as bone marrow stimulation with granulocyte colony stimulating factor (GCSF).

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18. ATC. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet


Critical appraisal of surgical revascularization for critical limb ischemia

Michael S. Conte, MD, San Francisco, Calif

Peripheral artery disease is growing in global prevalence and is estimated to afflict between 8 and 12 million Americans. Its most severe form, critical limb ischemia (CLI), is associated with high rates of limb loss, morbidity, and mortality. Revascularization is the cornerstone of limb preservation in CLI, and has traditionally been accomplished with open surgical bypass. Advances in catheter-based technologies, coupled with their broad dissemination among specialists, have led to major shifts in practice patterns in CLI. There is scant high-quality evidence to guide surgical decision making in this arena, and market forces have exerted profound influences. Despite this, available data suggest that the expected outcomes for both endovascular and open surgery in CLI are strongly dependent on definable patient factors such as anatomic distribution of disease, vein quality, and comorbidities. Optimal patient selection is paramount for maximizing benefit with each technique. This review summarizes some of the existing data and suggests a selective approach to revascularization in CLI, which continues to rely on vein bypass surgery as a primary option in appropriately selected patients. (J Vasc Surg 2013;57:S8S-13S.)

Peripheral artery disease (PAD) is a growing public health issue in the United States and around the globe. Currently estimated to afflict more than 8 million Americans, PAD and its related health care expenditures have increased dramatically with recent demographic and risk factor trends, particularly the rise in diabetes. Its most advanced form, critical limb ischemia (CLI), is associated with high rates of limb loss, morbidity, and mortality. Recent estimates of the Medicare expenditures associated with treatment for CLI exceed $3 billion annually. These costs are driven largely by in-hospital care related to procedures, primarily revascularizations, among which are the growing volume of endovascular interventions. Despite the magnitude of the problem, there is scant high-quality evidence to guide medical and surgical decision making in CLI.

CLI is defined clinically as a syndrome of advanced ischemia manifest by either rest pain in the foot or tissue loss (Rutherford classification 4-6, Fontaine III/IV). However, this definition encompasses a broad range of disease severity and natural history, which greatly complicates comparisons of results in the literature. Indeed, the lack of a more precise disease staging system has been a major impediment in the field. The diagnosis of CLI is supported by hemodynamic assessment demonstrating severely compromised foot perfusion, although there is a lack of consensus on threshold values. Commonly accepted values of ankle pressure (<30 mm Hg for rest pain, <70 mm Hg for tissue loss) or toe pressure (<30 mm Hg for rest pain; <50 mm Hg for tissue loss) define critical levels of ischemia. A dire natural history is generally ascribed to the diagnosis of CLI, with 15%-20% mortality and up to 40% limb loss within a year of diagnosis. CLI also has a profound negative impact on patient quality of life, with wound care and analgesic requirements, impaired ambulation, reduced level of function, and recurrent hospitalizations. The primary therapeutic goals in CLI are relief of pain, healing of wounds, preservation of a functional limb, and maintenance of ambulatory status. These goals are directly related to timely and effective revascularization of the lower extremity. For some patients, primary amputation is the most appropriate therapy. Most patients have significant comorbidities including other manifestations of atherosclerosis. Minimizing the risk of mortality and major cardiovascular events is central to the care of the patient with CLI and is addressed by the appropriate use of diagnostics, medical therapies, and risk factor modification.

REvascularization strategies in CLI: Key factors in the initial evaluation

Clinical decision making in the patient with CLI must carefully weigh a variety of patient, anatomic, and procedural variables (Fig). The complexity of these decisions emphasizes the importance of broad training in vascular disease and longitudinal patient care experience. The general health and life expectancy of the patient, as well as their ambulatory status, are a physician’s foremost considerations. Some patients with advanced comorbidities may not be suitable for open bypass surgery or a general anesthetic. Conservative therapy or less invasive modalities may be most appropriate in the frail or dependent patient. However, the available data suggest that the 30-day mortality rates for
endovascular intervention (2%-8%)\textsuperscript{4,7-10} and surgical bypass (2%-6%)\textsuperscript{11-16} in CLI are similar, whereas the rate is generally higher for primary amputation (6%-12%)\textsuperscript{17,19} than for either form of revascularization (Table I). Obviously, these data reflect primarily the medical acuity of the patients selected for each approach, and highlight the challenges inherent in the management of CLI.

A thorough examination of the limb and foot defines the severity of ischemia, the likelihood of functional salvage, and the presence of critical factors such as local sepsis, soft tissue compromise, venous disease, and prior surgical incisions. A careful history of prior vascular interventions in the limb is paramount to developing a strategy, and detailed reports should be obtained. The anatomic distribution of disease is determined by imaging studies such as computed tomography angiography, magnetic resonance angiography, duplex ultrasound scanning, and catheter-based angiography. Finally, the availability and quality of autogenous vein for bypass must be ascertained, and this is best done by ultrasound vein mapping. Only when all of this information is available can the optimal revascularization strategy be defined for the individual patient with CLI.

The anatomic distribution of arterial occlusive disease is a dominant factor in developing the strategy, because of its known relationship to the success of treatment modalities. This review focuses on infrapopliteal occlusive disease, where the typical anatomy encountered in the patient with CLI is challenging for endovascular therapy. Common femoral disease, long-segment femoropopliteal occlusions, multilevel disease, and diffuse infrapopliteal disease are common patterns in CLI.\textsuperscript{20} The current TransAtlantic Inter-Society Consensus (TASC) II guidelines provide a framework for decision making based primarily on disease anatomy, with surgery preferred for more severe lesions (TASC C/D), although there is considerable controversy around these guidelines and variability in their application. The TASC classification scheme does not take into account all of the aforementioned clinical and patient-level factors and has had the unintended consequence of encouraging a lesion-centric mentality in the care of the patient with PAD. Another important caveat about the TASC

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**Table I.** Periprocedural (30-day) mortality and major morbidity after treatment of critical limb ischemia (CLI)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Open bypass</th>
<th>Endovascular therapy</th>
<th>Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>2.1%-5.4\textsuperscript{11-16} (2.7%)\textsuperscript{a}</td>
<td>2%-8\textsuperscript{5,6-9} (2.7%)\textsuperscript{a}</td>
<td>6%-13\textsuperscript{13,17,18}</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>6.2%\textsuperscript{a}</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Amputation\textsuperscript{b}</strong></td>
<td>1.9%\textsuperscript{a}</td>
<td>3.1%\textsuperscript{a}</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>MALE</strong></td>
<td>6.1%\textsuperscript{a}</td>
<td>16.2%\textsuperscript{a}</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Value from the Society for Vascular Surgery Critical Limb Ischemia Objective Performance Goals data set\textsuperscript{22} (www.criticallimb.org).

\textsuperscript{b}Transtibial or above.

\textsuperscript{c}Estimated rates from reference\textsuperscript{4} range depending on Rutherford presentation (4-6).
PRINCIPLES OF REVASCULARIZATION IN CLI

Regardless of the mode of revascularization selected, certain fundamental principles are critical to a successful outcome in CLI. High-quality vascular imaging is mandatory, generally obtained by digital subtraction angiography, with multiple dedicated views of the ankle and foot. A goal of restoring straight-line flow to the foot is especially important in the setting of tissue loss. Pulsatile blood flow optimizes the local environment for wound healing. Treating proximal lesions in the presence of a distal occlusion will predictably be inadequate for patients with tissue loss or infection. After intervention, vigilant follow-up are required to assess, and to maintain, hemodynamic improvement. Sustained hemodynamic improvement in the treated limb is the most direct measure of effective revascularization therapy. At scheduled follow-up visits, clinical examination, ankle/ toe pressures, and duplex ultrasound scanning of the arteries or bypass graft are performed to identify recurrent narrowings or occlusions. Many, if not most, patients with CLI undergo repeat interventions over time because of the frequency of restenosis and graft disease. A low threshold for reintervention, including early conversion to open bypass surgery for endovascular treatment failure, is employed to avoid further tissue loss and maintain functional limb salvage.

ENDOVASCULAR THERAPY FOR CLI

Enthusiasm for endovascular treatment in CLI has been fueled by the continued evolution of catheter-based technologies, the broad dissemination of the requisite skills among vascular specialists, and the significant potential advantages of a less invasive approach in a sick population. These include presumed lower mortality and complication rates, although recent data suggest this assumption may be flawed. Recovery from a percutaneous procedure is faster than from open surgery and avoids wound morbidity and other surgical complications. Moreover, it is often argued that the treatments can be repeated as needed without “burning bridges” for the patient. Unfortunately, these potential advantages are not always realized in practice, and a review of the contemporary literature provides a more sanguine view of the outcomes obtained after endovascular interventions in CLI.

Like any therapy, there are also significant limitations and disadvantages to be considered for endovascular treatment of CLI. These include reduced efficacy of the revascularization, in terms of both acute hemodynamic improvement and sustained hemodynamic success. Clearly, there is a risk of limb deterioration related to failures and complications of the percutaneous intervention, and surgical options may be affected, for example, by the use of stents at preferred inflow or outflow anastomosis sites or by the loss of distal outflow to the foot. There is a cost to both the patient and the health care system of ineffective or nondurable treatments. Recurrent symptoms, delayed healing, further tissue loss, and repeat interventions are more likely when the initial revascularization is ineffective or improved perfusion is not sustained.

Recent data suggest that the early and midterm outcomes of endovascular treatment in CLI may be acceptable in well-selected patients and experienced centers (Table II). Limb salvage rates greater than 80% are reported at 1-3 years. All series demonstrate that restenosis and reintervention are extremely common. Unfortunately, comparison of outcomes between series is fraught with difficulty because techniques are not standardized, cohorts are heterogeneous, numbers are modest, and observations often limited by variable follow-up time and quality. Most series are heavily skewed to less severe presentations (Rutherford 4/5). A full review of this topic is well beyond the scope of the present article. However, consistent themes emerge with respect to the factors associated with poor outcome for endovascular treatment in CLI. Disease severity (TASC D anatomy), tissue loss, and diabetes consistently predict poorer outcomes after endovascular treatment. There remain many unknowns, particularly with respect to the outcomes of interventions for popliteal and infrapopliteal disease. Knowledge of the risks and limitations of endovascular treatment is important in decision making, which is finalized at the time of diagnostic angiography and prior to attempting guidewire traversal of lesions. Although technical success in the reported series is generally high, fueling the enthusiasm of practitioners, the data clearly indicate that technical success does not equate to clinical success for the patient. Most research emphasis in device technology has been driven toward the technical element, although the recent development of drug-coated balloons and stents offers hope for improving the durability of these interventions. The full potential benefit for endovascular interventions in CLI will not be realized until restenosis is dramatically reduced for the challenging disease patterns commonly encountered in these patients.

Table II. Key midterm outcomes of endovascular therapy for critical limb ischemia (CLI) from selected series

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Outcome Rate</th>
<th>Follow-up, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laird et al22</td>
<td>155</td>
<td>AFS 82%</td>
<td>0.5</td>
</tr>
<tr>
<td>Giles et al8</td>
<td>176</td>
<td>RAS/LS 39%/84%</td>
<td>1</td>
</tr>
<tr>
<td>DeRubertis et al33</td>
<td>184</td>
<td>LS 88%</td>
<td>1</td>
</tr>
<tr>
<td>Conrad et al7</td>
<td>447</td>
<td>LS 88%</td>
<td>1</td>
</tr>
<tr>
<td>Romiti et al7</td>
<td>2653</td>
<td>LS 82%</td>
<td>3</td>
</tr>
</tbody>
</table>

AFS, Amputation-free survival; LS, limb salvage; RAS, reintervention, amputation, or stenosis >60%.
Table III. Contemporary 1-year results of autogenous vein surgical bypass for critical limb ischemia (CLI) from multicenter prospective trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PREVENT III (n = 1404)</th>
<th>BASIL (n = 186)</th>
<th>SVS OPG23 (n = 838)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>84%</td>
<td>81%</td>
<td>86%</td>
</tr>
<tr>
<td>Limb salvage</td>
<td>88%</td>
<td>88%</td>
<td>89%</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>78%</td>
<td>72%</td>
<td>77%</td>
</tr>
<tr>
<td>Freedom from major</td>
<td>75%</td>
<td>80%</td>
<td>77%</td>
</tr>
<tr>
<td>Adverse limb event</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BASIL, Bypass Versus Angioplasty in Severe Ischaemia of the Leg; OPG, Objective Performance Goals; PREVENT III, Project of Ex Vivo Graft Engineering via Transfection III; SVS, Society for Vascular Surgery.

SURGICAL BYPASS FOR CLI: CONTEMPORARY OUTCOMES

Results of autogenous vein bypass grafting for CLI are well documented in many single-center reports, meta-analyses, and multicenter trials. Autogenous vein grafts to tibial or pedal targets for CLI function for 5 years or longer in 50%-70% of patients. Limb salvage rates generally exceed 80% at 5 years.2 The procedure is versatile with respect to anatomic circumstances and patient risk factors. Perioperative mortality is acceptably low (3%) and not dissimilar to percutaneous intervention. However, there are important limitations and risks to be considered, including postoperative morbidity, which is significant (20%). Wound complications are frequent (10%-20%) and may incur prolonged hospitalization, additional procedures, outpatient care, and patient discomfort. Systemic complications such as cardiac, pulmonary, and renal problems are not rare, and recovery in such cases may be prolonged. Availability of good-quality venous conduit is an important limitation in at least 20% of surgical candidates, and other alternatives such as prosthetic grafts are inferior. De novo stenosis within the vein graft conduit occurs in 30%-40% of patients within the first 2 years of bypass, mandating a program of surveillance and reintervention to preserve long-term patency. Most importantly, distal bypass surgery for limb salvage is one of the most technically demanding procedures in vascular surgery, and there is significant variability in training, experience, and skill among practitioners. It is likely that this plays a significant role in local practice patterns as well as in the outcomes realized.

