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## **Growing Impact of Restenosis on the Surgical Treatment of Peripheral Arterial Disease**

Douglas W. Jones, Andres Schanzer, Yuanyuan Zhao, Todd A. MacKenzie, Brian W. Nolan, Michael S. Conte, Philip P. Goodney and The Vascular Study Group of New England

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# Growing Impact of Restenosis on the Surgical Treatment of Peripheral Arterial Disease

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**Background**—Patients with peripheral arterial disease often experience treatment failure from restenosis at the site of a prior peripheral endovascular intervention (PVI) or lower extremity bypass (LEB). The impact of these treatment failures on the utilization and outcomes of secondary interventions is poorly understood.

**Methods and Results**—In our regional vascular quality improvement collaborative, we compared 2350 patients undergoing primary infrainguinal LEB with 1154 patients undergoing secondary infrainguinal LEB (LEB performed after previous revascularization in the index limb) between 2003 and 2011. The proportion of patients undergoing secondary LEB increased by 72% during the study period (22% of all LEBs in 2003 to 38% in 2011,  $P<0.001$ ). In-hospital outcomes, such as myocardial infarction, death, and amputation, were similar between primary and secondary LEB groups. However, in both crude and propensity-weighted analyses, secondary LEB was associated with significantly inferior 1-year outcomes, including major adverse limb event-free survival (composite of death, new bypass graft, surgical bypass graft revision, thrombectomy/thrombolysis, or above-ankle amputation; Secondary LEB MALE-free survival = 61.6% vs primary LEB MALE-free survival = 67.5%,  $P=0.002$ ) and reintervention or amputation-free survival (composite of death, reintervention, or above-ankle amputation; Secondary LEB RAO-free survival = 58.9% vs Primary LEB RAO-free survival 64.1%,  $P=0.003$ ). Inferior outcomes for secondary LEB were observed regardless of the prior failed treatment type (PVI or LEB).

**Conclusions**—In an era of increasing utilization of PVI, a growing proportion of patients undergo LEB in the setting of a prior failed PVI or surgical bypass. When caring for patients with peripheral arterial disease, physicians should recognize that first treatment failure (PVI or LEB) affects the success of subsequent revascularizations. (*J Am Heart Assoc.* 2013;2:e000345 doi: 10.1161/JAHA.113.000345)

**Key Words:** angioplasty • bypass • peripheral vascular disease • restenosis • revascularization • stents

The treatment of peripheral arterial disease (PAD) has changed dramatically in recent years, as the use of peripheral endovascular interventions (PVI) has increased and the use of lower extremity bypass (LEB) surgery has

decreased.<sup>1–3</sup> In fact, the increase in PVI has outpaced the decline in LEB by a factor of  $>3:1$ ,<sup>4</sup> suggesting either a shift in treatment threshold, a rising rate of repeat treatments for a single patient, or some combination thereof. As a result, the total number of procedures being performed for PAD has increased, a trend associated with markedly increased costs.<sup>1,4</sup>

When considering potential reasons for the increasing cost and complexity of caring for patients with PAD, many have expressed concern about a rising incidence of restenosis.<sup>4–6</sup> Repeat procedures, necessitated by initial treatment failure, may be responsible for the rising number of revascularizations being performed for PAD. Why might more secondary revascularizations be occurring in recent years? It is well known that physicians and patients commonly consider tradeoffs between the relative durability and the relative morbidity of competing treatments. For example, while the short-term failure rate for tibial angioplasty is high, it is much less invasive than that of surgical bypass and therefore has been adopted by many specialists as an initial strategy.<sup>7</sup> Part of this rationale is also predicated on the notion that failure of

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endovascular interventions can still be salvaged by either repeat PVI or bypass surgery, the validity of which has increasingly come into question.<sup>8–10</sup> It remains unclear how these shifting practice patterns have influenced the patient population undergoing LEB in recent years and whether “downstream effects” of prior failed interventions have an impact on the outcomes of bypass surgery.

The primary objectives of this study were to gain a better understanding of whether the characteristics of patients requiring surgical bypass for PAD have changed as practice patterns have evolved and to address whether prior treatments have downstream effects on the outcomes of surgical bypass. To address these goals, we analyzed all patients undergoing LEB in the Vascular Study Group of New England (VSGNE), a large regional dataset of patients with vascular disease. We used crude and inverse propensity-weighted analyses to compare the incidence and outcomes of primary LEB with those of LEB performed in the setting of a prior ipsilateral PVI or bypass (secondary LEB).

## Methods

### Database and Cohort Assembly

Patients undergoing LEB at 1 of the 26 community and academic centers in the Vascular Study Group of New England (VSGNE) between 2003 and 2011 were included in our study. While 6 centers participated in the VSGNE in 2003, 20 additional centers were added during the study period. Data from all 26 centers are presented here, but our overall findings were similar in size and effect when the analysis was limited to data from only the original 6 centers. Details regarding the VSGNE have previously been published<sup>11</sup> and are available online at <http://www.vsgne.com>. In this dataset, >70 preoperative, intraoperative, and postoperative variables are collected, as well as 1-year follow-up outcomes.<sup>5,8</sup> A claims-based audit system is used and has demonstrated 99% accuracy in capturing consecutive procedures performed at each center.<sup>5</sup>

Our main exposure variable was the occurrence of a secondary bypass at the time of entry into the dataset. A secondary bypass was defined as a bypass performed in a patient with a history of a prior ipsilateral PVI, a prior ipsilateral LEB, or both. Primary LEB patients were those who had no history of prior ipsilateral PVI or LEB recorded in the database. Differences in patient characteristics were compared across primary and secondary LEB patients using existing data elements in the VSGNE, using the first procedure per patient as the unit of analysis. Patients were excluded from this study if they had aneurysmal disease as the indication for their procedure, if no indication was specified, or if other variables were missing data. As a result, ≈12% of

patients undergoing LEB during the study period were excluded, a majority of whom were missing an indication. Among preoperative variables, indication for LEB was classified as either intermittent claudication or critical limb ischemia (CLI; defined as tissue loss or ischemic rest pain). Only the first LEB procedure was considered for each patient in the VSGNE dataset, and only infrainguinal LEB procedures were included. This procedure was defined as the index LEB. If a patient had an LEB within the VSGNE and required a subsequent ipsilateral LEB, these events were counted as treatment failures (not as a new LEB).

