Disparity in Outcomes of Surgical Revascularization for Limb Salvage

Race and Gender Are Synergistic Determinants of Vein Graft Failure and Limb Loss

Louis L. Nguyen, MD, MBA, MPH; Nathanael Hevelone, MPH; Selwyn O. Rogers, MD, MPH; Dennis F. Bandyk, MD; Alexander W. Clowes, MD; Gregory L. Moneta, MD; Stuart Lipsitz, ScD; Michael S. Conte, MD

Background—Vein bypass surgery is an effective therapy for atherosclerotic occlusive disease in the coronary and peripheral circulations; however, long-term results are limited by progressive attrition of graft patency. Failure of vein bypass grafts in patients with critical limb ischemia results in morbidity, limb loss, and additional resource use. Although technical factors are known to be critical to the success of surgical revascularization, patient-specific risk factors are not well defined. In particular, the relationship of race/ethnicity and gender to the outcomes of peripheral bypass surgery has been controversial.

Methods and Results—We analyzed the Project of Ex Vivo Vein Graft Engineering via Transfection III (PREVENT III) randomized trial database, which included 1404 lower extremity vein graft operations performed exclusively for critical limb ischemia at 83 North American centers. Trial design included intensive ultrasound surveillance of the bypass graft and clinical follow-up to 1 year. Multivariable modeling (Cox proportional hazards and propensity score) was used to examine the relationships of demographic variables to clinical end points, including perioperative (30-day) events and 1-year outcomes (vein graft patency, limb salvage, and patient survival). Final propensity score models adjusted for 16 covariates (including type of institution, technical factors, selected comorbidities, and adjunctive medications) to examine the associations between race, gender, and outcomes. Among the 249 black patients enrolled in PREVENT III, 118 were women and 131 were men. Black men were at increased risk for early graft failure (hazard ratio [HR], 2.832 for 30-day failure; 95% confidence interval [CI], 1.393 to 5.759; \( P = 0.0004 \)), even when the analysis was restricted to exclude high-risk venous conduits. Black patients experienced reduced secondary patency (HR, 1.49; 95% CI, 1.08 to 2.06; \( P = 0.016 \)) and limb salvage (HR, 2.02; 95% CI, 1.27 to 3.20; \( P = 0.003 \)) at 1 year. Propensity score models demonstrate that black women were the most disadvantaged, with an increased risk for loss of graft patency (HR, 2.02 for secondary patency; 95% CI, 1.27 to 3.20; \( P = 0.003 \)) and major amputation (HR, 2.38; 95% CI, 1.18 to 4.83; \( P = 0.016 \)) at 1 year. Perioperative mortality and 1-year mortality were similar across race/gender groups.

Conclusions—Black race and female gender are risk factors for adverse outcomes after vein bypass surgery for limb salvage. Graft failure and limb loss are more common events in black patients, with black women being a particularly high-risk group. These data suggest the possibility of an altered biological response to vein grafting in this population; however, further studies are needed to determine the mechanisms underlying these observed disparities in outcome.

Key Words: bypass grafts peripheral artery disease race women

C hronic critical limb ischemia (CLI) represents an advanced stage of peripheral arterial disease in which rest pain, ulceration, or gangrene heralds potential limb loss if left untreated. Lower extremity revascularization via surgical bypass has been demonstrated to provide effective treatment for CLI in conjunction with appropriate wound management.1,2 The autogenous vein is the conduit of choice in lower extremity bypass, especially when the distal target is infra-
genicular. Despite decades of experience and technical advances, vein graft failure remains a common clinical problem (30% to 50% within 5 years) with an origin that is incompletely understood. Technical factors, including conduit quality and handling, choice of anastomotic sites, and resistance of the runoff bed, are considered key primary determinants, particularly for early (perioperative) success. However, long-term clinical success is likely to be influenced by other critical elements, including variability in the biological processes that govern the vein arterialization response and disease progression in the inflow and outflow arteries.

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The differential prevalence of peripheral arterial disease across racial/ethnic groups and genders has been demonstrated previously. Black patients have a disproportionate risk for major limb amputation, which some have speculated to be directly related to lower rates of use of surgical or endovascular interventions. Known racial/ethnic differences exist in the prevalence of comorbidities such as diabetes mellitus, renal failure, and hypertension that may influence both the natural history of peripheral arterial disease and responses to treatment. However, the impact of race and gender on clinical outcomes after lower extremity revascularization is not well established. Black race has been associated with inferior graft patency and limb salvage in some studies, whereas no such associations have been seen in other studies. Female gender has been associated with increased risk of wound complications after revascularization, although effects on graft patency and limb salvage are not clear. Most of these prior reports consist of retrospective analyses of clinical registries or administrative databases lacking validated data on graft patency and limb status. Additionally, the interactions between race and gender on outcomes of revascularization have not been fully explored.