The Project of Ex Vivo graft Engineering via Transfection III (PREVENT III) and Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trials provide a broad snapshot of limb salvage surgery in both North America and the United Kingdom (Table III). The BASIL bypass cohort included 25% prosthetic grafts that performed poorly, whereas the PREVENT III cohort was composed exclusively of vein bypass grafts. The reader is referred to the key reports from these individual trials,10,12 the data from which have recently been combined in an effort by the Society for Vascular Surgery to develop performance goals in CLI.23 A perioperative (30-day) mortality rate of 3%, major adverse cardiovascular event (MACE) rate of 6%, graft occlusion rate of 5%, and amputation rate of 2% are the expected early results for open bypass surgery with vein. At 1 year, expected limb salvage is 88% and amputation-free survival is 77% for the broad CLI cohort represented by these surgical trials. A major adverse limb event outcome was defined as a key patient-centered end point consisting of major amputation, need for thrombolysis/thrombectomy, placement of a new open bypass, or major graft revision (other than simple patch). Freedom from major adverse limb events at 1 year was 77% in the Society for Vascular Surgery Objective Performance Goals surgery cohort.

It is important to note that all of the key CLI outcomes reported in the Society for Vascular Surgery Objective Performance Goals trial were strongly dependent on baseline patient factors, and heterogeneity across these variables would be expected to have a significant influence on the expected outcomes. The most important factors included age (>60), tissue loss, infrapopliteal disease, and a poor-quality venous conduit. Because these factors exert significant effects, nonrandomized comparisons between different cohorts without risk stratification are likely to lead to erroneous conclusions.

Technical factors are critical to the short- and long-term success of bypass surgery, with vein quality being paramount.24,25 A single-segment great saphenous vein graft with a diameter ≥3.5 mm is the optimal conduit for leg bypass. Nearly half of the patients in the PREVENT III trial had their bypasses completed with such conduits, experiencing a 1.7% 30-day failure rate, 87% secondary patency, and 91% limb salvage at 1 year. Moreover, the level of distal anastomosis (a surrogate for arterial disease pattern) is not an important limitation for a good-quality vein; that is, tibial/pedal bypasses with ≥3.5 mm single-segment great saphenous vein grafts perform equally as well as popliteal bypass grafts in terms of all measured outcomes including patency. Further, diabetes does not have a negative impact on infrapopliteal vein graft performance, a fact that has been reported in multiple large institutional series as well as in the multicenter PREVENT III cohort.26,27 Overall, these contemporary data confirm that a saphenous vein bypass graft remains the gold standard for durable revascularization in the patient with CLI.

Many authors have attempted to define preoperative factors that predict outcomes for infrapopliteal bypass surgery. Using the PREVENT III cohort, a risk score was recently developed and validated to predict amputation-free survival after surgical bypass for CLI.28 Five baseline variables—dialysis dependency, tissue loss, age >75, anemia (hematocrit <30%), and history of advanced coronary artery disease—can be used to stratify patients for expected outcome. A high-risk cohort was defined based on a weighted scoring system and was represented by 9% of the PREVENT III population and 6% of a multicenter surgical consortium database.29 For this high-risk group, amputation-free survival at 1 year was approximately 50%, suggesting that one in two such patients did not experience...
a meaningful benefit from the operation. Clearly, careful risk stratification is paramount to selecting candidates for both endovascular and surgical bypass in CLI.

At present, only one randomized trial—BASIL—has directly compared the outcomes of endovascular and open bypass strategies for advanced limb ischemia. The design of BASIL and its potential limitations have been described in detail elsewhere. However, it constitutes the only level I evidence currently available in the field.30,31 The investigators randomized 452 patients with “severe limb ischemia” to surgery-first or balloon angioplasty-first treatment strategies and had long-term follow-ups to 5 years or longer in most patients. Most of the patients randomized in BASIL had moderate to severe disease either above or below the knee, and commonly only a single segment was treated. Isolated tibial angioplasty was rarely performed, and 25% of the bypass grafts were prosthetic. All of these factors would tend to weigh in favor of better outcomes for angioplasty. At 1 year, there was no difference in amputation-free or overall survival. However, for patients who survived to 2 years (70% of the cohort), there was a survival advantage associated with the bypass-first assignment and a trend toward improved amputation-free survival. Moreover, crossover to bypass surgery was significant in the trial, and the analysis by treatment received suggested that patients who had bypass after a failed initial angioplasty fared much more poorly than patients who had an initial bypass.21 This observation directly refutes the “free-shot” notion of angioplasty in CLI and has been confirmed in other recent multicenter cohorts.22 The BASIL authors concluded that bypass surgery with vein offers the best long-term outcome and is the preferred treatment for patients expected to survive to 2 years or longer (approximately 70% of their cohort). They also opined that prosthetic bypass was associated with poor results, and therefore, angioplasty may be preferred where possible in patients lacking adequate venous conduit.

CONCLUSIONS

Any thoughtful review of the available data leads one to the conclusion that neither an “endo-first” nor a “bypass-first” dogma is an appropriate posture in patients with CLI. Instead current evidence, combined with individual experience, should be used to select the optimal approach in each case. Anatomic factors exert a strong influence on surgical decision making; however, the physiologic state of both the limb and the overall patient will dominate the outcome. In this highly vulnerable population, much is at stake, and adverse events are common. Early failures, generally a result of either a flawed revascularization strategy or a technical failure, often lead to rapid deterioration of the limb. Furthermore, most patients with true CLI will experience a recrudescence of symptoms if the intervention fails at a later time. Sustained hemodynamic success is therefore the primary objective of revascularization. Open surgical bypass continues to be a primary treatment choice in a significant proportion of patients and is not infrequently required after failed endovascular intervention. Aggressive medical management, technical proficiency, and postprocedural surveillance are cornerstones of success. Wound management and foot care are likewise critical both to achieve and to maintain long-term function. All patients with CLI should be cared for by dedicated specialists with training and experience in these realms, ideally in a coordinated multidisciplinary center. As technology continues to improve, better-quality evidence in the form of carefully conducted clinical trials and registries is sorely needed to improve patient outcomes and control costs.


31. Conte MS. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg 2010;51:695-7S.


Submitted Nov 23, 2011; accepted May 18, 2012.

A 57-year-old man presents with an acute onset of left foot pain, numbness, and partial loss of motor function. Four months ago, he underwent endovascular treatment for disabling claudication, which included placement of overlapping polytetrafluoroethylene-coated stents in the left superficial femoral and popliteal arteries. His popliteal and pedal pulses are absent, and the foot is cool and mottled. Angiography reveals complete occlusion of the stent, with thrombosis extending distally into the popliteal and tibial arteries below the knee. How should his case be managed?

THE CLINICAL PROBLEM

Acute limb ischemia is defined as a sudden decrease in limb perfusion that threatens the viability of the limb.1 The incidence of this condition is approximately 1.5 cases per 10,000 persons per year. The clinical presentation is considered to be acute if it occurs within 2 weeks after symptom onset. Symptoms develop over a period of hours to days and range from new or worsening intermittent claudication to pain in the foot or leg when the patient is at rest, paresthesias, muscle weakness, and paralysis of the affected limb. Physical findings may include an absence of pulses distal to the occlusion, cool and pale or mottled skin, reduced sensation, and decreased strength. These features of acute limb ischemia are often grouped into a mnemonic known as the six Ps: paresthesia, pain, pallor, pulselessness, poikilothermia (impaired regulation of body temperature, with the temperature of the limb usually cool, reflecting the ambient temperature), and paralysis.

The rapid onset of limb ischemia results from a sudden cessation of blood supply and nutrients to the metabolically active tissues of the limb, including skin, muscle, and nerves. In contrast to chronic limb ischemia, in which collateral blood vessels may circumvent an occluded artery, acute ischemia threatens limb viability because there is insufficient time for new blood-vessel growth to compensate for loss of perfusion. Urgent recognition with prompt revascularization is required to preserve limb viability in most circumstances.

Clinical events that cause acute limb ischemia include acute thrombosis of a limb artery or bypass graft, embolism from the heart or a diseased artery, dissection, and trauma (from severing of an artery or thrombosis). Acute thrombosis of a limb artery is most likely to occur at the site of an atherosclerotic plaque. Thrombosis may also occur in arterial aneurysms (particularly in the popliteal artery) and in bypass grafts. Thrombosis may complicate an autogenous vein bypass at anastomoses and sites of retained valve cusps, kinks, or other technical problems. Acute thrombosis of prosthetic grafts may occur anywhere in the graft conduit, even if there is no obvious predisposing abnormality. Thrombosis may also affect a previously normal limb artery in patients with thrombophilic conditions such as the antiphospholipid antibody syn-
drome and heparin-induced thrombocytopenia. Cardiac embolism is a particular concern in patients with atrial fibrillation, acute myocardial infarction, left ventricular dysfunction, or prosthetic heart valves who are not receiving anticoagulant therapy.

Rates of death and complications among patients who present with acute limb ischemia are high. Despite urgent revascularization with thrombolytic agents or surgery, amputation occurs in 10 to 15% of patients during hospitalization. A majority of amputations are above the knee. Approximately 15 to 20% of patients die within 1 year after presentation, often from coexisting conditions that predisposed them to acute limb ischemia.

Key Clinical Points

**ACUTE LIMB ISCHEMIA**

- Acute limb ischemia is a sudden decrease in limb perfusion that threatens limb viability and requires urgent evaluation and management.
- Causes of acute limb ischemia include acute thrombosis of a limb artery or bypass graft, embolism from the heart or a diseased artery, dissection, and trauma.
- Assessment of limb appearance, temperature, pulses (including by Doppler), sensation, and strength is used to determine whether the limb is viable, threatened, or irreversibly damaged.
- Prompt diagnosis and revascularization by means of catheter-based thrombolysis or thrombectomy or by surgical reconstruction reduce the risk of limb loss.
- Catheter-directed thrombolysis is the preferred treatment for a viable or marginally threatened limb, recent occlusion, thrombosis of synthetic grafts, and occluded stents. Surgical revascularization is generally preferred for an immediately threatened limb or occlusion of more than 2 weeks’ duration.
- Amputation is performed in patients with irreversible damage.

**STRATEGIES AND EVIDENCE**

**EVALUATION**

Acute limb ischemia should be distinguished from critical limb ischemia caused by chronic disorders in which the duration of ischemia exceeds 2 weeks and is usually much longer; these conditions include severe atherosclerosis, thromboangiitis obliterans, other vasculitides, and connective-tissue disorders. Other causes of limb ischemia include atheroembolism, vasospasm, the compartment syndrome, phlegmasia cerulea dolens (deep-vein thrombosis with severe leg swelling compromising perfusion), and vasopressor drugs. Nonischemic limb pain from acute gout, neuropathy, spontaneous venous hemorrhage, or traumatic soft-tissue injury may mimic acute ischemia.

A careful examination of the limbs is necessary to detect signs of ischemia, including decreased temperature and pallor or a mottled appearance of the affected limb. Sensation and muscle strength should be assessed. The vascular examination includes palpation of pulses in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries in the legs and in the brachial, radial, and ulnar arteries in the arms. The presence of flow, particularly in the dorsalis pedis and posterior tibial arteries supplying the affected foot or radial and ulnar arteries of the symptomatic hand, is routinely assessed with a Doppler instrument. If flow is audible, perfusion pressure to the ischemic limb can be measured with a sphygmomanometric cuff placed at the ankle or wrist just proximal to the Doppler probe; a perfusion pressure of less than 50 mm Hg indicates limb ischemia.

The severity of acute limb ischemia is categorized according to the clinical presentation and prognosis (Table 1). This categorization guides decisions about additional testing and revascularization. Optimal management requires prompt administration of intravenous heparin to minimize thrombus propagation. In patients with viable (stage I) or marginally threatened (stage IIA) limbs, it may be reasonable to perform imaging (duplex ultrasonography, computed tomographic angiography, or magnetic resonance angiography) to determine the nature and extent of the occlusion and...
to plan intervention (Fig. 1). Although such types of testing have not been studied specifically for acute limb ischemia, they have sensitivities and specificities exceeding 90% for chronic arterial disease.5-7 The availability of imaging and the time required to perform and interpret it must be balanced against the urgency for revascularization. In most patients with acute limb ischemia, catheter angiography remains the cornerstone approach (Fig. 2A). In the past, patients with immediately threatened limbs (stage IIb) were taken directly to the operating room. Hybrid operating rooms with angiographic capability and improved endovascular techniques for thromboembolectomy make it possible to perform imaging and revascularization in a single setting. Imaging and revascularization are not indicated if the limb is irreversibly damaged (stage III).

**TREATMENT**

Acute limb ischemia is treated by means of endovascular or open surgical revascularization. Often, the techniques are complementary. However, they are reviewed here as discrete entities.

**Endovascular Revascularization**

The goal of catheter-based endovascular revascularization is to restore blood flow as rapidly as possible to a viable or threatened limb with the use of drugs, mechanical devices, or both. Patients in whom ischemia for 12 to 24 hours would not be safe and those with a nonviable limb, bypass graft with suspected infection, or contraindication to thrombolysis (e.g., recent intracranial hemorrhage, recent major surgery, vascular brain neoplasm, or active bleeding) should not undergo catheter-directed therapies.