### Outcome Measures

Our primary outcome measures were chosen to target safety and efficacy of LEB using end points endorsed in the Society for Vascular Surgery’s Objective Performance Goals.<sup>12</sup> To evaluate the safety and short-term efficacy of LEB, we analyzed in-hospital outcomes, including mortality, myocardial infarction, and major amputation. We also examined outcomes at 1 year postoperatively, including overall survival and amputation-free survival. Additional efficacy outcomes included reintervention or amputation (RAO) and major adverse limb event (MALE), defined as follows: RAO-free survival is freedom from death, any reintervention, or above-ankle amputation of index limb, and MALE-free survival is freedom from death, major reintervention (new bypass graft, a jump or interposition graft placed during a revision, or thrombectomy/thrombolysis), or above ankle-amputation of index limb.<sup>12</sup> While summarizing outcomes using RAO and MALE as endpoints allows insight into the overall need for, and magnitude of, reinterventions, we also individually report their component outcomes.

### Statistical Analysis

Patient demographics were compared between groups using a Wilcoxon rank sum test for continuous variables and  $\chi^2$  test for categorical or dichotomous variables. The effects of primary or secondary LEB on the time-to-event end points (amputation-free survival, RAO-free survival, MALE-free survival, and overall survival) were estimated and contrasted using Kaplan–Meier curves and log-rank tests for significance in conjunction with inverse propensity weighting. This weighting approach corrects for imbalance due to measured confounders by weighting subjects in each treatment group in such a way that the weighted sample for each group represents the entire sample of subjects. Weighted Kaplan–Meier survival estimates were then calculated based on the inverse of the probability that each patient would receive a specific treatment (primary versus secondary LEB).<sup>13–16</sup> Where inverse propensity-weighted survival estimates were calculated, a Cox model was used to determine significance of

differences. Using this strategy, inverse propensity weighting addresses issues of confounding, and because patients in our database could not have been conceivably exposed to either primary or secondary LEB, it serves as a sensitivity analysis for consistency with our Cox models.

The propensity model for primary versus secondary LEB was generated using a multivariable logistic regression model. Backward stepwise logistic regression was used to determine which preoperative patient characteristics and operative details were most closely associated with secondary LEB at the time of index bypass surgery. Following inverse propensity weighting, patient characteristics were compared using Wilcoxon rank-sum test or  $\chi^2$  test, where appropriate, to examine the success of this technique in creating similar cohorts for analysis. Outcomes were then analyzed in a similar fashion as with the unweighted cohort. Data were analyzed using STATA version 11 (StataCorp) and SAS version 9.2 (SAS Institute).

## Results

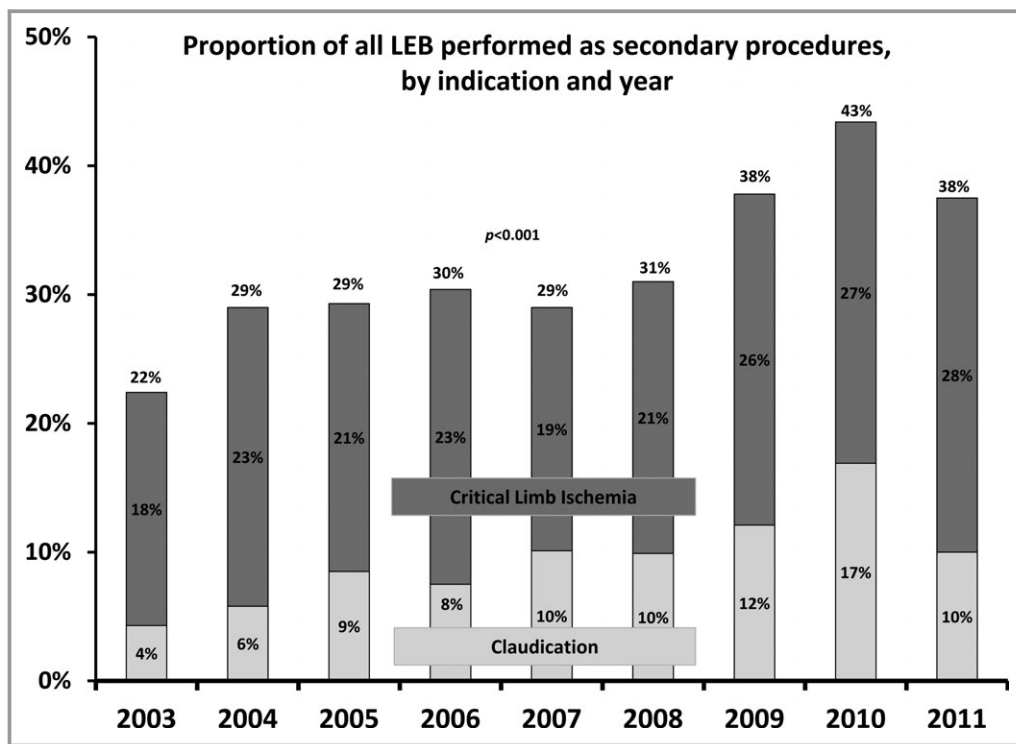
### Secular Changes in Secondary LEB

Between 2003 and 2011, the proportion of patients who underwent secondary LEB within the VSGNE increased significantly, from 22% to 38% of all index LEBs performed

