Design of the Revascularization With Open Bypass vs Angioplasty and Stenting of the Lower Extremity Trial (ROBUST) A Randomized Clinical Trial

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IMPORTANCE To our knowledge, there is no level 1 evidence comparing open bypass with angioplasty and stenting in TransAtlantic Inter-Society Consensus (TASC II) B and C superficial femoral artery lesions. The Revascularization With Open Bypass vs Angioplasty and Stenting of the Lower Extremity Trial (ROBUST) is the first prospective randomized clinical trial comparing both treatments.

OBJECTIVES To report the design of the ROBUST trial. The primary aim of the trial is to compare (1) the patency rate (primary, primary assisted, and secondary patency at 6 and 12 months), (2) improvement of quality of life, (3) clinical improvement (at least 1 Rutherford category), and (4) wound healing and limb salvage in patients presenting with critical limb ischemia; secondary aims include (1) cost-effectiveness by factoring procedure and hospital admission costs including rehabilitation, readmission, and reintervention costs, (2) amputation-free survival, (3) reintervention rate, and (4) 30-day operative mortality, morbidity, and wound and access complications.

DESIGN, SETTING, AND PARTICIPANTS ROBUST is a prospective randomized clinical trial with the aim to enroll 320 patients with intermittent claudication that does not respond to medical management and patients with critical limb ischemia. The maximum level of medical therapy will be administered using antiplatelet agents and statins, as well as measures to control hypertension and diabetes mellitus.

INTERVENTIONS Patients with TASC II B or C lesions are prospectively randomized to receive either femoropopliteal bypass or percutaneous transluminal angioplasty and stenting; patients with TASC II A and D lesions are not randomized and receive percutaneous transluminal angioplasty and stenting or femoropopliteal bypass, respectively. All patients will be evaluated at 1, 6, and 12 months postoperatively with physical examination, ankle brachial index, duplex, and a quality-of-life questionnaire.

RESULTS The trial is actively enrolling participants. At the time of writing, 29 patients have been enrolled; most are male (60%) and white (65%).

CONCLUSIONS AND RELEVANCE Providing level 1 evidence, ROBUST may help to establish guidelines for the treatment of superficial femoral artery lesions, eliminate unnecessary procedures, and reduce health care costs.

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Peripheral arterial disease (PAD) is the most underdiagnosed cardiovascular disorder. It affects the lives of 3% to 10% of the general population. One in 5 individuals older than 70 years is affected by this condition.1,3

The superficial femoral artery (SFA) is the most common location for atherosclerotic disease in the lower limbs causing PAD. Intermittent claudication (IC) is the most frequent symptom of PAD, characterized by reproducible muscular calf or thigh pain or tightness during walking relieved by rest. Critical limb ischemia (CLI) is the advanced stage of PAD characterized by tissue loss, ulceration, gangrene, or pain at rest.

The first treatment option for patients with PAD is structured exercise therapy. Patients with symptomatic PAD have difficulty exercising and are unable to significantly modify their risks, thus needing invasive intervention to treat the blockage. Treatment options for patients with symptomatic (IC or CLI) SFA stenosis/occlusion for whom 3 months of exercise therapy has failed include femoropopliteal bypass (FPB) using an autogenous vein or a synthetic graft and several minimally invasive techniques including percutaneous transluminal angioplasty (PTA) alone, PTA with stenting (PTA/S), atherectomy, and cryoplasty. Among these interventions, FPB and PTA/S are the most common.

Several prospective randomized trials have shown the patency of above-knee FPB to range between 74% and 76% 5 years after a procedure using an autogenous vein vs 40% to 52% using a polytetrafluoroethylene graft.4-7

The TransAtlantic Inter-Society Consensus (TASC II) has classified SFA lesions into 4 categories depending on the length and extent of the disease (Table 1). In 3 prospective randomized trials (Edwards Lifesciences Self-Expanding Stent Peripheral Vascular Disease Study [RESILIENT],9 the Femoral Artery Stenting Trial [FAST],10 and the Vienna study11), adding a self-expanding nitinol stent significantly improved the 6- to 12-month patency rate of PTA alone in TASC II A lesions (Table 2).