Patients are treated with concomitant low-dose unfractionated heparin through a peripheral intravenous cannula or the arterial sheath at the access site to prevent the formation of a pericatheter thrombus.8 Before revascularization, diagnostic angiography is performed to assess the inflow and outflow arteries and the nature and length of thrombosis (Fig. 2A). Thereafter, the operator crosses the occlusion with a guidewire and a multi–side-hole catheter, which allows direct delivery of the thrombolytic agent into the thrombus.9 Clinical and angiographic examinations are performed during the infusion to determine progress (Fig. 2B), and patients are monitored for potential complications. The blood count and coagulation profile are periodically measured.10 Once flow is restored, angiography is performed to detect any inciting lesion, such as graft stenosis or retained valve cusps, which can be managed with catheter-based techniques or surgery (Fig. 2C).

Thrombolytic agents work by converting plasminogen to plasmin, which then degrades fibrin. The agents that are currently in use for most peripheral procedures are alteplase (Genentech), a recombinant tissue plasminogen activator; reteplase (EKR Therapeutics), a genetically engineered mutant of tissue plasminogen activator; and tenecteplase (Genentech), another genetically engineered mutant of tissue plasminogen activator. These agents are intended to selectively activate plasminogen bound in the thrombus and are administered over a period of 24 to 48 hours,11,12 although none are approved by the Food and Drug Administration for this indication. Streptokinase, an indirect plasminogen activator, was the first agent used for intraarterial thrombolysis, but its use has been largely abandoned in the United States.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description and Prognosis</th>
<th>Sensory Loss</th>
<th>Muscle Weakness</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Limb viable, not immediately threatened</td>
<td>None</td>
<td>None</td>
<td>Audible</td>
<td>Audible</td>
</tr>
<tr>
<td>II</td>
<td>Limb threatened</td>
<td>None</td>
<td>None</td>
<td>Audible</td>
<td>Audible</td>
</tr>
<tr>
<td>IIa</td>
<td>Marginally threatened, salvageable if promptly treated</td>
<td>None</td>
<td>None</td>
<td>Often inaudible</td>
<td>Audible</td>
</tr>
<tr>
<td>IIb</td>
<td>Immediately threatened, salvageable with immediate revascularization</td>
<td>None</td>
<td>None</td>
<td>Usually inaudible</td>
<td>Audible</td>
</tr>
<tr>
<td>III</td>
<td>Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable</td>
<td>None</td>
<td>None</td>
<td>Inaudible</td>
<td>Inaudible</td>
</tr>
</tbody>
</table>

* Data are from the Society for Vascular Surgery standards.4
States because of lesser efficacy and higher rates of bleeding, as compared with other thrombolytic agents, and the potential for allergic reactions.\textsuperscript{8,13,14} The direct plasminogen activator urokinase is no longer available in the United States because of manufacturing issues resulting in a discontinuation of production.

Catheters can be successfully positioned across the thrombosed vessel (an essential prerequisite) in 95% of cases.\textsuperscript{15} Among patients with acute limb ischemia caused by an occluded native vessel, stent, or graft, complete or partial thrombus resolution with a satisfactory clinical result occurs after catheter-based thrombolysis in 75 to 92% of patients.\textsuperscript{3,8,15,16} Distal thrombus embolization commonly occurs as the thrombus is lysed, but the embolized thrombus typically clears during the thrombolytic infusion.\textsuperscript{3} The adjunctive use of glycoprotein IIb/IIIa receptor antagonists may accelerate reperfusion and reduce distal embolization, but the addition of these agents does not improve outcomes.\textsuperscript{17,18}

Bleeding occurs most commonly at the catheter-insertion site, but it can also occur remotely, particularly in recent operative fields. Major hemorrhage occurs in 6 to 9% of patients, including intracranial hemorrhage in less than 3%.\textsuperscript{19} Factors associated with an increased risk of bleeding include the intensity and duration of thrombolytic therapy, the presence of hypertension, an age of more than 80 years, and a low platelet count.\textsuperscript{20,21}

A variety of percutaneous mechanical devices for aspiration, rheolysis, mechanical fragmentation, and ultrasonography-assisted fibrinolysis, used either independently or in combination with pharmacologic thrombolysis, are available.\textsuperscript{8,10,22-24} These devices may rapidly restore flow through the occluded segment and therefore shorten the duration of therapy. However, data from trials comparing these devices with pharmacologic thrombolysis alone are lacking.

**Surgical Revascularization**

Surgical approaches to the treatment of acute limb ischemia include thromboembolectomy with a balloon catheter, bypass surgery, and adjuncts such as endarterectomy, patch angioplasty, and intraoperative thrombolysis. Frequently, a combination of these techniques is required. The cause of ischemia (embolic vs. thrombotic) and anatomical
features guide the surgical strategy. Thrombotic occlusion usually occurs in patients with a chronically diseased vascular segment. In such cases, correction of the underlying arterial abnormality is critical. Patients with suspected embolism and an absent femoral pulse ipsilateral to the ischemic limb are best treated by exposure of the common femoral artery bifurcation and balloon-catheter thromboembolectomy. After removal of the clot, intraoperative angiography is performed to confirm that the thrombectomy is complete and to guide subsequent treatment if there is persistent inflow or outflow obstruction.

The treatment of patients with acute limb ischemia caused by thrombosis of a popliteal-artery aneurysm warrants special mention, because major amputation occurs with high frequency in such patients. Diffuse thromboembolic occlusion of all major runoff arteries below the knee is frequently seen, and intraarterial thrombolysis or thrombectomy may be required to restore flow in a runoff artery before aneurysm exclusion and surgical bypass are performed (Fig. 3).

Restoration of a palpable foot pulse, audible arterial Doppler signals, and visible improvement of foot perfusion (e.g., capillary refill, increased temperature, and sweat production) suggest treatment success. In some cases, perfusion may be incomplete and close postoperative ob-

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Figure 2. Acute Ischemia of the Left Leg in a 68-Year-Old Woman with Chronic Renal Failure.

In Panel A, a digital subtraction angiogram of the proximal left thigh shows occlusion of the proximal superficial femoral artery, with reconstitution in the mid-thigh (arrows). An intraluminal filling defect is present in the proximal superficial femoral artery, which is consistent with an acute thrombus. The proximal and distal arteries, which were normal, are not shown. Tissue plasminogen activator was infused for 18 hours, at a rate of 0.5 mg per hour, directly into the thrombosed segment through a multi–side-hole infusion catheter. The angiogram in Panel B, obtained after the infusion, shows that the thrombus has largely resolved, revealing the underlying stenosis (arrow). The angiogram in Panel C, obtained after angioplasty and placement of a self-expanding stent, shows a widely patent artery. After this treatment, the patient’s symptoms resolved.
servation is required to monitor the limb status. Therapeutic anticoagulation with heparin is reinstituted after the procedure. Vasodilators (e.g., nitroglycerin and papaverine) may be useful if there is evidence of vasospasm.

**Endovascular versus Surgical Revascularization**

A meta-analysis of five randomized trials comparing catheter-directed thrombolytic therapy with surgery for acute limb ischemia showed similar rates of limb salvage, but thrombolysis was associated with higher rates of stroke and major hemorrhage within 30 days. Individual trial results were inconsistent, however, perhaps because of differences in patients’ characteristics, the duration and severity of ischemia, thrombolytic regimens, and length of follow-up. In one trial, rates of limb salvage were similar with catheter-based thrombolysis and with surgery, but 12-month rates of survival were significantly higher in the thrombolysis group. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial was halted early because of higher rates of ischemia, amputation, and complications among patients undergoing thrombolysis than among those undergoing surgery. However, this trial included patients with limb ischemia that had developed up to 6 months before enrollment. Post hoc analysis of patients undergoing thrombolysis, as compared with surgery, showed that the rate of amputation-free survival was higher among those with a symptom duration of less than 14 days but not among those with a longer duration of symptoms. In the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, the rates of limb salvage and survival did not differ significantly between the thrombolysis and surgery groups, but complication rates were higher in the thrombolysis group.

On the basis of these trials and more recent case series, catheter-directed thrombolysis has the best results in patients with a viable or marginally threatened limb, recent occlusion (no more than 2 weeks’ duration), thrombosis of a synthetic graft or an occluded stent, and at least one identifiable distal runoff vessel. Surgical revascular-
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Reperfusion Injury
Reperfusion may result in injury to the target limb, including profound limb swelling with dramatic increases in compartmental pressures. Symptoms and signs include severe pain, hypoesthesia, and weakness of the affected limb; myoglobinuria and elevation of the creatine kinase level often occur. Since the anterior compartment of the leg is the most susceptible, assessment of peroneal-nerve function (motor function, dorsiflexion of foot; sensory function, dorsum of foot and first web space) should be performed after the revascularization procedure. The diagnosis is made primarily from the clinical findings but can be confirmed if the compartment pressure is more than 30 mm Hg or is within 30 mm Hg of diastolic pressure. If the compartment syndrome occurs, surgical fasciotomy is indicated to prevent irreversible neurologic and soft-tissue damage. Since renal, pulmonary, and cardiac complications also may ensue after limb reperfusion, patients require close monitoring. Myoglobinuria should be treated by means of aggressive hydration.

Long-Term Management
Anticoagulation is continued after thrombolysis or surgical hemostasis has been ensured. Initially, unfractionated heparin is administered; alternatively, low-molecular-weight heparin may be used. Subsequent antithrombotic therapy depends on the cause of the limb ischemia. Long-term oral anticoagulation is indicated in patients with acute thrombosis of a native artery associated with thrombophilia and in those with cardiac embo-

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**Figure 4. Algorithm for the Diagnosis and Treatment of Acute Limb Ischemia.**
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lism. The traditional therapy in such patients is warfarin. Novel oral anticoagulants that inhibit thrombin or factor Xa, such as dabigatran or rivaroxaban, may be considered in patients with atrial fibrillation, but the efficacy of such drugs in patients with peripheral-artery thrombosis is not known. Occluded bypass grafts may require revision if technical issues (e.g., stenoses, kinks, or retained valve cusps) are identified after successful thrombolysis; thereafter, antiplatelet agents are used to preserve patency. Long-term antiplatelet therapy is also indicated when the cause of acute limb ischemia is thrombosis superimposed on an atherosclerotic plaque and after repair of an arterial aneurysm that was deemed to underlie an embolic occlusion.

**AREAS OF UNCERTAINTY**

Randomized trials are needed to assess the efficacy and safety of catheter-based delivery systems for thrombolytic drugs and novel mechanical devices for thrombolysis or thrombectomy. It is not known whether outcomes are better when patients are treated in hybrid operating rooms that facilitate the use of combined endovascular and open surgical procedures, as compared with standard facilities. The optimal treatment strategy for various causes of acute limb ischemia remains uncertain.

**GUIDELINES**

Guidelines for the evaluation and management of acute limb ischemia include the Guidelines for the Management of Patients with Peripheral Arterial Disease of the American College of Cardiology and the American Heart Association, the Trans-Atlantic Inter-Society Consensus on the Management of Peripheral Arterial Disease (TASC II), and the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Antithrombotic Therapy in Peripheral Artery Disease. Our recommendations are consistent with these guidelines.

**CONCLUSIONS AND RECOMMENDATIONS**

The patient who is described in the vignette presents with symptoms and signs consistent with acute limb ischemia. This is a potentially catastrophic condition that can progress rapidly to limb loss and disability if not recognized and treated promptly (Fig. 4). Clinical evaluation includes assessment of limb color and temperature, pulses, and motor and sensory function. Heparin should be administered as soon as the diagnosis has been made. In a patient with a viable or marginally threatened limb, imaging studies can be obtained to guide therapeutic decisions. In a patient with an immediately threatened limb, such as the patient described in the vignette, emergency angiography followed by catheter-based thrombolysis or thrombectomy or open surgical revascularization is indicated to restore blood flow and preserve limb viability.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**Surgical Intervention for Peripheral Arterial Disease**

Shant M. Vartanian, Michael S. Conte

**Abstract:** The prevalence of peripheral arterial disease (PAD) is increasing worldwide, with recent global estimates exceeding 200 million people. Advanced PAD leads to a decline in ambulatory function and diminished quality of life. In its most severe form, critical limb ischemia, rest pain, and tissue necrosis are associated with high rates of limb loss, morbidity, and mortality. Revascularization of the limb plays a central role in the management of symptomatic PAD. Concomitant with advances in the pathogenesis, genetics, and medical management of PAD during the last 20 years, there has been an ongoing evolution of revascularization options. The increasing application of endovascular techniques has resulted in dramatic changes in practice patterns and has refocused the question of which patients should be offered surgical revascularization. Nonetheless, surgical therapy remains a cornerstone of management for advanced PAD, providing versatile and durable solutions to challenging patterns of disease. Although there is little high-quality comparative effectiveness data to guide patient selection, existing evidence suggests that outcomes are dependent on definable patient factors such as distribution of disease, status of the limb, comorbid conditions, and conduit availability. As it stands, surgical revascularization remains the standard against which emerging percutaneous techniques are compared. This review summarizes the principles of surgical revascularization, patient selection, and expected outcomes, while highlighting areas in need of further research and technological advancement. (*Circ Res*. 2015;116:1614-1628. DOI: 10.1161/CIRCRESAHA.116.303504.)