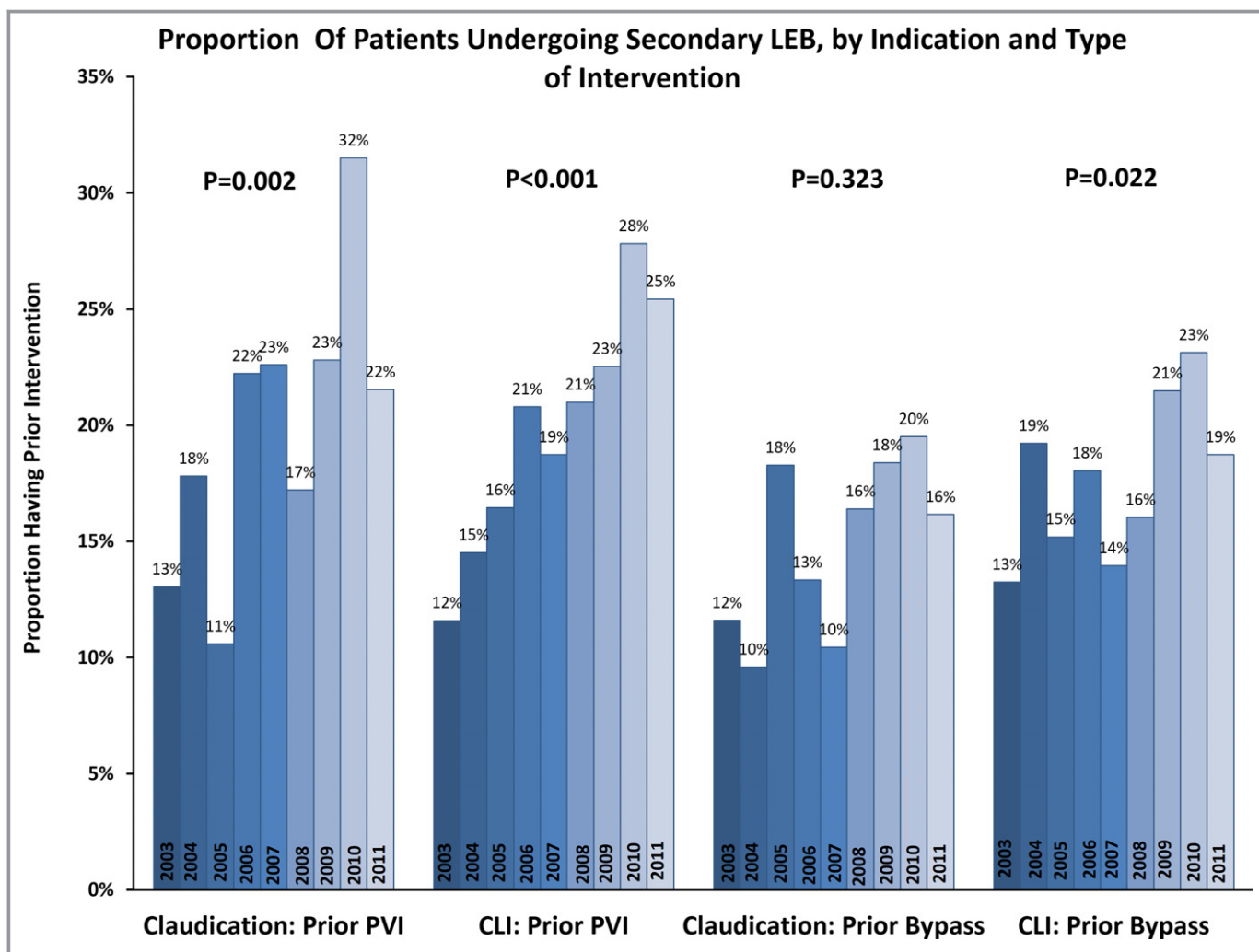
( $P<0.001$ ) (Figure 1). This increase was evident among patients undergoing LEB for both claudication (23% to 33%,  $P<0.001$ ) and CLI (22% to 38%,  $P<0.001$ ). When examining the data by indication and nature of the prior intervention, the greatest increases were seen in the frequency of prior PVI (Figure 2). For example, we found that a history of prior PVI increased from 13% to 22% for patients undergoing surgical treatment for claudication ( $P=0.002$ ), and similar increases were evident for patients with CLI (12% to 25%,  $P<0.001$ ). We observed a smaller increase in the proportion of patients with a history of LEB undergoing treatment for CLI (13% versus 19%;  $P=0.022$ ) and no significant change in the proportion of patients with a history of LEB undergoing treatment for claudication ( $P=0.323$ ).

### Patient Characteristics and Operative Details in Primary Versus Secondary LEB

Between 2003 and 2011, a total of 3504 patients underwent an index LEB procedure in the VSGNE database. Of these, 1154 (32.9%) were secondary LEBs, and 2350 (67.1%) were primary LEBs. Secondary LEB followed prior ipsilateral PVI in 552 of 1154 cases (48%), prior ipsilateral LEB in 437 of 1154 cases (38%), and both LEB and PVI in 165 of 1154 cases (14%). Overall, the indication for LEB was claudication in 29.7% (1039/3504) and CLI in 70.3% (2465/3504). These indications



**Figure 1.** Annual trends in secondary lower extremity bypass (LEB), as a proportion of total LEBs performed per year 2003–2011, stratified by indication.