Although there is no level 1 evidence comparing PTA/S with FPB regardless of the TASC II category of lesion, the results of PTA/S for TASC II A lesions are favorable in comparison with the results of FPB (similar patency rate but a less-invasive procedure that is better tolerated).12 For TASC II D lesions, several retrospective studies13 and one prospective study14 have demonstrated inferior patency rates of PTA/S compared with those of FPB. As a result, the most recent TASC II and the Society of Vascular Surgery guidelines have recommended an endovascular approach for TASC II A lesions and FPB for TASC II D lesions.7

There is no consensus, however, on treatment for the most common TASC II B and C lesions among different specialties (Table 1). Moreover, most of the literature focuses on patency, and the patient-centered outcome is not being addressed. There is a deficiency in the current literature on the quality-of-life improvement along with the clinical improvement for both procedure types.

The Revascularization With Open Bypass vs Angioplasty and Stenting of the Lower Extremity Trial (ROBUST) is an investigator-initiated, prospective randomized clinical trial comparing FPB with PTA/S. Currently, the trial has no outside sponsor or funding. Both procedures (FPB and PTA/S) are considered as standards of care for the treatment of symptomatic PAD. The study is actively enrolling participants.

ROBUST will establish level 1 evidence of the effectiveness of each treatment modality based not only on patency but also on improving quality of life. The trial will provide longitudinal data on the morbidity and mortality associated with FPB and PTA/S that will help to develop guidelines for treating symptomatic SFA lesions that have not responded to exercise therapy.

Methods

Population

Patients are identified at The Johns Hopkins Bayview Medical Center and The Johns Hopkins Hospital. The trial has been

### Table 1. TASC II SFA Classification and Treatment Recommendations

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Description</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASC II A</td>
<td>Single lesion with ≤10-cm stenosis; single lesion with ≤5-cm occlusion</td>
<td>PTA/S</td>
</tr>
<tr>
<td>TASC II B</td>
<td>Multiple lesions, each &lt;5 cm (stenosis or occlusion), totaling &lt;15 cm in length; single lesion 10-15 cm (stenosis or occlusion); any lesion 15-20 cm in length; restenosis after 2 endovascular interventions (any lesion)</td>
<td>PTA/S or open bypass</td>
</tr>
<tr>
<td>TASC II C</td>
<td>Multiple lesions (stenosis or occlusion) totaling 15-20 cm in length; restenosis after 2 endovascular interventions (any lesion)</td>
<td>Open bypass or PTA/S</td>
</tr>
<tr>
<td>TASC II D</td>
<td>Chronic total occlusion of SFA &gt;20 cm; chronic total occlusion of CFA; proximal trifurcation occlusions</td>
<td>Open bypass</td>
</tr>
</tbody>
</table>

Abbreviations: CFA, common femoral artery; PTA/S, percutaneous transluminal angioplasty and stenting; SFA, superficial femoral artery; TASC, TransAtlantic Inter-Society Consensus II.

*Adapted from Norgren et al.8

### Table 2. Summary of the Results of 3 Prospective Randomized Trials Comparing the Patency of PTA Alone vs PTA and Nitinol Stent

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Stent Type</th>
<th>Mean Length, cm</th>
<th>Patency, % (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESILIENT9</td>
<td>206</td>
<td>LifeStentb</td>
<td>6.5</td>
<td>45 (12)</td>
</tr>
<tr>
<td>FAST10</td>
<td>244</td>
<td>Luminexxc</td>
<td>4.5</td>
<td>61.7 (6)</td>
</tr>
<tr>
<td>Vienna11</td>
<td>104</td>
<td>Nitinol</td>
<td>5.9</td>
<td>37 (12)</td>
</tr>
</tbody>
</table>

Abbreviations: FAST, Femoral Artery Stenting Trial; PTA, percutaneous transluminal angioplasty; PTA/S, PTA and stenting; RESILIENT, Edwards Lifesciences Self-Expanding Stent Peripheral Vascular Disease Study. *LifeStent FlexStar Stent System (Bard Inc).

*bLifeStent FlexStar Stent System (Bard Inc).

*cLuminexx Vascular Stent (Bard Inc).
approved by The Johns Hopkins institutional review board, and all patients must sign written informed consent prior to participation. Patients presenting with symptoms of IC that have not responded to medical management or patients presenting with CLI undergo an evaluation starting with a history and physical examination. If arterial insufficiency is determined by history, physical examination, and pulse examination, patients then undergo noninvasive vascular testing (ankle brachial index [ABI]). Patients with abnormal resting or exercise ABI who meet the clinical inclusion criteria are enrolled. A vascular quality-of-health questionnaire (VascuQol) is completed by the patient, and the Rutherford classification is determined (Table 3). All patients then undergo lower extremity conventional angiography to determine the exact lesion anatomy.