**Key Words:** peripheral arterial disease ■ vascular surgical procedures

**Principles of Revascularization: Clinical Indications and Patient Selection**

The surgical management of patients with peripheral arterial disease (PAD) is derived from the wider context of the epidemiology and natural history of the disease, and the influence of coexisting medical conditions such as coronary artery disease, diabetes mellitus, and renal disease. The spectrum of clinical presentation of PAD is broad and can be classified into 3 categories: asymptomatic disease, intermittent claudication (IC) and limb-threatening ischemia (critical limb ischemia [CLI]). With rare exception (eg, to create an iliac conduit for a thoracic aortic endograft), reconstruction for occlusive disease is never indicated in asymptomatic patients. The clinical decision process for revascularization in IC and CLI is distinct and merits elaboration. Although the anatomic pattern of occlusive disease is a major factor in the revascularization strategy, it
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial indices</td>
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<tr>
<td>AIOD</td>
<td>aortoiliac occlusive disease</td>
</tr>
<tr>
<td>BASIL</td>
<td>Bypass versus Angioplasty in Severe Ischaemia of the Leg</td>
</tr>
<tr>
<td>CFA</td>
<td>common femoral artery</td>
</tr>
<tr>
<td>CLI</td>
<td>critical limb ischemia</td>
</tr>
<tr>
<td>GSV</td>
<td>great saphenous vein</td>
</tr>
<tr>
<td>IC</td>
<td>intermittent claudication</td>
</tr>
<tr>
<td>PAD</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>PTFE</td>
<td>polytetrafluoroethylene</td>
</tr>
<tr>
<td>TASC</td>
<td>Trans-Atlantic Inter-Society Consensus</td>
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should be stressed that the physiological state of the patient and the status of the limb primarily determines the appropriateness and urgency of intervention for PAD.

**Intermittent Claudication**

Although the cellular and biochemical changes in the limb with claudication are complex, symptoms of IC occur only during physical activity, when the metabolic demands of the muscles are not met by the capacity of the circulatory system. Many patients with PAD remain asymptomatic because their activity level does not exceed this threshold. In particular, patients with coexistent heart failure, severe pulmonary disease, or advanced musculoskeletal disease such as arthritis may never manifest symptoms despite having hemodynamics just above the inception of rest pain. Conversely, competitive cyclists may have symptoms of thigh claudication during exercise as a result of external iliac artery endothelialization, despite having a normal pulse examination and normal anatomic imaging at rest. The classic symptoms of claudication are calf muscle aching, fatigue, or cramping, although it can also involve the buttocks, thigh or hip. The hallmark features are symptoms that are reproducibly elicited with physical activity and are alleviated during rest with abatement during a period of 10 to 15 minutes. A detailed history and a careful physical examination can help differentiate PAD from other causes of lower extremity pain such as spinal stenosis (pseudoclaudication), radiculopathy, arthritis, symptomatic Bakers cysts, benign nocturnal cramps, or other less common diagnoses.

The principal disability in IC is limited exercise performance and walking ability. This translates into a subjective reduction in physical functioning and quality of life. Outside of special populations, the natural history of claudication is often stable during subsequent years. In a classic study from England, of the 1476 patients followed up for ≤10 years, only 11% of claudicants had a clinical deterioration during the observation period. These findings have been reiterated in numerous other reports. Hemodynamic assessment by ankle-brachial indices (ABI) suggests that some populations have a gradual deterioration over time, particularly those at the lowest strata of ankle pressures. Nevertheless, a decline in ABI does not necessarily translate into clinical deterioration, which may be a result of molecular and biochemical adaptation, gradual collateral network formation, a change in the patient’s perception of their disability or the patient altering their gait or activity level to alleviate symptoms. In the absence of diabetes mellitus, <2% of claudicants experience major amputation during a 5-year period. Patient education, risk factor reduction (especially smoking cessation), medical management, and exercise therapy are the primary initial treatment strategies in IC and are reviewed elsewhere in this Compendium.

Revascularization, either percutaneous or surgical, may be appropriate for selected patients with IC who are significantly disabled, impaired in their occupation or activities of daily life, and who have not improved with conservative management. Evidence suggests that successful revascularization in claudicants leads to improved quality of life and functional performance; however, there is little in the way of comparative effectiveness studies in this arena. More clinical trials are needed to develop evidence-based guidelines for the treatment of IC across all subgroups using patient-oriented outcome measures. Until then, the approach for revascularization in IC is individualized—taking into account risks, anticipated benefit, and clinical durability. Ideal patients are those who have a significant disability from IC, have optimized medical management including a trial of exercise, and have revascularization options with a favorable risk:benefit ratio. Given the non–limb-threatening nature of the problem, invasiveness of the procedure, anatomic durability, and freedom from repeat interventions are important considerations in the equation. Patients with bilateral symptoms may not realize functional gain without a successful outcome in both limbs, another factor that must be carefully weighed before deciding to intervene.

**Critical Limb Ischemia**

CLI is a clinical syndrome of chronic, advanced limb ischemia manifested as rest pain, nonhealing ulcers, and gangrene (necrosis). It is typically associated with markedly impaired perfusion as measured by noninvasive hemodynamic studies (ankle pressure <50 mm Hg or toe pressure <30 mm Hg). In contrast to IC, the fate of both the patient and the limb with CLI is starkly dissimilar. High-quality data from several prospective studies shows annual 10% to 20% mortality for this patient population. The Circulase trial, a randomized placebo-controlled pharmacotherapy trial for CLI patients without revascularization options, demonstrated an all-cause mortality of 10% within the first year in both placebo and treatment arms. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial randomized patients with advanced ischemia to either percutaneous or open surgical revascularization. At 2 years, all-cause mortality was 25% independent of treatment type.

The fate of the limb with CLI is also disadvantaged. Natural history data are muddled as most patients receive some form of therapy. Survey data show ranges of primary amputation ≤40% in some centers, whereas other centers offer revascularization in 90% of cases. Data from prospective trials in CLI suggest that the rate of major adverse limb events, defined as any above ankle amputation or major revascularization, approaches 20% in the first year after an intervention.
are no proven options to preserve the limb and relieve ischemic symptoms at this stage of disease other than effective revascularization. Unremitting pain, nonhealing wounds, loss of ambulatory function, and recurrent infections accompany untreated CLI. Therefore, all patients with CLI who have a reasonable life expectancy and functional status should be evaluated for revascularization.

The principle trade-off between endoluminal and open surgical revascularization is the reduced periprocedural morbidity for endovascular interventions versus enhanced hemodynamic gain and long-term durability of bypass surgery. Most of the benefit of reduced short-term morbidity with endovascular interventions comes from avoiding the complications of surgical wounds and the associated recovery, but major adverse cardiovascular events and periprocedural mortality are broadly similar between the 2.16 Evidence-based treatment algorithms in CLI are a moving target, especially as new generations of endovascular technologies are being developed for clinical applications, such as drug-eluting balloons and stents.17,18 An additional limitation of comparative data in this field is the lack of an adequate staging system for the limb to appropriately stratify outcomes. The Society for Vascular Surgery has proposed a Threatened Limb Classification System (wound, ischemia, and foot infection) to fill this void, taking into consideration characteristics of tissue loss, severity of infection, and the extent of ischemia.19 This scheme should allow for more rigorous comparison of outcomes and optimization of treatment protocols.

The only prospective comparative effectiveness data in CLI come from the BASIL trial, now over a decade old.16 In this randomized trial of open versus endovascular interventions for advanced limb ischemia, early results were broadly similar. However, those patients who received a bypass procedure first and survived at least 2 years had lower mortality and greater amputation-free survival in comparison with those treated first with endovascular interventions.11 In addition, patients who required a surgical bypass after a failed endovascular intervention fared worse than those who underwent a bypass first. Current guidelines suggest that patients who are of appropriate surgical and anesthetic risk and who are projected to survive at least 2 years should preferentially receive a vein bypass graft for advanced limb ischemia.20 Higher risk patients with shorter life expectancy, lower functional status, those with favorable occlusive anatomy for percutaneous revascularization, or those who lack adequate autologous conduit should be considered for endovascular treatment.21 A new generation of comparative effectiveness studies to readdress this important question is underway, including 2 large multicenter randomized trials in the US (Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia [BEST-CLI1] and UK [BASIL-2]).22

Imaging

Patients with symptomatic PAD who are deemed suitable candidates for revascularization should undergo imaging to define the anatomic pattern of occlusive disease. High-quality vascular imaging studies are paramount for developing an operative strategy. Catheter-based digital subtraction angiography is generally required for evaluating infrageniculate arterial anatomy before distal bypass surgery. It is of particular importance in CLI, where reliable imaging of the tibial and pedal arteries is mandatory for evaluating the runoff vessels into the foot. Duplex ultrasound also plays an important role in defining the pattern of infrainguinal disease and suitability for endovascular treatment, but is not often used as a stand-alone technique for surgical planning.

In contrast, for aortoiliac disease, surgeons often proceed directly to open surgical revascularization based on computed tomography and MR angiogram imaging alone. Computed tomography angiogram, in particular, informs the operator about the location and distribution of calcified lesions, important in the planning of open aortic surgery. However, diagnostic catheter-based angiography may still be preferred in some cases, such as in the presence of prior stenting or those with spine hardware artifact, which can render computed tomography or MR less accurate.

Revascularization Strategy

The emergence of endovascular techniques has changed the landscape of vascular therapy in PAD, but has not fundamentally altered the selection of candidates most likely to benefit from revascularization. As summarized in previous sections, the indication for treatment is predicated on the severity of clinical presentation, with broadly dissimilar initial management strategies (primarily medical versus primarily revascularization) depending on whether the symptoms are claudication or CLI.

Once it is determined that revascularization is an appropriate treatment option, determination of the optimal strategy is highly individualized. Choosing between open versus endovascular approaches takes into consideration a wide variety of factors, including but not limited to the pattern of occlusive disease, anesthetic risk, severity of comorbid conditions, durability of the intervention, extent of tissue loss, previous failed interventions, or other specific anatomic considerations. In contemporary practice, vascular surgeons and interventionalists should be broadly trained with deep understanding of both approaches to provide flexible solutions for the wide range of disease and patient-specific factors encountered and to minimize the downstream consequences of failure on subsequent interventions.

The principle advantages of endovascular interventions are reduced periprocedural morbidity and shorter hospital stays, whereas the frequent drawback is less hemodynamic gain and inferior long-term durability compared with bypass surgery. Aortoiliac disease is particularly well suited for endovascular interventions given the excellent durability in larger caliber vessels and the attendant risks of open aortic reconstruction. However, as noted in the section on aortoiliac revascularization, some situations call for open revascularization, such as a concomitant aortic aneurysm, prior failed interventions, or a significant burden of disease (ie, aortic occlusion). For femoropopliteal disease, technical success for initial treatment can almost always be accomplished with endovascular techniques; however, consideration should be given to the known specific factors that limit durability (lesion length, diameter of vessel, etc). The choice of revascularization is even more complicated in tibioperoneal disease, as most patients with CLI have significant comorbidities that translate into shorter life
expectancy, and endoluminal interventions in tibioperoneal vessels have poor long-term durability (eg, <40% primary patency at 1 year).23

Fundamental Concepts in Surgical Revascularization

Endarterectomy

Endarterectomy is the direct removal of obstructive plaque from an arterial segment and it is best applied for focal lesions in large caliber vessels, particularly at bifurcations (eg, carotid, aortoiliac, common femoral arteries; Figure 1). Initially described by dos Santos,25 then popularized by Wylie in the 1950s, it takes advantage of a cleavage plane between the plaque and the underlying deep media. The advantages of endarterectomy are its autogenous nature without need for conduit. Limitations of endarterectomy relate to adequate securing of the end points, thrombogenicity of the resulting surface in low flow environments, and the subsequent healing response of the artery (intimal hyperplasia), which may lead to recurrent stenosis.

The success of angioplasty and stenting in the aortoiliac segment, particularly for focal disease, has largely led to abandonment of endarterectomy in this location. However, femoral endarterectomy remains a common and important procedure in PAD, allowing for durable reconstruction of the common femoral artery (CFA) and the profunda femoris artery, the key source of collateral circulation to the lower leg. It may be performed in an isolated fashion or as part of a hybrid or open bypass revascularization. Femoral endarterectomy is performed most commonly via longitudinal arteriotomy, with removal of the plaque followed by patch closure (prosthetic or biological materials) allowing for a degree of scarring to occur without subsequent lumen compromise (Figure 1).

Bypass

Surgical bypass is a versatile and flexible tool allowing for revascularization across a broad range of disease patterns, from the aorta down to the foot. The principal elements of technical success are unobstructed inflow, good-quality conduit, and adequate outflow. The inflow source should be free of any hemodynamically significant disease, and outflow should be sufficient to resolve the clinical ischemic syndrome and maintain sufficient flow rates through the conduit. The large caliber arteries and the high-flow environment of aortoiliac reconstructions favor prosthetic grafts for reconstruction. Both Dacron and PTFE have excellent long-term results. Modern fabrication practices with either collagen or gelatin-impregnated Dacron or PTFE have resulted in synthetic materials that have minimal blood loss through the graft, excellent long-term structural integrity, and ability to incorporate into native tissues. A randomized multicenter trial of aortoiliac reconstructions comparing PTFE to knitted Dacron showed no difference in 5-year patency by graft type.26 In general, all commercially available prosthetic grafts perform well in this location. The limitations of prosthetic conduits in these environments relate to the potential for infection (an infrequent, although highly morbid complication), anastomotic pseudoaneurysms, and thrombosis (Tables 1 and 2).

In contrast, small caliber conduits typically required for infrainguinal bypass (≤6 mm) face a more demanding hemodynamic environment for patency. The ideal bypass conduit is an arterial autograft, with its antithrombotic endothelial surface, fidelity to the physiological and mechanical properties of native arterial wall, resistance to infection, and resistance to inflammatory changes that result in stenosis or occlusion. Unfortunately, unlike coronary disease, arterial autografts are not a viable solution for PAD. Superficial extremity veins of appropriate caliber may be readily harvested in relevant lengths and offer a nonthrombogenic, autogenous solution. Venous conduits were first used for surgical reconstructions in the 1940s, initially by Dos Santos as a patch for enterectomy, and later by Kunlin27 for peripheral bypass. In today’s practice, great saphenous vein (GSV) is the dominant conduit. The quality of the vein is a single greatest determinant of long-term outcomes of lower extremity bypass. Despite significant advances in material sciences, small caliber synthetic conduits have significant limitations, particularly at the graft–vessel interface.