**Figure 2.** Annual trends in secondary LEB, as a proportion of total LEBs performed per year 2003–2011, stratified by indication and type of intervention. CLI indicates critical limb ischemia; LEB, lower extremity bypass; PVI, peripheral endovascular intervention.

were similar in primary and secondary LEB groups (Table 1). However, patients undergoing a secondary LEB were more likely to be younger (proportion under age 70: 58.5% versus 52.9%,  $P<0.001$ ) and to have a higher rate of smoking (88.6% versus 81.7%,  $P<0.001$ ) and were less likely to be receiving dialysis (5.6% versus 8.2%,  $P=0.004$ ) than were primary LEB patients. Patients undergoing a secondary LEB were also more likely to be receiving aspirin (76.1% versus 72.2%,  $P=0.014$ ), clopidogrel (19.3% versus 8.3%,  $P<0.001$ ), or a statin (70.8% versus 63.3%,  $P<0.001$ ) in the preoperative period. Additional differences in patient characteristics are shown in Table 1.

Univariate analyses revealed differences in operative characteristics between the 2 groups (Table 1). Secondary LEB patients were more likely to have undergone the procedure on an urgent or emergent basis (21.0% versus 18.6%,  $P=0.023$ ), to have prosthetic conduit used for their bypass graft (35.6% versus 27.3%,  $P<0.001$ ) or to have a spliced vein graft consisting of >1 piece of vein (7.5% versus

4.9%,  $P<0.001$ ). Finally, secondary LEB patients were more likely to be discharged on clopidogrel (25.9% versus 16.8%,  $P<0.001$ ), warfarin (27.7% versus 21.4%,  $P<0.001$ ), and statins (79.5% versus 74.0%,  $P=0.002$ ) (Table 1).

Multivariable logistic regression analysis of patient demographics and operative details revealed multiple variables associated with secondary LEB (Table 2). Using these differences, inverse propensity weighting was successful in creating 2 cohorts that were appropriate for comparison while accounting for differences in demographics and operative details (Table 3).

### In-hospital Outcomes in Primary Versus Secondary LEB, by Indication

Of the 3504 LEBs performed, unweighted postoperative in-hospital outcomes showed no differences in mortality (1.6% versus 1.5%,  $P=0.795$ ) or myocardial infarction (4.1% versus

**Table 1.** Complete Demographics and Operative Details of Patients Who Underwent Infrainguinal LEB in the Vascular Study Group of New England From 2003 to 2011, With Univariate Analysis by Primary Versus Secondary LEB

Characteristic	Unweighted Data		
	Primary LEB, %	Secondary LEB, %	P Value*
No. of patients	2350	1154	
<b>Demographics</b>			
Male sex	69.6	66.6	0.078
White race	96.6	96.4	0.771
Age, y			
<70	52.9	58.5	<0.001
70 to 79	27.8	29.4	
≥80	19.3	12.1	
Smoking (prior or current)	81.7	88.6	<0.001
COPD	25.8	28.8	0.063
Hypertension	85.7	88.0	0.072
Coronary artery disease	35.6	37.6	0.236
Prior CABG or coronary intervention	32.0	34.5	0.143
Congestive heart failure	16.5	15.5	0.466
<b>Diabetes</b>			
No diabetes	48.5	50.3	0.581
Non-insulin-dependent diabetes	25.8	24.4	
Insulin-dependent diabetes	25.7	25.3	
Creatinine ≥1.8	9.1	7.2	0.076
Dialysis	8.2	5.6	0.004
Living nursing home preoperatively	4.4	3.2	0.085
Transferred from hospital/rehabilitation unit	7.6	7.6	0.973
Independently ambulatory preoperatively	78.3	78.8	0.755
<b>BMI, kg/m<sup>2</sup></b>			
<20	9.3	10.7	0.125
20 to 30	62.4	61.6	
30 to 40	24.6	25.3	
≥40	3.7	2.3	
<b>Cardiac stress test</b>			
Not done	61.7	61.6	0.803
Normal	25.6	25.0	
Abnormal	12.6	13.4	

Continued

**Table 1.** Continued

Characteristic	Unweighted Data		
	Primary LEB, %	Secondary LEB, %	P Value*
<b>Preoperative medication regimen</b>			
Preoperative β-blockers	77.4	80.1	0.076
Preoperative aspirin	72.2	76.1	0.014
Preoperative clopidogrel	8.3	19.3	<0.001
Preoperative statin use	63.3	70.8	<0.001
<b>Surgical history</b>			
CEA	9.2	12.7	0.001
Aneurysm repair	2.8	6.2	<0.001
Ipsilateral major amputation	0.0	0.4	0.025
Ipsilateral minor amputation	5.8	7.8	0.023
<b>Indication</b>			
Claudication	29.5	30.1	0.705
Critical limb ischemia	70.6	69.9	
<b>Operative details</b>			
<b>Urgency</b>			
Elective	81.4	79.0	0.023
Urgent	18.2	19.8	
Emergent	0.5	1.2	
Graft origin—common femoral artery	66.5	73.1	<0.001
<b>Graft recipient</b>			
Above knee	28.3	29.0	<0.001
BK popliteal	31.5	35.8	
Tibial	28.2	29.6	
Pedal	12.0	5.7	
<b>Graft type</b>			
Prosthetic	27.3	35.6	<0.001
Any graft vein type	75.0	66.8	<0.001
<b>No. of vein segments</b>			
0	26.1	33.4	<0.001
1	69.0	59.1	
2	4.6	6.7	
≥3	0.3	0.8	
<b>Concomitant proximal procedures (ipsilateral)</b>			
PVI	10.8	9.3	0.297
Endarterectomy	49.6	43.1	0.007

Continued

**Table 1.** Continued

Characteristic	Unweighted Data		
	Primary LEB, %	Secondary LEB, %	P Value*
<b>Anesthesia type</b>			
Spinal	13.8	11.0	0.006
Epidural	6.7	5.0	
General anesthesia	79.4	84.0	
Right side (origin)	51.4	53.4	0.261
<b>Adjuncts</b>			
No vein cuff	98.2	96.6	0.003
Vein cuff	1.8	3.5	
No sequential graft	97.9	97.2	0.234
Sequential graft	2.1	2.8	
<b>Discharge medications</b>			
Aspirin	80.7	82.9	0.123
Clopidogrel	16.8	25.9	<0.001
Warfarin	21.4	27.7	<0.001
Statin	74.0	79.5	0.002
β-Blocker	76.4	78.2	0.284

BK indicates below knee; BMI, body mass index; CABG, coronary artery bypass graft surgery; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease; LEB, lower extremity bypass; PVI, peripheral endovascular intervention. \*P value from  $\chi^2$  test (testing differences between patients without prior PVI or bypass and those with either).