**Clinical Inclusion Criteria**
Patients are evaluated on presentation. To be included in the study, the patient
1. must be aged 18 years or older;
2. has been informed of the nature of the study, both procedures have been described, and the patient has provided written informed consent;
3. has symptoms of IC or CLI;
4. has IC that has not responded to at least 3 months of an exercise program;
5. has a resting ABI of less than 0.9 or an abnormal exercise ABI if the resting ABI is normal; patients with noncompressible arteries (ABI >1.3) must have a toe brachial index of less than 0.8;
6. has a de novo or restenotic lesion with more than 50% of stenosis documented angiographically;
7. agrees to return for all required follow-up visits; and
8. has no childbearing potential or has a negative pregnancy test result.

**Anatomic Inclusion Criteria**
The anatomic inclusion criteria include
1. the presence of superficial femoral artery TASC II B and C lesions;
2. at least 1 tibial vessel runoff with less than 50% stenosis;
3. a lesion that starts at least 1 cm distal to the origin of the deep femoral artery (DFA);
4. a lesion that ends at least 3 cm above the knee joint; and
5. the target vessel reference diameter is larger than 3 mm and smaller than 6.5 mm.

**Clinical Exclusion Criteria**
The clinical exclusion criteria include
1. a known allergic reaction to iodinated contrast material that cannot be overcome by medication;
2. a known allergic reaction to any of the study medications: aspirin, clopidogrel bisulfate, and ticlopidine hydrochloride;
3. a bleeding disorder or refusal to receive a blood transfusion;
4. prior stenting or bypass of SFA (prior PTA is not an exclusion criterion);
5. unstable angina or a recent myocardial infarction (within 1 month);
6. a malignant tumor or other condition limiting life expectancy to less than 2 years;
7. chronic renal insufficiency (serum creatinine >2.0 mg/dL [to convert to micromoles per liter, multiply by 76.25]);
8. any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe (eg, severe morbid obesity); and
9. other medical comorbidities precluding the use of general anesthesia (eg, severe chronic obstructive pulmonary disease with forced expiratory volume in the first second of expiration <1.0 L, congestive heart failure stage III or IV).

**Anatomic Exclusion Criteria**
The anatomic exclusion criteria include
1. the lesion originates within 1 cm from the orifice of the DFA;
2. the lesion extends to less than 3 cm from the knee joint;
3. there is chronic total occlusion of the common femoral artery; and
4. proximal tibial trifurcation occlusion is present.

**Perioperative Medical Management**
The goal of medical management is to reduce the risk of cardiovascular and cerebrovascular events. This goal is accomplished in accordance with the TASC II recommendation and includes tobacco cessation, antiplatelet therapy, statin therapy, and weight reduction as well as strict control of diabetes mellitus and hypertension.

**Randomization**
Patients with angiographic evidence of TASC II A lesions receive PTA/S during the same procedure. Patients with TASC II B and C SFA lesions are to be randomized into FPB or PTA/S groups. Patients with TASC II D lesions undergo FPB (Figure). Randomization using a permuted block design assigns a patient with equal probability to receive either FPB or PTA/S. Allocation is made by The Johns Hopkins Bayview Vascular and Endovascular Clinical Research Center after baseline information is received and clinical and anatomic eligibility are verified.

**Procedures**

**Femoropopliteal Bypass**
Bypass is performed within 4 weeks of randomization. Only study-approved vascular surgeons can perform the bypass procedures. The criteria for study approval are vascular surgery
Percutaneous Transluminal Angioplasty and Stenting

The primary aim of ROBUST is to compare the (1) patency rate (primary, primary assisted, and secondary patency at 6 and 12 months); (2) improvement of quality of life; (3) clinical improvement (at least 1 Rutherford category); and (4) wound healing and limb salvage in patients presenting with CLI. Secondary aims of ROBUST include (1) cost-effectiveness by factoring procedure and hospital admission costs including rehabilitation, readmission, and reintervention costs; (2) amputation-free survival; (3) reintervention rates; and (4) 30-day operative mortality, morbidity, and wound and access complications.

Reintervention

Criteria for reintervention include recurrent symptoms of IC or new-onset CLI with documented loss of distal pulses on physical examination and documented 50% to 99% restenosis on arterial duplex ultrasonography (defined by peak systolic velocity >350 cm/s or ratio >3.5). Patients with duplex ultrasonography showing restenosis or occlusion then undergo conventional contrast angiography to confirm restenosis. Patients without symptoms with documented restenosis of greater than 50% by duplex ultrasonography undergo reintervention if stenosis is confirmed on an angiogram to improve the primary patency (primary-assisted patency). The type of reintervention is at the discretion of the treating physician and following standard of care.