For infrainguinal reconstructions, autologous vein is well established as the optimal conduit. The quality of the vein is the single greatest determinant of long-term outcomes of lower extremity bypass. A single high-quality segment of GSV has been shown in prospective trials to be superior to all other conduits in primary and assisted patency.23 Unfortunately,
Cryopreserved venous homografts have limited long-term interface. Recent improvements in prosthetic graft technology, notably heparin-bonding surface technology, may improve patency, is the life-long risk of prosthetic infection, which can be a life- and limb-threatening complication. Although it is expected that the majority of lower extremity revascularizations can be performed with autogenous vein, there are circumstances where prosthetic grafts may be necessary. Prospective trials have shown a short-term equivalency between prosthetic and vein grafts for femoral to above knee popliteal bypass, with favorable runoff. However, the preponderance of evidence suggests that for above knee bypass, autogenous vein outperforms prosthetic grafts at ≥2 years. When good-quality vein is not available, a prosthetic is a suitable alternative for bypass to the popliteal level. Some authors have also reported acceptable patency for prosthetic grafts to more distal targets. Other putative advantages of prosthetic are shorter operative times and less surgical dissection. However, a major limitation, in addition to reduced patency, is the life-long risk of prosthetic infection, which can be a life- and limb-threatening complication.

Unlike vein grafts, the level of the distal anastomosis has a significant effect on the durability of prosthetic bypasses. Whereas the 5-year patency of prosthetic grafts to the above knee popliteal artery is on the order of 40% to 50%, at the tibioperoneal level, the 5-year patency falls to 15% to 30%. When forced to use prosthetic grafts for infrageniculate bypass, surgical modifications of the distal anastomosis, such as with the Miller cuff, Taylor patch, or St. Mary’s boot, may improve patency by altering the compliance at the graft-vessel interface. Recent improvements in prosthetic graft technology, notably heparin-bonding surface technology, may improve on the comparatively lower patency rates reported above. Cryopreserved venous homografts have limited long-term patency as well, with outcomes akin to prosthetic grafts.

### Table 2. Expected 5-Year Patency Rates for Direct and Extra-Anatomic Surgical Revascularization for Aortoiliac Occlusive Disease

<table>
<thead>
<tr>
<th>Intervention</th>
<th>5-y Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortofemoral bypass</td>
<td>80%–95%</td>
</tr>
<tr>
<td>Femorofemoral bypass</td>
<td>55%–85%</td>
</tr>
<tr>
<td>Axillobifemoral bypass</td>
<td>50%–75%</td>
</tr>
</tbody>
</table>

≤40% of patients needing revascularization will not have adequate ipsilateral GSV available. In this scenario, contralateral GSV, lesser saphenous, and arm veins are the next best options, either as single segments or spliced grafts. Because of the central importance of venous conduit to success of the operation, it is recommended that routine preoperative evaluation includes ultrasound vein mapping.

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### Table 2. Expected 5-Year Patency Rates for Various Infracruinal Revascularization Procedures

<table>
<thead>
<tr>
<th>Intervention</th>
<th>5-y Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral endarterectomy</td>
<td>90%</td>
</tr>
<tr>
<td>Femoral-popliteal bypass with vein</td>
<td>70%–75%</td>
</tr>
<tr>
<td>Femoral-tibial bypass with vein</td>
<td>60%–70%</td>
</tr>
<tr>
<td>Femoral-popliteal bypass with prosthetic</td>
<td>40%–60%</td>
</tr>
<tr>
<td>Femoral-tibial bypass with prosthetic</td>
<td>10%</td>
</tr>
<tr>
<td>Pedal bypass with vein</td>
<td>60%–70%</td>
</tr>
</tbody>
</table>

They are primarily used when treating graft infections or tunneling a graft through a grossly infected field in the absence of available autogenous conduit, as they are more infection resistant than prosthetic materials.

### Hybrid Approaches

As endovascular interventions evolve, vascular surgeons are increasingly using hybrid approaches, a combination of catheter-based and open techniques to achieve limb revascularization with less invasiveness. Common examples include open common femoral endarterectomy with concomitant angioplasty and stenting of aortoiliac disease, iliac stenting combined with femoral-iliac or femoral-distal bypass, and superficial femoral artery angioplasty combined with popliteal to pedal bypass. Contemporary vascular surgeons and interventionalists must be broadly trained and competent with both open and endovascular techniques to provide creative and flexible solutions for the range of disease encountered.

### Specific Strategies and Expected Outcomes

Strategies for surgical revascularization of PAD are based on the clinical presentation and the anatomic pattern of occlusive disease. Classically, 3 anatomic levels of disease are described: aortoiliac (inflow), femoropopliteal, and tibiopedal (both outflow). The CFA is the center point of the limb and is considered a special case of inflow disease. In general, inflow optimization always precedes outflow reconstruction. Claudicants may present with multiple levels of disease, but typically treatment is focused on the most proximal involved segment first, and progresses distally only if required. In some patients with CLI and tissue loss, simultaneous multilevel reconstruction is immediately required to achieve pulsatile flow to the foot for limb salvage.

### CFA Disease

Unobstructed inflow to the CFA and outflow via the profunda femoris is the single most important determinant of adequate circulation to the lower extremity. Because the first common femoral endarterectomy performed by Portuguese surgeon Dos Santos in 1948, a variety of techniques have been described, including the closed, semiclosed, eversion, and the most common, the patch angioplasty (Figure 1). Because of ease of surgical exposure of the CFA and the ability to perform the procedure under regional anesthesia, even patients with advanced comorbid conditions and isolated disease are candidates for this procedure. Nevertheless, isolated CFA disease is uncommon. Given the importance of the common femoral and profunda femoris arteries, femoral endarterectomy is usually an adjunct procedure during other inflow or outflow revascularizations. However, in patients with rest pain or minor tissue loss in the setting of common femoral disease and a superficial femoral artery (SFA) occlusion, treating the common femoral and profunda femoris alone may often be an adequate solution.

The surgical management of common femoral disease has been challenged by aggressive application of percutaneous techniques. Flexion and extension of the CFA, both during ambulation or when transferring from the seated to the supine position, creates significant motion at the iliopopliteal junction. Even flexible self-expanding stents fare poorly in this location
and are prone to stent fracture. In addition, stents that cross a bifurcation stimulate neointimal hyperplasia across the covered orifice, potentially compromising flow to the profundaplasty. Finally, CFA stents can limit future surgical or percutaneous access to the femoral artery. For these reasons, application of endovascular techniques in the CFA is generally limited.

Endarterectomy for isolated femoral bifurcation disease can be performed under regional anesthesia with low procedural morbidity and excellent long-term results (Table 2). Technical success of femoral endarterectomy is the rule, with early failures, a result of inadequately treated inflow disease or residual dissection distal to the endarterectomy. Long-term outcomes are excellent, with a 10-year primary patency rate of >90%. Late failures are typically the result of progression of atherosclerotic disease beyond the endarterectomy site or neointimal hyperplasia, the clinical significance of which can be delayed with a patch angioplasty closure of the arteriotomy (Figure 1). Prosthetic and bioprosthetic (eg, bovine pericardium) patches handle well and have a low rate of infection (<2%). Autologous patch with saphenous vein eliminates the infectious risk but has a low rate of aneurysmal degeneration (≈2%), slightly more common than the rate of pseudoaneurysm formation with prosthetic patches. Wound complications such as infection, hematoma, or lymphocele occur in <10% of patients.

Aortoiliac Disease
Aortoiliac occlusive disease (AIOD) is largely a disease of smokers, although other risk factors for PAD are commonly associated with it including advancing age, hypercholesterolemia, hypertension, and diabetes mellitus. Typically, isolated AIOD in patients presents with lower extremity IC symptoms involving the proximal muscles of the hip, thigh, or calf. Occlusive disease of the common iliac or internal iliac arteries can present with pelvic ischemia, presenting with symptoms of buttock claudication and impotence in males. First recognized by French surgeon Rene Leriche, the syndrome now bears his name. Symptoms of limb-threatening ischemia, such as rest pain, nonhealing wounds, or gangrenous changes are rare with isolated AIOD and typically require multilevel atherosclerotic changes including involvement of the infrapopliteal circulation.

Many patients with IC present with palpable femoral pulses. Hemodynamically significant AIOD can be identified during the initial evaluation with noninvasive vascular laboratory studies. Doppler waveform analysis may reveal a delayed upstroke and reduced amplitude at the common femoral level. Although resting ABI can be diagnostic, hemodynamic testing with exercise ABIs is particularly useful in discriminating mild atherosclerotic changes of the aortoiliac segment from pseudoclaudication syndromes, such as spinal stenosis or radiculopathies, which often coexist in this patient population. Treadmill walking or 2-minute heel raises reduce the distal peripheral vascular resistance, creating a pressure gradient across hemodynamically significant stenosis while reproducing symptoms of IC.

There is mounting evidence that a supervised exercise program can produce functional outcomes equivalent to revascularization procedures for select patients with IC. The Claudication: Exercise vs. Endoluminal Revascularization (CLEVER) trial, a randomized controlled trial comparing endovascular treatment of AIOD against optimal medical therapy with a supervised exercise program, showed greater short-term improvement in walking performance in the exercise therapy group in comparison with percutaneous treatment, although patient satisfaction scores favored revascularization. Similar findings have been noted from randomized trials comparing exercise therapy with endovascular treatment of infrapopliteal disease. In summary, interventional therapy for IC should be reserved for patient with debilitating symptoms, despite optimal medical therapy and a trial of exercise, for whom the risk:benefit ratio is low and a durable result is expected.

Although the patient’s functional status and comorbid conditions help frame the risks and benefits of the intervention, the underlying anatomic pattern of disease is supremely important in determining the operative strategy and durability of the procedure. The most widely used anatomic classification system for AIOD was devised as part of a multidisciplinary, multispecialty consensus statement, the most recent iteration of which was published in 2007. Among the conclusions of the Trans-Atlantic Inter-Society Consensus (TASC) II guidelines, patterns of AIOD disease are described that facilitate classification when comparing revascularization methods. By expert consensus, it is generally agreed that patients with focal and discrete aortoiliac lesions (TASC A or B) should be preferentially treated with endovascular interventions first given the high likelihood of technical success, reasonable durability, and comparatively lower procedural morbidity. Conversely, advanced patterns of AIOD (TASC D), such as extensive aortic disease, diffuse iliac disease, long chronic total occlusions, or concomitant abdominal aortic aneurysms should be treated with surgical revascularization unless the operative risk is prohibitive.

Direct Aortoiliac Revascularization
The modern era of direct surgical revascularization began with a successful endarterectomy of the CFA by Portuguese surgeon dos Santos in 1948. Wylie at University of California, San Francisco, first extended the endarterectomy technique to the aortoiliac segment in 1951. However, it was not for another decade until prosthetic grafts were used to bypass aortoiliac disease, first as aortoiliac grafting, until the more durable aortobifemoral bypass procedure became widely adopted.

The principle advantage of direct surgical revascularization is the durability of the intervention (Table 1). Ten-year patency rates of 85% for both aortofemoral bypass and aortoiliac endarterectomy are unmatched by endovascular interventions. For patients with unilateral disease, the 5-year patency rates for unilateral iliopopliteal bypass exceed 90% in most series. Nevertheless, certain patient populations warrant special consideration. Female patients have consistently lower patency rates, in part because of smaller vasculature. Patients with multilevel disease also have worse long-term outcomes. Several reports also highlight that young patients with premature PAD (age <50 years) have markedly higher failure rates. This may be a reflection of poorly controlled risk factors, particularly tobacco abuse, as well as an aggressive vascular disease phenotype. The same holds true for endovascular
Aortobifemoral Bypass

The typical aortobifemoral bypass grafts a bifurcated prosthetic graft from the infrarenal abdominal aorta to each CFA (Figure 2). Developing the operative strategy requires careful consideration of the patient’s arterial anatomy and prior surgical history. Imaging studies are critical for determining the level of aortic and iliac artery control, the presence of coexistent renal or visceral arterial disease, the presence of concomitant aortoiliac aneurysms, and the status of the outflow vessels. Central to developing the operative strategy is careful management of the pelvic circulation (Figure 2). Inadvertent exclusion of pelvis flow can result in ischemic colitis, bilateral buttock claudication, and rarely spinal ischemia.

The proximal aortic anastomosis may be created in an end-to-end or end-to-side fashion, although the former is usually preferred (Figure 2). The aorta immediately distal to the renal arteries is more likely to be disease free and less likely to progress over time. In addition, the hemodynamics favor turbulent flow with the end-to-end anastomosis and the end-to-side anastomosis requires a longer segment of disease-free aorta, which is less frequently encountered with current patient selection algorithms. With the end-to-end anastomosis, pelvic perfusion is maintained via retrograde flow from the external iliac arteries and proximal lumbar and mesenteric collaterals.

The abdominal aorta is usually exposed via a transperitoneal approach through a midline incision. Transverse exposures offer generous access to the aorta, especially to the visceral segment; however, the incision requires division of the inferior epigastric arteries, which are major collateral pathways in AIOD. In the event of graft thrombosis, preservation of collateral networks will allow the patient to revert back to the original circulation rather than progressing to acute limb ischemia. Retropertitoneal approaches may be desirable in patients with significant prior intra-abdominal surgical histories, such as those with stomas; however, it can be challenging to develop the tunnel for the right limb of the bypass graft via a left retropertitoneal exposure.