PREVENT III was a multicenter clinical trial of patients undergoing vein bypass for CLI. To date, it is the largest prospective cohort of surgically treated CLI patients with detailed clinical and imaging follow-up to 1 year. Although the primary results of the trial have been previously reported, this database has provided a unique opportunity to examine risk factors and outcomes of limb salvage surgery in contemporary vascular surgery practice. Univariate analyses with ANOVA for the continuous variable (age) and Fisher exact test for categorical variables (edifoligide assignment; institution type; tissue loss; site of proximal and distal graft anastomoses; vein graft diameter; estimated glomerular filtration rate; use of β-blockers, statins, and antithrombotics; and history of coronary artery disease, diabetes mellitus, hypercholesterolemia, hypertension, and smoking) were performed to examine the potential association of race/gender groups with patient demographic characteristics and comorbidities. Univariate logistic regression models were used to analyze the relationship of patient characteristics and perioperative variables to clinical end points, including perioperative (30-day) events, and Cox proportional-hazard models were used for 1-year outcomes (graft patency, limb salvage, and patient mortality).

Propensity score modeling was used to control the 16 covariates to allow multivariable analysis of the associations and interactions between race and gender with outcomes. The propensity score model included type of institution, technical variables (edifoligide assignment, tissue loss, vein graft diameter, and site of proximal and distal graft anastomoses), selected comorbidities (estimated glomerular filtration rate, history of coronary artery disease, diabetes mellitus, hypercholesterolemia, hypertension, and smoking), and use of medical therapies (β-blockers, statins, and antithrombotics). These variables were then used in logistic regression models for the 4 possible race and gender combinations. Patient data were then adjusted by the inverse probability of being in 1 of the 4 groups. Covariate balance was checked after adjustment (Table 1, weighted values). This propensity score method serves several purposes in our analysis. It addresses the confounding between race/gender and the covariates while not altering the effect of race/gender on clinical outcomes. Furthermore, because our objective was to analyze the effects of the 4 combinations of race and gender, the propensity score adjustments allowed us to nest the other covariates into the primary outcomes models for easier interpretation. Multivariable Cox proportional-hazard models were then used to analyze the effect of the 4 race/gender combinations on clinical outcomes.

Clustering institutional effects were controlled by the inclusion of investigational site in the multivariable models. Because of the low distribution of black patients among the institutions (mean, 4.4; range, 0 to 37), random-effects models were not used to control for institutional effects. Patient compliance with postoperative graft surveillance was examined by generating an aggregate compliance score based on having a duplex graft scan if the patient was eligible to receive the scan (ie, patient alive with limb intact at time of study window). Models adjusting for surveillance compliance did not differ significantly from the primary outcome models and were
In all analyses, both unadjusted and propensity-adjusted comparisons were performed. All tests were considered statistically significant at \( P < 0.05 \). All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Table 1. Univariate Analysis of Race/Gender With Unweighted and Propensity-Weighted Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Black Women Unweighted</th>
<th>Black Men Unweighted</th>
<th>Nonblack Women Unweighted</th>
<th>Nonblack Men Unweighted</th>
<th>( P )</th>
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</thead>
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<tr>
<td>Age (mean), y</td>
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<td>65.08</td>
<td>70.60</td>
<td>68.23</td>
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<td></td>
<td>69.04</td>
<td>67.20</td>
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<td>Tissue loss</td>
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<td>78.63</td>
<td>72.49</td>
<td>75.33</td>
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<td></td>
<td>75.49</td>
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<td>History of CAD</td>
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<td>36.76</td>
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<td></td>
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<td>40.91</td>
<td>43.08</td>
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<td>Smoking (ever)</td>
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<td>84.73</td>
<td>60.67</td>
<td>80.94</td>
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<td></td>
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<td>78.51</td>
<td>74.03</td>
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<tr>
<td>eGFR, stage 1 or 2</td>
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<td>43.19</td>
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<td></td>
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<td>0.0500</td>
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<td>25.76</td>
<td>22.20</td>
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<td>49.87</td>
<td>48.45</td>
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<td>9.96</td>
<td>10.06</td>
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<td>7.63</td>
<td>27.76</td>
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<td>15.58</td>
<td>22.00</td>
<td>22.09</td>
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<td>62.60</td>
<td>46.27</td>
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<td>54.12</td>
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(Continued)
Results