Sample Size

Using the estimates from a retrospective cohort study, Table 4 reports the sample sizes needed to detect differences in 12-month patency rates (the primary outcome) between the 2 procedure type groups, assuming a statistical power of 80% and a significance level of .025 (2-sided). This significance level has been modified using the Bonferroni correction.
correction to account for the treatment comparison within each of the 2 lesion types (maintaining an overall significance level of .05). A sample size of 73 patients in each group will allow statistical detection of a 20% or larger difference in the patency rate between the FPB and PTA/S groups when the bypass patency rate is approximately 70%. After adjusting for a potential loss to follow-up of 10%, approximately 80 patients are needed in each group. Thus, a total of 160 patients are needed with each lesion type (TASC II B and C) for an overall recruitment of 320 patients.

Statistical Analysis
All data will be analyzed according to the intention-to-treat principle at 6 and 12 months. Stratified randomization within lesion type should ensure that the 2 treatment groups within a lesion type are similar in baseline demographic and clinical characteristics. These characteristics will be compared between treatment groups using a \( \chi^2 \) or Fisher exact test for categorical variables and paired, 2-tailed \( t \) tests or Mann-Whitney tests for continuous variables. For each lesion type, using a simple logistic regression model, we will examine the relationship between the end points and the treatment group (FPB vs PTA/S). Multiple logistic regression analysis adjusting for lesion type, treatment group, and patient characteristics will also be performed. If warranted, the potential effect modification of the association of outcome with treatment by lesion type will be assessed by lesion-treatment interactions in the multiple logistic regression model.

The Kaplan-Meier method will be used for estimating time-to-event differences between the 2 treatment groups; comparison will be performed with the log-rank test. Cox proportional hazards regression will be used to estimate the hazard ratios for these time-to-event analyses. In addition, separate longitudinal data analyses incorporating the outcomes at each follow-up time will be performed using generalized estimating equations to investigate the relationship between each outcome and treatment group by lesion type over the planned follow-up time. Subanalysis will be performed to analyze the effect of autogenous veins vs synthetic grafts used for bypass. Subanalysis will also be performed to separately compare the results among individuals with claudication and patients with CLI. \( P \) values (2-sided) will be computed, and \( P < .05 \) will be considered statistically significant. Data analysis will be performed using Stata, version 11.0 (StataCorp LP).

Data Safety and Monitoring
Data are maintained in a secure database. All identifiers will be removed before analysis. A unique identifier is assigned to each participant. An independent data safety monitoring committee has been set up. The committee comprises a biostatistician, 2 cardiologists, and a vascular surgeon. It meets at least annually and otherwise whenever necessary. It monitors and ensures patient safety by reviewing the data collected, including all adverse events. The committee also reviews enrollment, protocol adherence, and deviations. The data safety monitoring committee reports to the principal investigator (M.B.M.) and institutional review board at least annually.

### Table 4. Sample Size Calculation per Group for Evaluation of 12-Month Patency

<table>
<thead>
<tr>
<th>Patency, %</th>
<th>No. of Patients</th>
<th>Detectable Difference</th>
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</thead>
<tbody>
<tr>
<td>15%</td>
<td>183</td>
<td>103</td>
</tr>
<tr>
<td>20%</td>
<td>134</td>
<td>73</td>
</tr>
<tr>
<td>25%</td>
<td>113</td>
<td>60</td>
</tr>
</tbody>
</table>

Results
At the time of writing, 38 participants had consented to participate in ROBUST; 29 of these individuals were enrolled; most are male (60%) and white (65%). Eight potential participants were determined to be ineligible during the angiogram because they did not meet the anatomic inclusion criteria of the study, and 1 patient withdrew consent before the procedure.

Discussion
The goals of the treatment of PAD include prevention of systemic atherosclerotic disease progression, clinical cardiovascular events, and limb loss, as well as improvement in the functional capacity of patients with intermittent claudication. Several studies have shown that an exercise program may improve functional capacity. However, there are several limitations to exercise therapy. The most common treatment options for patients with symptomatic SFA stenosis/occlusion that has failed to respond to 3 months of exercise therapy include FPB using an autogenous vein or a synthetic graft and PTA/S. The efficacy of each treatment option depends on the TASC II subtype (Table 1).