The key to optimizing the durability of the aortofemoral bypass (AFB) graft is ensuring adequate outflow. Most patients who require surgical revascularization also have coexistent infrainguinal occlusive disease. Typically, unobstructed flow into the profunda femoris is sufficient outflow to maintain graft patency. Even in the setting of a complete SFA occlusion, a well-collateralized profunda system is adequate runoff and will often result in significant hemodynamic improvement of the limb distally.

Aortofemoral bypass grafting for AIOD has excellent durability. Irrespective of surgical indication, whether claudication or CLI, 5-year patency rates exceed 90% and 10-year patency rates approach 85%—unmatched by endovascular results. Unilateral iliофemoral bypasses fare at least as well in modern surgical series, with 5-year patency rates >90%. The most common cause of failure of direct surgical reconstruction for AIOD is progression of atherosclerosis in the femoral artery or neointimal hyperplasia at the distal anastomosis. Appropriate management of femoral disease at the time of the index operation is the key to maximizing the benefit and durability of any revascularization for AIOD.

Improvement in patient selection, preoperative optimization, operative management, anesthetic and postoperative care has translated into a ≤2% in-hospital mortality for AFB. Nevertheless, as major vascular surgery, a composite morbidty end point of major and minor complications approaches 15% to 30%. Major adverse cardiac events occur in <5% of patients and can be minimized with the appropriate use of antihypertensive medications, antplatelet agents, and statins in accordance with current practice guidelines. Pulmonary complications are not infrequent, occurring in ≤7% of patients. Techniques to minimize pulmonary difficulties, especially important in patients with underlying chronic obstructive pulmonary disease, include epidural anesthesia to optimize pain control allowing for adequate postoperative pulmonary mechanics and avoidance of volume overload. Other common complications include renal failure for patients requiring supra-renal aortic clamping or renal embolization during aortic cuff endarterectomy, wound complications particularly in the groin (lymphocele, lymphocutaneous fistula, wound infections), and postoperative hemorrhage. Finally, atheroemboli can be liberated during the procedure, manifesting as end organ ischemia in the skin, pelvis, spinal cord, and bowel. Late complications include pseudoaneurysm formation because of material fatigue or suture fracture. An index of
...suspicion for occult graft infections should be present when treating all pseudoaneurysms. Nonvirulent bacteria such as *Staphylococcus epidermidis* can present with pseudoaneurysm formation long after the index procedure. Although late graft infections are rare, occurring in <2% of aortofemoral bypass grafts, they pose a challenging clinical problem. Other signs of graft infection include febrile draining sinus tracts, induration, or cellulitis. Graft infections emanating from an enteric fistula to the prosthetic graft may present with only decreased appetite and failure to thrive. Less subtle symptoms include abdominal tenderness, recurring gastrointestinal bleeds, ileus, or sepsis.

**Iliofemoral Bypass**

An iliofemoral bypass graft is typically applied for unilateral distal iliac disease, grafting a prosthetic graft from the common iliac artery to the CFA. Progression of atherosclerosis in the nonaffected limb is possible, but concerns over future obstructive disease should not preclude consideration of a unilateral iliofemoral bypass. By basing the graft distally without mobilizing the infrarenal aorta extensively, the option to return for direct revascularization of the contralateral side remains viable. Conversely, for high-risk patients, those that have had extensive prior abdominal surgeries or those with failure of a prior graft limb, a crossover femoral–femoral bypass graft is a useful approach. Unilateral axillary-femoral grafts are rarely indicated in elective scenarios, as the long-term results are inferior to direct revascularization or axillary-bifemoral bypasses.

**Other Direct Revascularization Options**

Before the widespread adoption of prosthetic surgical bypass for AIOD, endarterectomy was the standard of care, with excellent technical success rates and durability. Advantages of the technique include avoidance of complications related to implanting prosthetic material, such as infection or pseudoaneurysm and potentially improved inflow into the hypogastric arteries. Although the technique has been largely surpassed by AFBG, the occasional patients with embolic complications of focal lesions in a large caliber vessel, who are otherwise not well served with percutaneous techniques, are good candidates for this type of intervention.

Finally, there are rare patients who are candidates for direct surgical revascularization but otherwise have an inaccessible abdominal aorta. This may be a result of failed previous aortic bypass, abdominal radiation, or significant atherosclerotic disease above the renal arteries. The thoracic aorta can be used as a source of inflow in these cases via a lateral thoracotomy or thoracoretroperitoneal approach. The durability of this procedure rivals that of aortofemoral grafting.

**Extra-Anatomic Bypass**

In patients with extensive comorbid conditions, such as uncorrectable coronary artery disease, poor ventricular function, advanced pulmonary disease, renal failure, or hostile abdominal anatomy, the increased risks of open surgery may make direct revascularization prohibitive, even in the setting of TASC D lesions. Aggressive endovascular techniques, which can achieve high levels of technical success by experienced providers, may be appropriate despite the absence of long-term outcome data. Conversely, extra-anatomic bypasses are an alternative approach in such patients, particularly when the indication for intervention is limb-threatening ischemia. These techniques, such as the femorofemoral bypass or the axillobifemoral bypass, limit the morbidity associated with major vascular surgery but come at the price of limited durability. Accordingly, these techniques are reserved for patients with CLI and are not generally performed for symptoms of IC.

**Femorofemoral Bypass**

The archetypal femorofemoral bypass grafts a prosthetic conduit from 1 CFA to the other (Figure 3). The principle advantage of the procedure is that it can be performed under local or regional anesthesia, avoiding the potential complications of direct surgical reconstruction of the aorta in patients at higher surgical risk. The procedure is well suited for patients with unilateral AIOD or those who have contralateral side that is free from hemodynamically significant stenosis. Classic examples include patients with a previous iliofemoral bypass or aortobifemoral bypass with a single thrombosed limb. The donor artery should be free of any hemodynamically significant upstream disease. When limited inflow disease (eg, iliac stenosis) is present, it can be corrected first or simultaneously in a hybrid procedure, where angioplasty or stenting of the iliac artery is combined with a downstream cross femoral bypass. Multiple groups have reported satisfactory outcomes with this technique.55

In contrast to the in-line AFB, the durability of extra-anatomic bypasses does not fare nearly as well although it does have acceptable mid-term results for patients who otherwise have a limited life expectancy.51 The 5-year patency rates for femorofemoral bypasses average ≈65%.56,57 Patency rates are most strongly influenced by outflow disease. Results of hybrid endovascular iliac revascularization combined with femorofemoral bypass have acceptable short- and mid-term results, with no apparent difference in patency when compared against historical controls.55 As is
the case with most retrospective single center surgical series, a selection bias may be at least partially attributable to these results.

**Axillofemoral Bypass**

The axillofemoral bypass is well suited for patients with limb-threatening ischemia because of advanced AIOD who would otherwise be considered high risk for direct aortic reconstruction. Other indications include patients with hostile abdomens, such as those with extensive previous surgical history, previous radiation therapy, intestinal stomas, or intra-abdominal sepsis. As the source of inflow pedicles on a long graft from the axillary artery, the amount of hemodynamic improvement for the lower extremities is limited and the maximum flow provided from the graft may be inadequate to fully relieve symptoms of IC. For this reason, this operation is limited to patients with limb-threatening ischemia.

Although the original report describes the procedure performed entirely under local anesthesia, it is typically performed under general anesthesia as 3 distinct and remote surgical fields are exposed. Typically, the right axillary artery is used as a source of inflow, as the left subclavian artery is athero-prone; however, a simple blood pressure measurement is sufficient to determine laterality (Figure 3). As with all aortoiliac reconstructions, optimizing the outflow is key to maintaining the durability of the procedure.

Of the various surgical revascularization options for severe AIOD, the axillofemoral bypass has the lowest 5-year primary patency, with modern series reporting rates averaging 50% to 70%. Outflow through both femoral arteries, rather than a unilateral axillofemoral bypass, has been shown to increase flow in the graft adjacent to the axillary artery and improves the long-term patency of the procedure.

Nevertheless, many of these patients have shortened life expectancy and the long-term outcome data are biased by survivors with a lesser burden of disease. Even so, stratifying results by indication shows that results are inferior to aortofemoral grafting.

The surgical morbidity of extra-anatomic bypasses are similar to those of other bypass procedures with prosthetic. There are risks of hemorrhage, wound complications, hematoma, graft infection, and pseudoaneurysm formation. The femorofemoral bypass graft has the unique complication of tunneling subfascial with subsequent bowel and bladder perforation. For axillofemoral grafts, trauma to the brachial plexus, atheroemboli to the hand, and graft avulsion during arm abduction has been reported.

**Femoropopliteal Disease**

Because the first femoropopliteal bypass with a saphenous vein was performed in 1949 by French surgeon Dr Kunlin, technical advances have broadened the application of the technique to a variety of clinical and anatomic scenarios (Figure 4). In appropriately selected patients, femoropopliteal bypass has proven not only effective but also the most durable intervention for advanced occlusive disease of the femoropopliteal segment. To maximize performance and to minimize infectious complications, the saphenous vein is the preferred conduit. The application of the graft in a reversed or nonreversed orientation, or left in situ, is largely a matter of surgeon preference with no significant impact on surgical outcomes. Up to 40% of patients will not have adequate ipsilateral saphenous vein for use as conduit. Contralateral GSV should be considered next unless the donor limb also has evidence of advanced PAD by either clinical or hemodynamic assessment.

For patients without adequate autologous conduit, prosthetic grafts can be used depending on the indication and pattern of disease. Unlike autologous grafts, there seems to be a significant decrease in patency rates by distal target vessel location, with a progressive decline from the above knee to the below knee location, and an even larger reduction in long-term patency for distal bypass. Only subtle differences in outcomes have been observed among different prosthetics grafts in the below knee popliteal position, whether using Dacron, PTFE, ringed PTFE, and more recently, heparin bonded PTFE.

Short-term results with bypass surgery are also excellent, with early graft failure occurring in ≈5% of vein bypass procedures, largely a result of technical errors. Virtually all patients develop lower extremity edema postoperatively with symptoms that may last for several months. The putative pathogenesis of angioedema is autonomic dysfunction from chronic ischemia, inflammation, and interruption of lymphatics during surgical exposure. Compliance with leg elevation is typically enough to keep lower leg edema in control. Wound complications, although usually minor, are common and can be seen in ≤15% of patients.

Although vein grafts have intrinsic antithrombotic properties, low-dose aspirin therapy is continued through the perioperative period. The effect of antiplatelet therapy on patency is marginal and the benefits are derived from lowering peri-procedural cardiac events. Both dual antiplatelet therapy and anticoagulation have been rigorously studied without any meaningful improvement on patency of vein grafts. The addition of dual antiplatelet therapy or anticoagulation for prosthetic grafts has not been shown to unequivocally improve patency and its use is somewhat controversial. In patients with prior graft failure, poor runoff or with those other features placing the graft at high risk, additional anticoagulation may be considered, but at risk of adding to the 15% of patients who develop wound complications. There is some suggestion that statins may improve long-term outcomes, in both patient survival and graft patency, although definitive studies are pending.

Vein graft stenosis is a common occurrence, being detected in as many as 40% of vein bypasses, typically observed within the first 18 postoperative months. Although a change in symptoms or a change in the ABI of >0.2 should warrant further investigation, ultrasound surveillance is a more sensitive method of detection and early intervention can prolong the longevity of the graft. A surveillance program consisting of a duplex ultrasound at 1, 3, 6, and 12 months after surgery, then every 6 months thereafter is suggested. Changes in the peak systolic velocity (>300 cm/s),
a change in the velocity ratio (>3.5) or a low velocity with blunting of waveforms (<40 cm/s) should prompt a diagnostic angiogram with possible reintervention, even in the absence of a change in the clinical examination. A successful surveillance program will prolong the primary-assisted patency of vein grafts, which is particularly important as the long-term outcomes of a thrombosed vein graft that is salvaged yield poor results. As the modes of failure of prosthetic grafts are distinct, typically the result of anastomotic neointimal hyperplasia, surveillance has not been shown to prolong prosthetic graft patency.

**Tibial–Pedal Disease**

Infrageniculate revascularization is a durable and efficacious intervention for appropriately selected patients (Figure 5). When using high-quality autologous conduit, the level of the distal anastomosis does not affect long-term outcomes, with equivalency demonstrated between bypasses to the popliteal, tibial, or pedal level (Figure 4).

The most basic measure of surgical revascularization is patency. Contemporary results from carefully conducted surgical trials routinely report >80% 5-year patency for vein grafts to infrainguinal targets. By far the most important factor in determining the durability of the operation is the quality of the conduit used. High-quality vein grafts that comprised a single segment of saphenous vein >3.5 mm in diameter perform equally well over time irrespective of the level of the distal anastomosis, including popliteal, tibial, or pedal targets. Long-term results suffer with compromised conduit quality, such as vein grafts that are small in size (<3 mm), spliced vein grafts, and nonsaphenous vein grafts.

In addition, multiple studies have demonstrated that diabetes mellitus is not a risk factor for vein graft failure, including both single center series and prospective data accrued from multicenter trials. As diabetics have a pattern of disease that includes a heavy burden of disease in tibioperoneal arteries, the level of distal anastomosis has proved to be a much weaker predictor of graft failure than conduit quality.