3.9%,  $P=0.822$ ) (Table 4). Secondary LEB patients were slightly more likely than were primary LEB patients to require a major amputation (below-knee or above-knee) during the index hospitalization (0.5% versus 0.1%,  $P=0.031$ ).

After adjustment for intergroup differences with inverse propensity weighting, there were no significant differences in overall rates of in-hospital mortality, myocardial infarction, or ipsilateral major amputation (Table 4). However, on weighted analysis, patients undergoing secondary LEB were more likely to return to the operating room for graft thrombosis or have graft occlusion at discharge than was the primary LEB cohort (Table 4). Subgroup analyses stratified by symptom type (claudication versus CLI) demonstrated similar results in both the crude and inverse propensity-weighted cohorts (Table 5).

### Outcomes at 1-Year Follow-up in Primary Versus Secondary LEB, by Indication and Procedure Type

Outcomes at 1 year differed significantly between primary and secondary LEB patients. In crude analyses of all patients at 1 year after LEB, RAO-free survival and MALE-free survival were significantly inferior compared with primary LEB patients

**Table 2.** Multivariate Analysis of Patient Demographics and Operative Details, by Secondary LEB

Variable	Odds Ratio	95% CI	P Value
Male sex	0.78	0.66 to 0.92	0.003
<b>Age, y</b>			
<70	Reference		
70 to 79	0.93	0.78 to 1.11	0.445
≥80	0.58	0.46 to 0.74	<0.001
<b>BMI, kg/m<sup>2</sup></b>			
<20	Reference		
20 to 30	0.78	0.60 to 1.01	0.059
30 to 40	0.75	0.56 to 0.99	0.043
≥40	0.39	0.23 to 0.66	<0.001
Smoking (prior or current)	1.53	1.21 to 1.94	<0.001
Previous arterial aneurysm repair	2.72	1.88 to 3.93	<0.001
Preoperative clopidogrel	2.57	2.06 to 3.21	<0.001
Preoperative statin use	1.31	1.11 to 1.55	0.001
Prior ipsilateral minor amputation	1.69	1.24 to 2.32	0.001
<b>Graft recipient</b>			
Above knee	Reference		
BK popliteal	1.42	1.15 to 1.74	0.001
Tibial	1.39	1.11 to 1.74	0.005
Pedal	0.64	0.46 to 0.91	0.013
Any graft vein type	0.52	0.32 to 0.86	0.010
<b>No. of vein segments</b>			
0	Reference		
1	1.13	0.69 to 1.83	0.637
2	2.18	1.22 to 3.87	0.008
≥3	4.18	1.21 to 14.48	0.024

AUC=0.67. AUC indicates area under the curve; BK, below knee; BMI, body mass index; LEB, lower extremity bypass.

(Figure 3, Table 5). Individual components of these summary outcomes, such as survival and amputation, are shown in Table 6. Following inverse propensity weighting, secondary LEB was significantly associated with inferior RAO-free survival (hazard ratio=1.22, 95% CI 1.09 to 1.37,  $P<0.001$ ) and inferior MALE-free survival (hazard ratio=1.23, 95% CI 1.10 to 1.38,  $P<0.001$ ) (Figure 4).

Subgroup analyses stratified by indication (claudication versus CLI) demonstrated similar results in patients with CLI but not claudicants (Table 5). For patients with CLI, MALE-free survival at 1 year was inferior among secondary LEB patients



**Table 3.** Selected Demographics and Operative Details of Patients (N=3504) Who Underwent Infrainguinal LEB in the Vascular Study Group of New England From 2003 to 2011, With Univariate Analysis by Primary Versus Secondary LEB, With Inverse Propensity Weighting