Several prospective randomized trials have illustrated the superiority of using an autogenous vein vs a polytetrafluoroethylene graft. The 5-year primary patency rate of FPB above the knee bypass with an autogenous vein is 70%, and the primary-assisted patency can be improved to approximately 80%. Thus, FPB remains the criterion standard for revascularization of symptomatic SFA occlusion. However, FPB is invasive and may require general anesthesia. There is significant morbidity and low, but possible, associated mortality. The need for a less-invasive treatment modality led to the development of endovascular techniques. The outcomes of PTA without stenting in TASC II A SFA lesions have been studied primarily in retrospective series. The overall 5-year patency rate is approximately 50%. Three prospective randomized trials showed no benefit of adding a balloon-expandable, stainless steel stent (Palmaz; Cordis) to PTA. Improved durability of stenting in the femoral artery has been reported with the use of nitinol stents, with better flexibility as well as reduced kinking and fracture rates. Several prospective randomized trials have shown superiority of adding a self-expanding nitinol stent to angioplasty alone by significantly improving the 12-month patency rate (Table 2).
Lower limb revascularization is commonly performed across the United States by a variety of specialists, including vascular surgeons, cardiologists, and interventional radiologists. The treatment selection (FPB or PTA/S) is often not based on the effectiveness and durability of the chosen revascularization method but rather on the treating physician’s comfort level, specialty, and experience. Most surgeons tend to use bypass for most TASC II C and D lesions; however, cardiologists and interventional radiologists tend to stent the same categories of lesions. To our knowledge, there is no evidence in the literature regarding the comparative effectiveness of both procedures based on quality-of-life improvement. In general, the long-term success of revascularization is often based on the patency of the bypass graft or the PTA/S segment. One study compared walking distance and quality-of-life improvement between PTA and exercise. To our knowledge, no prospective randomized trial has compared a PTA/nitinol bare metal stent with FPB.

Historically, FPB with an autogenous vein has been the treatment of choice for revascularization of symptomatic SFA occlusions. In the past, most patients underwent a bypass, including those with short, nonocclusive lesions. Presently, patients selected to undergo FPB tend to have much more advanced disease compared with the previous population. It is not surprising that these bypasses would have lower patency than those included in the historically reported data. On the other hand, recent advances in stenting technology have dramatically improved patency.

Our institution’s recently published retrospective data analysis confirmed that most TASC II A and B lesions are being treated with PTA/S, and TASC II C and D lesions are undergoing an FPB. This treatment selection bias may be a significant contributor toward the results indicating that the FPB group required significantly more reintervention to maintain patency similar to that of the stent group. This finding does not indicate that the endovascular approach is better but rather that these lesions might be treated with a less durable approach.

Conclusions
To our knowledge, ROBUST is the first prospective randomized clinical trial comparing FPB and PTA/S and will provide the much-needed level 1 evidence necessary for treatment guidelines. This important trial may help to establish treatment guidelines for such lesions as well as eliminate unnecessary procedures and reduce health care costs.

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Author Contributions: Drs Malas and Qazi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Malas, Qazi, Glibova, Reifsnyder, Black, Freischlag.
Acquisition, analysis, or interpretation of data: Malas, Qazi, Arhuidese, Black, Perler, Freischlag.
Drafting of the manuscript: Malas, Qazi, Arhuidese, Freischlag.
Critical revision of the manuscript for important intellectual content: Malas, Glibova, Reifsnyder, Black, Perler, Freischlag.
Statistical analysis: Arhuidese.
Administrative, technical, or material support: Malas, Qazi, Glibova, Black, Freischlag.
Study supervision: Malas, Reifsnyder, Perler, Freischlag.

Conflict of Interest Disclosures: None reported.

Disclaimer: Dr Freischlag is the editor of JAMA Surgery but was not involved in the editorial review or the decision to accept the manuscript for publication.

REFERENCES


CORRECTION

Errors in Table 1 and Figure: In the Original Investigation titled “Cost-effectiveness of Cervical Total Disc Replacement vs Fusion for the Treatment of 2-Level Symptomatic Degenerative Disc Disease” published in the October 8, 2014, online issue of JAMA Surgery (2014;149[12]:doi:10.1001/jamasurg.2014.716), there were typographical errors in Table 1 and in the Figure. In Table 1, the first heading should have been: “After ACDF for treatment of 2-level symptomatic disc disease, %.” In the Figure, the first health state listed under Utility should have been “Mild” instead of “Moderate.” This article was corrected online.