Although graft patency by itself is unaltered in diabetics, amputation-free survival is lower in this patient population. Other nonmodifiable risk factors affecting amputation-free survival include race, sex, infection, and certain comorbid conditions. For example, chronic renal insufficiency is an independent risk factor for limb loss and mortality. Up to 15%
of lower extremity bypass patients with end-stage renal disease may go on to major amputation despite having a patent bypass graft.77 In fact, there is a nearly linear relationship between the degree of chronic renal insufficiency and mortality among patients undergoing lower extremity bypass surgery and the relationship develops well before the onset of end-stage renal disease.78

Finally, although improving ambulatory function is the ultimate goal for IC, it remains a distant goal for more than half the patients with CLI.79 The most important measure of success in CLI is functional outcomes such as ambulatory status, ability to live independently, improved quality of life, and complete wound healing. A minority of patients undergoing bypass for CLI meet all of these functional goals, underscoring the severity of the systemic disease in this patient population. The most predictive factor for high functional outcomes in these patients is preoperative ambulatory status.80 Successful bypass surgery has been shown to improve quality of life in CLI, but maintaining that benefit depends on avoiding reinterventions and achieving complete wound healing.81 This underscores the importance of selecting a durable and effective revascularization in this otherwise high-risk patient population.

**Scientific Challenges and Major Unmet Needs**

### Control of Neointimal Hyperplasia

Neointimal hyperplasia is the end result of the prototypic response of blood vessels to injury. An inflammatory response, followed by activation of vascular smooth muscle cells, leads to a proliferative lesion with subsequent elaboration of extracellular matrix and fibrosis. When excessive, this scarring response leads to lumen narrowing (restenosis), the most common cause of failure of all types of endovascular and open vascular interventions. Prevention of restenosis remains the greatest unmet need in the vascular surgical patient. In vein bypass grafts, an early adaptive remodeling occurs in response to increased shear stress and wall tension, resulting in overall vessel enlargement and increased wall thickness.85,86 If the hyperplastic response continues, or is accompanied by a constrictive fibrosis, stenosis may ensue. Vein graft stenosis is most typically focal, for example, in the perianastomotic regions and at valve sites; more rarely it occurs diffusely throughout the graft. Prosthetic graft failure is commonly a result of progressive hyperplasia in the perianastomotic region of the native artery, typically at the outflow side. The process seems pathologically similar, but its course may also be influenced by the chronic host response to the artificial implant and the compliance mismatch across the anastomosis.
Despite progress in the use of antiproliferative drugs to limit restenosis after endovascular interventions (drug-eluting stents and balloons), there is as yet no proven approach to attenuate neointimal hyperplasia in the surgical setting. The Project of Ex vivo Vein graft Engineering via Transfection (PREVENT) trials tested a genetic strategy using a transcription factor (E2F) decoy to block proliferation in vein grafts. Two large randomized trials demonstrated no improvement in either lower extremity or coronary vein graft patency. Although a great deal of translational research continues in this arena, to date no other candidate therapy has reached the stage of advanced clinical testing. Vein grafts offer unique opportunity for targeted molecular/pharmacological intervention at the time of implantation, with the goal of promoting favorable remodeling and subsequent long-term patency.

Small Caliber Vascular Conduits
As previously mentioned, a significant numbers of patients with advanced PAD lack adequate autogenous conduit for infrainguinal revascularization. For these patients, prosthetics and other available conduits (eg, cryopreserved homografts) offer a compromised solution, with reduced patency particularly for tibial and pedal bypass grafts. The significant need for a small caliber arterial substitute has been a driver of bioengineering research for 2 to 3 decades. Many lessons have been learned and much progress has been made in the efforts to create an off-the-shelf tissue engineered vascular graft. The current favored approach uses human vascular cells to populate scaffolds, elaborate, and organize matrix during in vitro conditioning. Tissue engineered vascular graft have now been used in humans as patches, conduits, and for dialysis access. Two constructs are currently in early stage clinical investigation and are likely to be tested in patients with PAD in the near future. Other approaches being investigated include the use of stem/progenitor cells to populate scaffold constructs, with subsequent recruitment of host vascular cells after implantation. In the coming decade, it seems likely that a commercially available tissue engineered vascular graft will provide a useful new alternative for lower extremity reconstruction.

Adjuvant Medical and Biological Therapies
Optimal medical management of patients after revascularization has to date focused on prevention of major complications and cardiovascular events. After limb revascularization, inflammation, thrombosis, ischemia–reperfusion injury, and remote organ injury may all ensue to various subclinical and clinical degrees. There is considerable room for improved periprocedural interventions to attenuate these deleterious responses and to augment the local tissue response to revascularization. Anti-inflammatory, antithrombotic, and pro-resolving strategies could minimize injury, maintain vessel patency, and promote homeostasis and tissue repair. This could involve nutritional, pharmacological, cell- or even gene-based therapies applied in adjuvant fashion. Future research in this arena offers great opportunity to broadly improve clinical outcomes in vascular patients undergoing invasive treatments.

Conclusions
Surgical revascularization remains a cornerstone of treatment for advanced, symptomatic PAD. The emergence of percutaneous techniques has expanded the armamentarium but has not altered the fundamental principles of revascularization nor the indications for intervention. Rather, the emphasis is placed on patient selection for these complementary modalities. Patient-specific factors are critical in selecting the most efficacious and durable outcome, with particular importance placed on comorbid conditions, estimated life expectancy, functional status, pattern of disease, and availability of conduit.

Disclosures
None.

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Shant M. Vartanian and Michael S. Conte

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Emerging National Trends in the Management and Outcomes of Lower Extremity Peripheral Arterial Disease

Michael S. Hong, Adam W. Beck, and Peter R. Nelson, Gainesville, Florida

Background: In this study, we sought to analyze emerging national trends in the treatment of lower extremity peripheral arterial disease and associated outcomes.

Methods: The Nationwide Inpatient Sample was queried between 2001 and 2007. Patients diagnosed with lower extremity atherosclerosis were selected by using the International Classification of Diseases, 9th Revision codes 440.20-440.24, resulting in an average of 307,000 annual hospitalizations. Within this group, we determined the annual number of lower extremity bypasses, endovascular interventions, and major and/or minor amputations (below-the- and/or above-the-knee amputation versus toe and/or foot amputation). Chi-square analysis was performed on discharge-weighted data to compare two periods (2001-2003 and 2004-2007) to determine changes in management and differences in outcome. Multivariate logistic regression was used to identify predictors of amputation.

Results: Comparing the two periods, it was found that the average annual number of endovascular interventions increased by 78% (37,692 vs. 67,248, \( p < 0.001 \)), and open lower extremity bypasses decreased by 20% (68,326 vs. 54,348, \( p < 0.001 \)). Annually, the total number of interventions increased by 15% (106,018 vs. 121,596, \( p < 0.001 \)), whereas the number of total amputations (59,693 vs. 50,254, \( p < 0.001 \)), major amputations (39,543 vs. 31,043, \( p < 0.001 \)), and minor amputations (20,150 vs. 19,211, \( p < 0.001 \)) performed all significantly decreased. Diabetes was the leading predictor of amputation, especially those involving the toe and forefoot. After adjusting for age and comorbidities, African Americans were found to have a 2.4 times odds of amputation as compared with Caucasians, whereas those with Medicare or Medicaid had a 1.5 times odds as compared with those having private insurance or Health Maintenance Organization.

Conclusions: Between the periods examined, we observed that the treatment of lower extremity peripheral arterial disease has evolved with increased use of lesser invasive endovascular techniques and fewer open lower extremity bypasses. These trends are associated with fewer major lower extremity amputations. Significant socioeconomic disparities persist in amputation rates, with racial minorities and those with Medicare or Medicaid having higher odds of amputation.

INTRODUCTION

Peripheral arterial disease (PAD) affects over 8 million Americans, and can lead to decreased function and loss of limb. Until recently, open peripheral arterial bypass has been the first-line surgical treatment option for PAD. Although open bypass has been shown to be successful in improving symptoms, quality of life, and limb salvage, the invasive nature of the surgery can limit optimal overall...
outcome. In fact, Nicoloff et al. reported that almost one-fourth of lower extremity bypass procedures are complicated by prolonged wound closure.

Angioplasty/stenting, despite being a less invasive procedure, has been shown to have similar limb salvage rates in those with critical limb ischemia. This procedure has the benefit of fewer wound complications and a shorter hospital stay. Quality of life has also been shown to significantly improve after endovascular therapy, as a result of better function and reduced pain. As expected, endovascular therapy is increasingly being considered as a first-line treatment option in carefully selected patients with PAD.

Our study quantifies the pace and extent to which endovascular therapy is being adopted nationally for treating PAD, and addresses outcomes associated with this evolving trend.

MATERIALS AND METHODS

The Nationwide Inpatient Sample (NIS) is an administrative database of inpatient admissions, collected from participating states, that comprises approximately 20% of all admissions in the United States. As of 2007, the NIS included samples from 40 states and 90% of admissions in the country. Weights are applied per admission on the basis of the known number of discharges from a given hospital, as reported by the American Hospital Association, so that the sampled data accurately reflect the national population.

The NIS contains inpatient discharge-specific rather than patient-specific data, which has several important implications. First, long-term outcomes for specific procedures cannot reliably be obtained because all outcomes are limited to the time frame of the same index hospitalization as the revascularization. Second, in the case of amputations, such as that of a gangrenous toe, revascularization performed during the same hospitalization may represent planned procedures for improved wound healing, rather than a failure of the revascularization. Therefore, amputations recorded during the same hospitalization as the endovascular therapy or open bypass more likely reflect differing treatment strategies rather than true outcomes. Third, an approximation of amputation outcomes is possible, but only globally (for reasons mentioned previously), as amputations (those that reflect revascularization failure) usually result in a new admission and unique entry in the database. With these three concepts in mind, we limited our analysis to more general outcomes rather than procedure-specific outcomes. In other words, although we cannot determine whether a specific revascularization reduced the need for amputation, we can make associations on a larger scale to determine whether there is a change in national amputation rates associated with changes in the use of endovascular therapy.

Because the NIS maintains de-identified data, this study was approved as exempt by the Institutional Review Board of the University of Florida College of Medicine.

We used the NIS between 2001 and 2007 to study general trends in the treatment of PAD. To limit the number of revascularizations or amputations for indications other than PAD, such as trauma or malignancy, we selected our study population by first identifying those diagnosed with atherosclerosis of the extremities, using code 440.20-440.24 from the International Classification of Diseases, 9th Revision (ICD-9). Within this group with PAD, we then identified two surgical revascularization groups, on the basis of whether a peripheral endovascular or open bypass procedure was performed. For peripheral endovascular procedures, we used ICD-9 procedure codes 39.50 (angioplasty or atherectomy), 39.90 (placement of a stent), and 00.55 (placement of a drug-eluting stent). For open bypass, we used codes 39.25 (aorto-distal bypass) and 39.29 (other vascular shunt or bypass).

An a priori list of clinically relevant comorbidities and complications was selected. The patient demographics of interest were age, gender, race, and payer type. Comorbidities included coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, obesity, and chronic renal disease.

To characterize trends in endovascular therapy, open bypass, and amputation over time, we analyzed two periods centered before and after the point at which endovascular and open bypass procedures were being performed at a similar rate. The period before this point (2001-2003) represents an open bypass era and the period after (2004-2007) represents a more endovascular predominant era (Fig. 1).

Primary outcomes of interest were trends in the use of endovascular therapy and open repair, as well as lower extremity amputation. Amputation was classified into major and minor. Major amputation was defined as above-the-knee, knee disarticulation, below-the-knee, and ankle disarticulation. Minor amputation was defined as toe and forefoot. Secondary outcomes included inpatient mortality and length of hospital stay.
All statistics incorporated discharge-level weights provided in the NIS database. We used the Student’s independent sample $t$-test to compare numerical means, and Pearson’s $\chi^2$ to compare categorical variables from $2 \times 2$ contingency tables. Statistical significance was set at an alpha level of 0.05. Individual predictors of amputation were identified with logistic regression analysis. Statistically significant variables ($p < 0.05$) were then incorporated to a multivariate analysis to identify independently predictive factors, and adjusted odds ratios with 95% confidence intervals were calculated. All statistical analysis was performed with SPSS 17 for Windows (SPSS Inc, Chicago, IL).

**RESULTS**

**Overall Cohort**

A total of 2,148,924 hospital admissions involving patients diagnosed with lower extremity PAD were identified over a period of 7 years, on an average 307,000 ± 18,000 admissions per year with no increase in the number of admissions with diagnosis of PAD over time (Fig. 1). Patient characteristics are outlined in Table I. The average age of the patients was 69 ± 11 years, and 56% were men and 44% were women.

**Trends over Time**

With the widespread adoption of endovascular therapy, there has been a profound shift in practice patterns for lower extremity PAD in the past decade. Since 2001, there has been a consistent increase in the number of inpatient endovascular procedures being performed for lower extremity disease. Comparing the earlier period (2001-2003) with the latter (2004-2007), a statistically significant increase in endovascular procedures performed in the latter period was seen, with the average annual number of endovascular interventions increasing by 78% (37,692 vs. 67,248, $p < 0.001$). In addition, we observed an inversely proportional and statistically significant decrease in open bypass by 20% (68,326 vs. 54,348, $p < 0.001$). When only the earliest (2001) and latest (2007) years were compared in our study, the changes were even more dramatic, with a 115% increase in endovascular therapy and a 31% decrease in bypass (Fig. 1).

One of the purported benefits of endovascular therapy is that it allows for better limb salvage, by both offering a minimally invasive therapy to those whose anatomy or prohibitive comorbidities preclude open bypass and also assisting in maintaining patency and adequate flow after a primary intervention. We found that the trends in amputation were consistent with the increase in endovascular therapy and its purported benefits in limb salvage. The number of major amputations (ankle to above-the-knee level) decreased from an average of 39,543 in the earlier period (2001-2003) to 31,043 in the latter (2004-2007), representing a decrease of 21% ($p < 0.001$).