Characteristic	Unweighted Data			Inverse Propensity-Weighted Analysis		
	Primary LEB, %	Secondary LEB, %	P Value*	Primary LEB, %	Secondary LEB, %	P Value†
No. of patients	2350	1154		2350	1154	
<b>Demographics</b>						
Male sex	69.6	66.6	0.078	68.1	68.4	0.874
White race	96.6	96.4	0.771	96.6	96.2	0.569
Age, y						
<70	52.9	58.5	<0.001	55.0	55.0	0.995
70 to 79	27.8	29.4		28.2	28.1	
≥80	19.3	12.1		16.8	16.9	
Smoking (prior or current)	81.7	88.6	<0.001	83.9	83.2	0.592
COPD	25.8	28.8	0.063	25.9	26.5	0.721
Hypertension	85.7	88.0	0.072	85.5	88.0	0.051
Coronary artery disease	35.6	37.6	0.236	36.3	35.3	0.599
Prior CABG or coronary intervention	32.0	34.5	0.143	33.4	33.1	0.842
Congestive heart failure	16.5	15.5	0.466	16.1	15.8	0.804
<b>Diabetes</b>						
No diabetes	48.5	50.3	0.581	48.3	50.2	0.400
Non-insulin-dependent diabetes	25.8	24.4		25.7	26.0	
Insulin-dependent diabetes	25.7	25.3		26.0	23.9	
Creatinine ≥1.8%	9.1	7.2	0.076	8.7	7.0	0.092
Dialysis	8.2	5.6	0.004	7.9	6.2	0.075
<b>Preoperative medication regimen</b>						
Preoperative β-blockers	77.4	80.1	0.076	77.8	79.9	0.167
Preoperative aspirin	72.2	76.1	0.014	72.7	73.8	0.509
Preoperative clopidogrel	8.3	19.3	<0.001	12.1	11.9	0.892
Preoperative statin use	63.3	70.8	<0.001	66.5	66.7	0.914
<b>Surgical history</b>						
CEA	9.2	12.7	0.001	9.9	11.4	0.203
Aneurysm repair	2.8	6.2	<0.001	3.7	3.8	0.948
Ipsilateral major amputation	0.0	0.4	0.025	0.1	0.3	0.056
Ipsilateral minor amputation	5.8	7.8	0.023	6.3	6.1	0.896
<b>Indication</b>						
Claudication	29.5	30.1	0.705	30.3	29.4	0.594
Critical limb ischemia	70.6	69.9		69.7	70.6	
<b>Operative details</b>						
<b>Urgency</b>						
Elective	81.4	79.0	0.023	82.4	80.6	0.137
Urgent	18.2	19.8		17.2	18.6	
Emergent	0.5	1.2		0.4	0.9	
Graft origin—common femoral artery	66.5	73.1	<0.001	67.9	71.8	0.021

Continued

Table 3. Continued

Characteristic	Unweighted Data			Inverse Propensity-Weighted Analysis		
	Primary LEB, %	Secondary LEB, %	P Value*	Primary LEB, %	Secondary LEB, %	P Value†
<b>Graft recipient</b>						
Above knee	28.3	29.0	<0.001	29.0	29.5	0.991
BK popliteal	31.5	35.8		33.2	33.0	
Tibial	28.2	29.6		28.0	27.6	
Pedal	12.0	5.7		9.9	9.9	
<b>Graft type</b>						
Prosthetic	27.3	35.6	<0.001	29.8	30.2	0.791
Any graft vein type	75.0	66.8	<0.001	72.5	72.4	0.915
<b>No. of vein segments</b>						
0	26.1	33.4	<0.001	28.3	28.4	0.984
1	69.0	59.1		66.0	65.8	
2	4.6	6.7		5.4	5.4	
≥3	0.3	0.8		0.3	0.4	
<b>Concomitant proximal procedures (ipsilateral)</b>						
PVI	10.8	9.3	0.297	11.0	9.1	0.203
Endarterectomy	49.6	43.1	0.007	49.4	44.4	0.038
<b>Discharge medications</b>						
ASA	80.7	82.9	0.123	81.1	82.1	0.492
Clopidogrel	16.8	25.9	<0.001	19.1	21.5	0.107
Coumadin	21.4	27.7	<0.001	21.3	27.0	<0.001
Statin	74.0	79.5	0.002	76.1	77.8	0.328
β-Blocker	76.4	78.2	0.284	76.9	77.7	0.645

ASA indicates aspirin; BK, below knee; CABG, coronary artery bypass graft surgery; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease; LEB, lower extremity bypass; OR, operating room; PVI, peripheral endovascular intervention.

\*P value from  $\chi^2$  test (testing differences between weighted groups).

†P value from  $\chi^2$  test (testing differences between propensity-weighted groups).

(55.3% versus 63.1%,  $P=0.002$ ), as was RAO-free survival (53.0% versus 60.0%,  $P=0.003$ ). Finally, to determine whether the nature of the prior revascularization procedure (PVI, LEB, or both) had a differential effect on the outcomes of secondary LEB, we stratified outcomes based on prior intervention type. We found that, regardless of the nature of the prior intervention (endovascular or surgical), all secondary LEB patients had inferior RAO-free survival ( $P=0.005$ ) and MALE-free survival ( $P=0.004$ ) outcomes (Figure 5). To further clarify the impact of prior PVI on subsequent LEBs, we compared primary LEBs with only those secondary LEBs performed after PVI and found that differences in RAO-free survival ( $P=0.005$ ) and MALE-free survival ( $P=0.005$ ) persisted.

## Discussion

With the continuing evolution of endovascular techniques for the treatment of PAD, several studies have demonstrated

dramatic increases in the volume of interventions being performed during the past decade, suggesting a major shift in practice patterns toward a more aggressive use of revascularization.<sup>1–3</sup> Our data suggest that, currently, nearly half of the patients undergoing surgical lower extremity revascularization in New England represent a failure of a prior revascularization attempt in that limb, a relative increase of 72% over the study interval. In both crude and weighted analyses, these secondary bypass operations are associated with significantly worse mid-term outcomes compared with patients undergoing primary bypass, even when adjusting for differences in patient characteristics. Furthermore, primary bypass outcomes were superior to secondary bypass outcomes, regardless of whether the prior failed intervention was endovascular or surgical in nature. Thus, both the incidence and the impact of treatment failure on the treatment of PAD appear to be increasing dramatically in recent years, with treatment failure contributing

**Table 4.** In-hospital Outcomes and Discharge Characteristics of Patients Who Underwent Infrainguinal LEB, With Univariate Analysis by Primary Versus Secondary LEB and Inverse Propensity Weighting

Outcome/Discharge Characteristic	Unweighted Data			Inverse Propensity-Weighted Analysis		
	Primary LEB, %	Secondary LEB, %	P Value*	Primary LEB, %	Secondary LEB, %	P Value†
No. of patients	2350	1154		2350	1154	
Postoperative complications						
Return to OR						
Return to OR for bleeding	1.6	1.3	0.478	1.6	1.0	0.192
Return to OR for infection	0.9	0.9	0.975	1.0	0.6	0.316
Return to OR for thrombosis	2.2	3.3	0.061	2.3	3.6	0.036
Graft occlusion at discharge	1.3	2.0	0.126	1.1	2.0	0.026
Postoperative length of stay, d‡	4 (0 to 89)	4 (0 to 154)	0.384	4 (0 to 89)	4 (0 to 154)	0.199
In-hospital mortality	1.5	1.6	0.795	1.3	1.3	0.994
In-hospital MI	3.9	4.1	0.822	3.9	3.7	0.738
In-hospital ipsilateral amputation	0.1	0.5	0.031	0.2	0.4	0.122

LEB indicates lower extremity bypass; MI, myocardial infarction; OR, operating room.