Differences in Risk Factors and Other Key Variables by Race/Gender

Of the 1404 patients enrolled in PREVENT III, 249 (17.7%) were black, with 118 black women (47.4%) and 131 black men (52.6%). Nonblack women were older (mean age, 70.9 years); black men were the youngest group (65.1 years; P=0.0001; Table 1, unweighted values). Nonblack men had a higher prevalence of coronary artery disease (48.3%), and men of both race groups had higher rates of prior or current smoking (82.7% for nonblack men, 84.7% for black men; P=0.0001). Black patients of both genders had a higher prevalence of renal insufficiency (P=0.0002). Nonblack women had a higher rate of hypercholesterolemia (51.2%; P=0.0015), and black women had a greater prevalence of hypertension (94.1%; P=0.0002). Black men were less likely to have been treated with statins (22.9%; P<0.0001), although no differences were seen across the subgroups for β-blocker or antithrombotic medication use. The subgroups also differed in the sites of proximal (P<0.0001) and distal (P=0.0019) anastomoses, although no generalizable trend was observed. Black women were more likely to have smaller-diameter (<3 mm) vein grafts (10.2%; P<0.0001), a factor previously identified to be associated with graft failure in this cohort.4 No statistical differences between the race/gender subgroups were seen with respect to stage of presentation of the affected limb (rest pain versus tissue loss), diabetes mellitus, or study drug (edifoligide) assignment.

Perioperative Events

Overall perioperative (30-day) mortality was 2.7%. Major complications included myocardial infarction (4.7%) and cerebrovascular event (1.4%). No differences in 30-day mortality were seen among the race and gender subgroups. Early PP was 94.8%. Although black race and gender were not individually associated with PP at 30 days, the subgroup of black men demonstrated a higher rate of early graft failure compared with nonblack men (odds ratio, 2.986 for loss of PP compared with nonblack men; 95% confidence interval [CI], 1.742 to 6.057; P=0.002; Table 2). This association persisted even when the analysis excluded high-risk grafts (odds ratio, 3.0309; 95% CI, 1.290 to 7.124; P=0.0110), which were defined prospectively in PREVENT III as those using spliced vein, non–greater saphenous vein, or small-caliber (<3 mm) conduits. No differences were seen for 30-day SP or mortality among the race/gender subgroups.

Outcomes at 1 Year: Graft Patency, Limb Salvage, and Survival

The overall 1-year PP, PAP, and SP rates were 61%, 77%, and 80%, respectively. No significant differences in PP were seen when gender and race groups were compared separately or in subgroup combinations (Figure, A, and Table 2). However PAP and SP rates showed significant disparity across race/gender groups. Black patients were more likely to have experienced loss of PAP than nonblack patients (hazard ratio [HR], 1.427; 95% CI, 1.065 to 1.912; P=0.0173). Female gender alone had a nonsignificant trend of association with reduced PAP (HR, 1.299; 95% CI, 0.935 to 1.605; P=0.1186). The subgroup of black women had nearly double the risk for loss of PP at 1 year compared with nonblack men (HR, 1.919; 95% CI, 1.279 to 2.879; P=0.002; Figure, B, and Table 2). Similarly, black patients overall were more likely to experience loss of SP than nonblack (HR, 1.491; 95%
CI, 1.078 to 2.061; \( P = 0.0156 \)), with black women in particular more likely than nonblack men (HR, 1.968; 95% CI, 1.282 to 3.021; \( P = 0.002 \); Figure, C, and Table 2), whereas a nonsignificant trend was seen for women compared with men (HR, 1.320; 95% CI, 0.937 to 1.859; \( P = 0.1122 \)).

The overall limb loss rate at 1 year was 12%. Black patients were more likely to receive major amputation compared with nonblack patients (HR, 2.002; 95% CI, 1.201 to 3.336; \( P = 0.0077 \)). In particular, black women were at greatest risk for limb loss compared with nonblack men (HR, 2.042; 95% CI, 1.150 to 3.626; \( P = 0.015 \); Figure, D, and Table 2). Female gender per se did not have a significant association with amputation (HR, 1.102 versus all men; 95% CI, 0.737 to 1.649; \( P = 0.6366 \)). Overall mortality at 1 year was 16%. No significant differences among race or gender subgroups were seen in patient survival (Figure, E), amputation-free survival, or amputation- and reintervention-free survival (Table 2).