We were also interested in observing whether the increased use of endovascular therapy was associated with a change in the number of minor
amputations. These amputations, defined as involving the toe and forefoot, showed a moderate decrease of 5% (20,150 vs. 19,211, \( p < 0.001 \)) (Fig. 2).

Subset analyses of amputations by race and insurance status revealed that all subsets had significant (\( p < 0.001 \)) decreases in the number of major amputations and amputation rates per PAD admission from the earlier (2001-2003) to the latter (2004-2007) period (Figs. 3 and 4).

To place these changes in the context of possible shifts in the overall patient population, either through better diagnosis or changing therapeutic strategies, we separately analyzed the patients by severity of their PAD. The two extremes of PAD, namely claudication and gangrene, showed the most dramatic changes: as compared with the earlier (2001-2003), there were 13% more patients with claudication (68,112 vs. 77,109, \( p < 0.001 \)) and 12% fewer patients with gangrene (84,153 vs. 74,426, \( p < 0.001 \)) admitted in the latter (2004-2007) period. Rest pain and ulceration changed more moderately at 10% (19,249 vs. 21,271, \( p < 0.001 \)) and 4% (43,156 vs. 41,451, \( p < 0.001 \)), respectively (Fig. 5).

We also observed the Rutherford classification of those who underwent major or minor amputation. There were consistent annual decreases of those with gangrene who underwent major amputation (decrease of 23% from 2001-2003 to 2004-2007), closely mirroring the decrease of major amputations overall. The decreases were again moderate with minor amputation (decrease by 5% in 2004-2007) (Fig. 6A, B).

### Comparison of Endovascular Therapy and Open Bypass

The patient characteristics of those undergoing endovascular therapy and open bypass are shown in Table I. The patient groups were relatively similar, with a few notable differences. Chronic renal insufficiency and coronary artery disease was higher in the endovascular therapy group, whereas chronic obstructive pulmonary disease and tobacco dependence was higher in the open bypass group. Interestingly, a larger proportion of those who received endovascular therapy were acutely admitted through the emergency room.

Both the endovascular therapy and open bypass groups showed changes in the proportion of the different Rutherford severity groups. With endovascular therapy, the most striking change is the substantial increase in patients treated for claudication (16,587 in 2001 vs. 36,072 in 2007). However, it is also interesting to note that the total number of patients with rest pain, ulceration, and gangrene all consistently increased, and approximately doubled when comparing the years between 2001 and 2007. In contrast, the total number of open bypass procedures consistently decreased for all subclasses of PAD severity (Fig. 7A, B).

### Table I. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall PAD (( n = 2,148,924 ))</th>
<th>Endovascular (( n = 382,067 ))</th>
<th>Open bypass (( n = 379,162 ))</th>
<th>( p )-value (endovascular vs. open)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.4</td>
<td>69.5</td>
<td>68.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80+</td>
<td>41.8%</td>
<td>35.4%</td>
<td>28.9%</td>
<td>&lt;0.001</td>
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<tr>
<td>Female</td>
<td>43.8%</td>
<td>45.4%</td>
<td>41.1%</td>
<td>&lt;0.001</td>
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<tr>
<td>White</td>
<td>74.1%</td>
<td>77.5%</td>
<td>77.4%</td>
<td>0.265</td>
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<tr>
<td>AA</td>
<td>14.4%</td>
<td>11.9%</td>
<td>13.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.0%</td>
<td>7.1%</td>
<td>6.7%</td>
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<tr>
<td>Asian</td>
<td>1.2%</td>
<td>1.0%</td>
<td>0.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>Native American</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>45.8%</td>
<td>42.0%</td>
<td>41.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>Obesity</td>
<td>4.1%</td>
<td>3.6%</td>
<td>3.7%</td>
<td>0.013</td>
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<tr>
<td>HTN</td>
<td>49.2%</td>
<td>54.2%</td>
<td>56.7%</td>
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<td>45.1%</td>
<td>38.8%</td>
<td>&lt;0.001</td>
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<tr>
<td>CHF</td>
<td>21.9%</td>
<td>14.2%</td>
<td>14.1%</td>
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<tr>
<td>COPD</td>
<td>19.4%</td>
<td>17.1%</td>
<td>22.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRI</td>
<td>21.1%</td>
<td>17.6%</td>
<td>14.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco dependence</td>
<td>15.2%</td>
<td>18.0%</td>
<td>22.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ED admission</td>
<td>31.8%</td>
<td>13.8%</td>
<td>11.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AA, African American; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; ED, emergency department.
In-hospital mortality was low in both the endovascular therapy and open bypass groups at 1.4% and 2.2%, respectively ($p < 0.001$). Length of hospital stay was shorter in the endovascular therapy group at 4.8 days as compared with 8.7 days with open bypass ($p < 0.001$).

**Predictors of Major Amputation**

Multivariate analysis for predictors of major amputation showed that diabetes and chronic renal insufficiency were the two comorbidities conferring the highest risk of major amputation. Socioeconomic factors, such as being on Medicare/Medicaid, as well as belonging to a racial minority, were also associated with an increased risk of amputation (Table II).

When each race was analyzed separately, we saw that every racial minority was associated with an elevated risk of major amputation in comparison with Caucasians after adjusting for comorbidities, demographics, and insurance status. African Americans had more than 2.4 times the odds of a major amputation as compared with Caucasians, whereas Hispanics, Native Americans, and Asians had more moderately elevated odds (Table III).

**Predictors of Minor Amputation**

Multivariate analysis for predictors of minor amputation showed similar results to that of major amputation. For amputations of the toe and forefoot, diabetes increased the odds of amputation by more than three-fold. Factors such as chronic renal insufficiency, being a racial minority, and having Medicare/Medicaid had more moderately elevated odds (Table IV).

Similar to major amputation, there were elevated odds of minor amputation among each racial minority group. The results of adjusted odds ratios for minor amputation for each racial minority group are summarized in Table V.

**DISCUSSION**

Endovascular therapy is being used with increasing frequency and is associated with a decrease in the number of open bypass surgeries being performed. Although endovascular procedures are most commonly performed for claudication, its use is on the rise for all Rutherford severity subclasses. For those eligible for endovascular treatment of lower extremity PAD, this minimally invasive alternative to open bypass has several appealing advantages. Our study demonstrated that patients who underwent endovascular therapy had a shorter length of hospital stay and lower inpatient mortality.

Further, rates of major amputation decreased on an annual basis. Several explanations exist for this finding. First, there were more patients diagnosed with claudication and fewer with gangrene in the later time frame. Although the difference in disease severity alone may result in fewer amputations, it could be argued that successful earlier revascularization reduces the number of patients who develop
more severe PAD. Second, endovascular therapy may offer a treatment option for those who were precluded from open bypass. Those with severe comorbidities, unsuitable conduit, or poor target vessels, who may have been previously only offered primary amputation, might now qualify for angioplasty or stenting. Third, endovascular therapy is frequently used for secondary procedures involving postsurgical intimal hyperplasia. The cumulative effect of improvements in primary-assisted and secondary-assisted patency by endovascular methods has most likely contributed toward fewer amputations. Finally, improvements in medical management (or possibly other unknown factors) may also have contributed toward the overall trend.

Considering major amputation, defined as ankle disarticulation to above-the-knee level, comorbidities associated with the greatest odds of amputation

Fig. 3. Amputations by race per year.

Fig. 4. Amputations by insurance status per year.
were diabetes and chronic renal insufficiency. In minor amputation, defined as toe and forefoot level, the greatest risk factor was diabetes, which increased the odds of amputation by more than three-fold. These results, showing increased odds of amputation for those with diabetes or chronic renal disease, confirm findings that have been repeatedly shown in previous studies. One additional observation regarding minor amputations was the moderate 5% reduction that was observed. This either implies a lesser effect of endovascular therapy on forefoot procedures, or possibly suggests a trend toward “distalizing” amputations (i.e., limiting what would otherwise require major amputation to a forefoot procedure). This is an interesting concept but cannot be determined from the data set.

Although the trends in amputation are encouraging, significant socioeconomic disparities in outcome persist. Compared with Caucasians, those in racial minority groups, particular African Americans, have much higher odds of major amputation. In addition, those with Medicare or Medicaid also have elevated odds of major amputation as compared with those who have private insurance or belong to Health Maintenance Organizations. However, all subgroups, whether grouped by race or by insurance status, demonstrate an overall decrease in amputations over time suggesting that the positive effect of the current treatment paradigm is seen across these groups.

The persistently higher amputation rates in racial minorities may be explained by several factors, including socioeconomic disparities, difference in the distribution of PAD in the limbs, and postoperative healing and remodeling. Socioeconomic differences have been mentioned in numerous studies. Oh-Park et al. found disparities in amputation among Hispanics in comparison with Caucasians, and concluded that low socioeconomic status was largely responsible for higher amputation rates in this group, whereas Resnick et al. found that low education level correlated with higher odds of amputation in the diabetic American Indian population. Finally, using the Medicare database, Regenbogen et al. demonstrated that socioeconomic disparities were clinically relevant in that African Americans were less likely to have access to specialists and high-volume centers.

In addition to socioeconomic disparities, differences in disease presentation seem to also contribute toward higher amputation rates among minorities, particularly African Americans. Using a Florida administrative database, Huber et al. showed that African Americans who underwent diagnostic angiograms were still more likely to undergo primary amputation rather than revascularization, which suggests differences in disease distribution. In the study by Regenbogen et al., increased rates of amputation persisted among African Americans who were treated in high-volume centers by vascular specialists at urban teaching hospitals.

Furthermore, differences in amputation rates may also be because of poorer outcomes after either...
revascularization or primary amputation. In a study of racial differences in the Project of Ex Vivo Vein Graft Engineering via Transfection III randomized trial database, African Americans who underwent vein bypass had reduced secondary patency and limb salvage at 1-year follow-up as compared with Caucasians. Meanwhile, a single institution study at Northwestern reported that African Americans who underwent primary amputation were 2.5 times more likely than Caucasians to undergo repeat amputations.

Several limitations exist in our study. First, as with all studies involving ICD-9 coding-based databases, information regarding severity of disease is often lacking. Although codes for PAD do contain information about severity, we do not have information regarding the Trans-Atlantic Inter-Society Consensus classification or the severity of
comorbidities. The lack of such clinically relevant information poses a challenge when attempting to compare two surgical groups and their outcomes.

Second, because the NIS does not track patients, but rather counts each new admission as a new data point, repeat admissions may have been counted multiple times. As Rucker-Whitaker demonstrated in the study from Northwestern, these multiple admissions as well as repeat amputations, exaggerate the differences in amputation rates in African Americans. A similar effect can be found with endovascular therapy because endovascular therapy is generally less durable than open bypass, and may require a greater number of reinterventions. For this reason, we elected to view general trends using raw numbers rather than a proportion of patients receiving a certain procedure.

Third, the number of amputations decreased, associated with the dramatic shift in treatment strategies in the same study period. However, it remains...
Table II. Predictors of major amputation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.786</td>
<td>1.770-1.803</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicare/Medicaid</td>
<td>1.538</td>
<td>1.516-1.560</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Racial minority</td>
<td>1.536</td>
<td>1.523-1.550</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRI</td>
<td>1.370</td>
<td>1.355-1.385</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>1.235</td>
<td>1.222-1.248</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.006</td>
<td>1.005-1.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>0.979</td>
<td>0.968-0.991</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.965</td>
<td>0.956-0.973</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN</td>
<td>0.745</td>
<td>0.738-0.753</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.567</td>
<td>0.551-0.583</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco dependence</td>
<td>0.560</td>
<td>0.550-0.570</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>0.508</td>
<td>0.503-0.512</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency.

Table III. Predictors of major amputation by race

<table>
<thead>
<tr>
<th>Compared with Caucasian</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>2.406</td>
<td>2.376-2.436</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.471</td>
<td>1.446-1.496</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Native American</td>
<td>1.307</td>
<td>1.216-1.404</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>1.288</td>
<td>1.234-1.345</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*After adjusting for age, gender, insurance status, DM, HTN, obesity, tobacco dependence, chronic renal disease, CAD, CHF, and COPD.

to be seen whether these lower amputation numbers will be durable over time, or whether we might see a rebound of amputations several years later. Although uncertain, as an endovascular-first approach has not been shown to preclude future revascularization (either repeat endovascular therapy or open bypass), any “rebound effect”, if seen, is most likely to be fairly moderate.16,17 In addition, despite lingering questions regarding long-term epidemiological outcomes, it is worth noting that for individuals, a successful delay in amputation, particularly in those with a reduced life expectancy, is a positive outcome.

Finally, the NIS only maintains in-patient data. A large proportion of vascular procedures, particularly endovascular procedures, are performed on an outpatient basis and therefore not captured by the NIS. We were therefore not able to include outpatient procedures in our analysis. As a result, our estimates for the frequency and trends in endovascular procedures may be an underestimate and the effect of these procedures may be even more profound than we have reported. We were not able to study this trend with our database.

CONCLUSION

We have shown that there has been an impressive change in the treatment of PAD in just the last several years. Endovascular therapy is now the primary treatment of choice for PAD in carefully selected patients. Although much of the increase in endovascular therapy is because of patients with claudication, it is also increasingly being used to treat those with critical limb ischemia as well. The aggressive use of endovascular therapy in all Rutherford severity subgroups may explain why the increase in endovascular procedures are associated with a decrease in open bypass, as well as a significant decrease in amputation rates.

Overall, the higher likelihood of amputation in those with diabetes and chronic renal disease...
remains a consistent finding. We also observed increased likelihood of amputation in racial minorities, in particular African Americans. This disparity is most likely multi-factorial, involving socioeconomic disparities affecting access to specialized care, but also biologic difference in disease distribution and postoperative healing. Further studies are required to clarify these biologic differences in greater detail.

REFERENCES