\*P value from  $\chi^2$  test (testing differences between unweighted groups).

†P value from  $\chi^2$  test (testing differences between propensity-weighted groups).

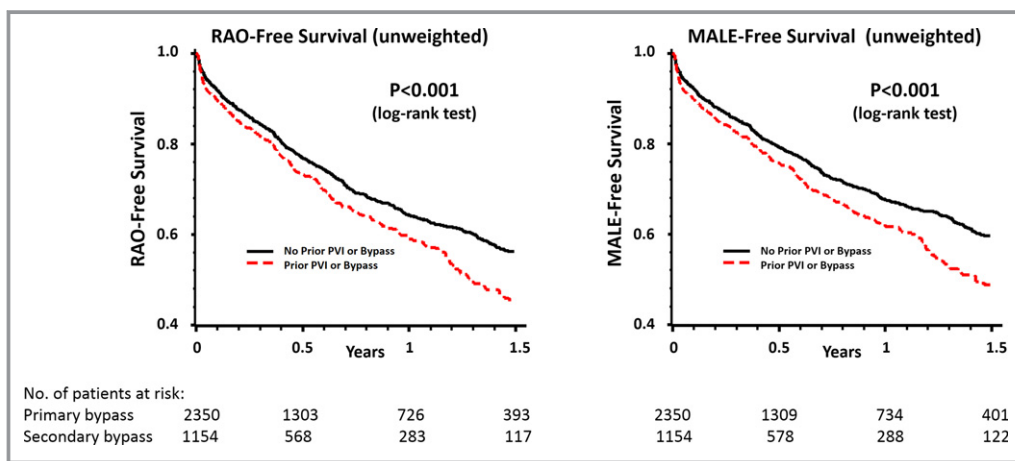
‡Median (range), P value from Wilcoxon rank sum test.

significantly to the overall burden of PAD on patients and the health care system.

In recent years, many have advocated an “endovascular first” strategy when treating patients with severe PAD.<sup>17–19</sup> This shift in approach has occurred concomitantly with the continued evolution and proliferation of catheter-based technologies and their diffusion across multiple disciplines and venues of care. Among the reasons cited for more aggressive use of endovascular revascularization, many argue that a failed primary endovascular intervention causes little harm, as long as the target for bypass surgery remains available.<sup>18</sup> However, our data indicate that LEBs performed in the setting

of failed prior interventions are substantially more likely to fail within 1 year, in comparison to primary operations. This was true regardless of whether the prior intervention was endovascular (PVI) or surgical (LEB) in nature. Moreover, the survival curves suggest that the degree of inferiority for secondary LEB continues to increase with time and would likely be substantially greater with additional years of observation.

Although these data describe the effects of evolving treatment paradigms for PAD on patients presenting for surgical bypass, they do not, in any way, address the question of which primary interventions are appropriate and which are



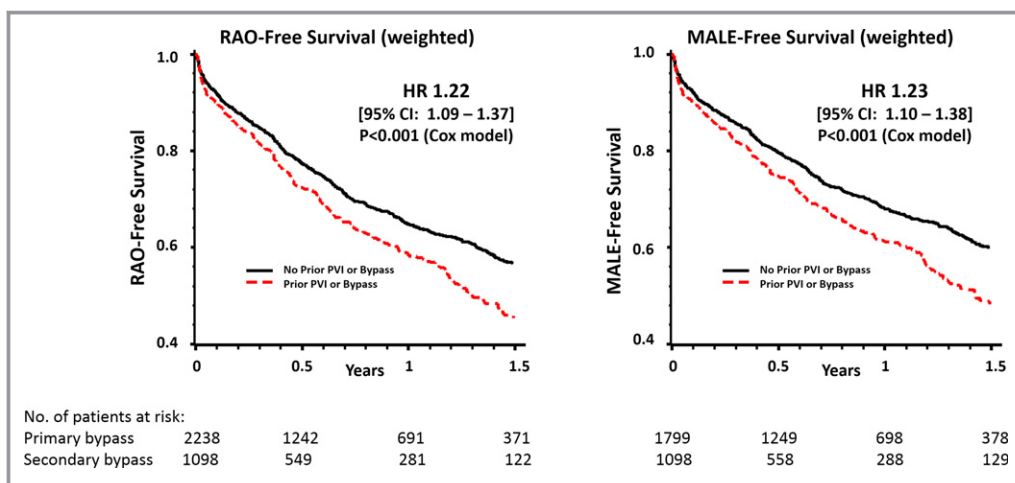
**Figure 3.** Crude (unweighted) analysis of RAO-free survival and MALE-free survival in primary versus secondary LEB. LEB indicates lower extremity bypass; MALE, major adverse limb event; PVI, peripheral endovascular intervention; RAO, reintervention or amputation.