**Discussion**

The incidence of peripheral arterial disease in the US population is rising, and the disease disproportionately affects black patients in both frequency and severity.\(^{27,28}\) Among patients with CLI undergoing infrainguinal bypass surgery in this large multicenter trial, race and gender were associated with certain patterns of demographic, comorbidities, and technical variables. However, after such factors were controlled for with propensity score modeling, black patients in general and black female patients in particular had notably inferior vein graft patency and limb salvage outcomes. The combination of female gender and black race appeared to have synergistic negative effects on clinical outcomes, with the notable exception of mortality. These findings suggest a potentially altered biological response to this intervention in a population that has demonstrated a growing risk for advanced peripheral arterial disease and therefore has important clinical implications.
Inferior outcomes for black and female patients have been previously reported from single-center retrospective series of lower extremity bypass.\textsuperscript{10,29–31} However, the PREVENT III database, prospectively collected from >1400 patients undergoing limb salvage surgery across >80 North American institutions, provides a unique perspective. It is important to note that the PREVENT III trial protocol included postoperative ultrasound surveillance (1, 3, 6, and 12 months) and criteria for prophylactic reintervention of ultrasound-defined lesions\textsuperscript{18,26} that mirror modern vascular surgery practice. As such, the study provides a detailed look at the occurrence and nature of clinical failures within the first year of vein bypass surgery for CLI. The lack of difference in primary patency across race/gender subgroups suggests that the rate of development of the first significant graft lesion is similar across these populations. However, the markedly inferior PAP and SP seen in the black cohorts suggest a more aggressive process of early vein graft disease, leading to either complete occlusion or graft abandonment at an elevated rate within the first year of surgery. This population should therefore be considered higher risk, with efforts focused on aggressive medical management (antithrombotics and statins) and close surveillance to maximize the long-term benefits of limb revascularization.

Among the potential mechanisms linking race and gender to vein graft outcomes may be differences in biological factors. Classically, early (30-day) and midterm failures (>2 years) are ascribed to technical factors and neointimal hyperplasia, respectively. The latter process predominates in the first year after surgery and manifests clinically as a fibroproliferative lesion within the vein composed primarily of vascular smooth muscle and myofibroblast cell types. All vein grafts undergo a requisite adaptive response to arterIALIZation that includes some degree of outward remodeling and wall thickening.\textsuperscript{32,33} The factors that determine whether a particular graft adapts favorably or develops pathological remodeling are a subject of investigation. However, differences in key biological factors such as thrombotic balance,\textsuperscript{34} inflammation,\textsuperscript{35,36} fibrosis, and endothelial dysfunction\textsuperscript{37,38} may broadly affect the graft healing response in a given population. In this regard, observations from other clinical arenas suggest hypotheses for future exploration. For example, keloids are abnormally thick dermal scars that occur more frequently in black and Asian populations. The increased deposition of collagen, fibronectin, and extracellular matrix\textsuperscript{39} seen in these lesions is similar to the morphology of vein graft hyperplasia. Failures of solid-organ transplantation also are related to an aggressive form of vasculopathy and show a parallel relationship to black race.\textsuperscript{40} Genetic determinants such as the frequency of mutations or polymorphisms of genes broadly related to vascular injury or wound healing (eg, transforming growth factor-β\textsuperscript{41} and endothelial nitric oxide synthase\textsuperscript{42}) may play a role in these observations. Unfortunately, PREVENT-III did not include a prospective biomarker or genomics analysis, which may have provided further insights into these outcomes.

Socioeconomic factors, as related to race, also have been implicated in inflammation and atherosclerosis.\textsuperscript{43} The complete separation of the biology of race and gender from the socioeconomic effect of these factors cannot be made within the context of this analysis. We controlled for differences in variables that could be accounted for in our study, including medications prescribed and compliance with surveillance. However, we lack data on important factors such as active smoking, patient compliance with prescribed medications, and diet. It is possible that the mild (and sometimes undetectable) effects of race and gender alone are more evident when analyzed together, as in the present study. This may explain the variability in results seen with previous studies on this topic.

In contrast to lower extremity bypass grafts, studies examining differences in outcome among race/gender groups after coronary artery bypass grafting have been more mixed.\textsuperscript{44–46} Potential explanations for this difference may include inherent differences in the biology of vein grafts placed in the coronary versus lower extremity circulation. One important difference in the nature of these observations relates to the ease and accuracy of noninvasive ultrasound to monitor patency of grafts in the leg versus the heart. Differences in patient selection for the bypass surgeries themselves can also bias the association of race and gender on outcomes.

Our analysis of the impact of race and gender on clinical outcomes for CLI has several limitations. All of the patients in this analysis volunteered to participate in a randomized clinical trial at institutions chosen for their high volume of peripheral vascular surgery and may not reflect the general population of CLI patients treated in the United States. Additionally, evidence suggests that rates of participation in clinical trials by race/ethnic and gender minority groups may not be representative of the available population with the disease.\textsuperscript{47} Thus, we do not know information about patients eligible for but not enrolled in the PREVENT III trial. Second, the simultaneous analysis of 2 patient factors of interest requires novel techniques to fairly represent their independent and synergistic effect on outcomes. Among the few techniques available to perform this analysis, we chose propensity score modeling to create hierarchical models so that race and gender could be varied in their 4 combinations while controlling for the other factors. Although recently developed, this analytical technique has been applied successfully by other groups.\textsuperscript{24,25} As with other uses of propensity score methodology, the validity of weight adjustments depends on the inclusion of relevant cofactors. For this analysis, all 16 relevant cofactors were included in the propensity model because no prior assumption of causation was made. Clustering effects were controlled by adding a variable for institution in the regression models. More complex modeling methods were considered but found to be limited because many of the institutions enrolled <5 patients in the study. Nevertheless, the participating institutions were selected because of their expertise in the care of CLI patients, so institutional treatment variability in this study was likely lower than typical of the general population.

In addition, an analysis of race and gender on clinical outcomes must attempt to address the question of whether the biology of race and gender itself is the cause of differential outcomes or whether the social and economic environments associated with race and outcome are the true drivers of
disparities. Even the determination of race itself is not without debate among experts in sociology, anthropology, and related disciplines. Those determinations are beyond the scope of this study. Arguably, the question may never be answered adequately because randomization of gender and race is practically impossible and assuredly unethical. Nevertheless, results from large observational studies or randomized clinical trials testing related interventions may build evidence to increase our understanding of these complex interactions and effects. It is very possible that the biology of race and gender is so intertwined with social and economic conditions that they cannot be easily separated for study as independent factors. In that case, race and gender would serve as proxies for the biology and environment they represent.

Conclusions

Black patients, particularly women, have worse clinical outcomes after vein bypass surgery for CLI than their white counterparts. The effects of female gender and black race/ethnicity appear synergistic and may explain variations in the detection of an effect for these factors in previous studies. Further investigation into the biological mechanisms and socioeconomic environments associated with black women may identify potential interventions to alter the current disparities in outcome.

Acknowledgment

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Disclosures

Dr S Bandyk, Clowes, Moneta, and Conte have served as paid consultants to Corgentech, Inc. Dr Conte has served as a paid consultant to Bristol-Myers Squibb. Dr Moneta owns stock in Bristol-Myers Squibb. The other authors report no conflicts.

References


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**CLINICAL PERSPECTIVE**

Racial and ethnic disparities in the prevalence of peripheral artery disease and its most severe complication, limb loss, have been described. However, the variability in outcomes for revascularization therapies such as surgery or angioplasty is poorly characterized. Surgical bypass using an autogenous vein is an effective and durable treatment for many patients with the most advanced form of peripheral arterial disease, critical limb ischemia. We examined the relationship between patient demographics (race and gender) and the outcomes of vein bypass procedures for critical limb ischemia using a large (n=1404) multicenter randomized trial database from >80 North American institutions. Aggressive bypass graft surveillance with duplex ultrasonography was incorporated into the study protocol to reliably identify significant vein graft lesions. Propensity score methods were applied to control for covariates while focusing on the interaction between race and gender. Our findings demonstrate that black patients, particularly women, are at increased risk for vein graft failure and limb loss after surgical revascularization for critical limb ischemia. The data suggest the possibility of an altered response to vein bypass surgery in this subgroup. Aggressive medical therapy and close surveillance are mandated in these higher-risk cohorts to improve the chances of long-term success. Further studies are indicated to determine the mechanisms underlying these observations.
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