**Table 5.** In-hospital and 1-Year Outcomes, by Indication (Unweighted and Propensity Weighted)

Variable	Unweighted In-hospital Outcomes Stratified by Indication						Inverse Probability Weighted In-hospital Outcomes Stratified by Indication					
	Of 1039 With Claudication			Of 2465 With CLI			Of 1039 With Claudication			Of 2465 With CLI		
	Primary LEB (n=692)	Secondary LEB (n=347)	P Value*	Primary LEB (n=1658)	Secondary LEB (n=807)	P Value*	Primary LEB (n=692)	Secondary LEB (n=347)	P Value*	Primary LEB (n=1658)	Secondary LEB (n=807)	P Value*
In-hospital mortality	0.4%	0.0%	0.219	1.9%	2.2%	0.547	0.6%	0.0%	0.165	1.9%	0.672	
In-hospital MI	1.0%	0.9%	0.817	5.1%	5.5%	0.731	1.1%	1.0%	0.808	4.9%	0.743	
In-hospital ipsilateral amputation	0.0%	0.0%	NA	0.2%	0.7%	0.030	0.0%	0.0%	NA	0.6%	0.127	
	Unweighted 1 Year-Outcomes Stratified by Indication			Inverse Probability-Weighted 1-Year Outcomes Stratified by Indication			Unweighted 1 Year-Outcomes Stratified by Indication			Inverse Probability-Weighted 1-Year Outcomes Stratified by Indication		
RAO-free survival	77.6%	73.9%	0.123	59.3%	53.3%	0.001	77.3%	72.9%	0.064	60.0%	53.0%	0.003
MALE-free survival	81.8%	77.6%	0.107	62.4%	55.6%	0.001	81.0%	76.9%	0.075	63.1%	55.3%	0.002
Amputation-free survival	93.0%	94.1%	0.566	71.3%	68.6%	0.060	93.2%	94.9%	0.578	72.3%	68.5%	0.058
Overall survival	95.9%	97.6%	0.865	82.8%	84.3%	0.080	96.0%	98.1%	0.870	83.7%	82.2%	0.933

Cox model with the treatment as the covariate for adjusted 1-year outcomes. CLI indicates critical limb ischemia; LEB, lower extremity bypass; MALE, freedom from death, amputation, or major reintervention; MI, myocardial infarction; RAO, freedom from death, amputation, or any reintervention.

\*P value from  $\chi^2$  test for in-hospital outcomes; log-rank test of overall distribution functions across strata for unadjusted 1-year outcomes.



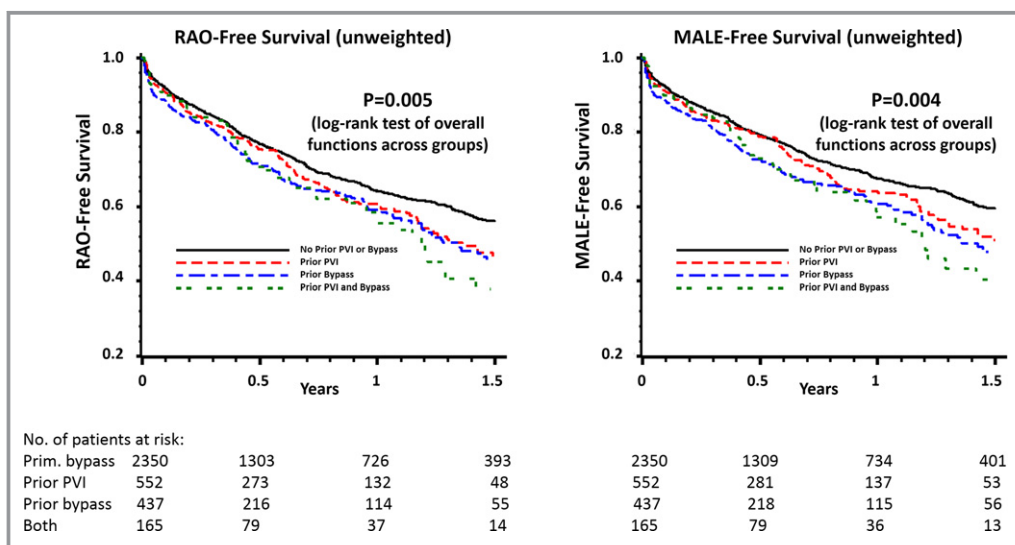
**Figure 4.** Inverse-propensity weighted analysis of RAO-free survival and MALE-free survival in primary versus secondary LEB. HR indicates hazard ratio; LEB, lower extremity bypass; MALE, major adverse limb event; PVI, peripheral endovascular intervention; RAO, reintervention or amputation.

not. Obviously, not all patients who undergo an initial endovascular intervention will ultimately require surgical bypass, and we readily agree that for many patients, endovascular intervention is a reasonable, safe, and effective initial option for treatment in PAD. In future work, we plan to use the Vascular Quality Initiative, a recently formed national quality improvement collaborative derived from regional efforts in New England, to examine the need for surgical revascularization among all patients undergoing an initial endovascular intervention, as well as the outcomes beginning with the first PVI or bypass.

Our study was not designed to establish whether primary bypass is a superior strategy to primary endovascular approach with surgical “backup” for failures. Further evidence from randomized trials will be necessary to address this

question.<sup>9</sup> However, given our findings, we believe physicians who care for patients with vascular disease should consider the significant influence of treatment failure on future events. Downstream effects may not become evident for years; therefore, outcomes reports with limited follow-up may grossly underestimate the impact of treatment failures in PAD. In this regard, the 1-year outcomes reported here are also a notable limitation, though the trends suggest that the strength of these findings would only increase with longer observation times.

Importantly, findings from our observational dataset reflect data from existing randomized trials.<sup>9</sup> Patients surviving  $\geq 2$  years in the Bypass versus Angioplasty in Severe Ischemia of the Limb trial (BASIL) (70% of the cohort) appeared better served by an initial LEB, and LEB procedures that were



**Figure 5.** Subgroup analysis of RAO-free survival and MALE-free survival, stratified by prior intervention type. MALE indicates major adverse limb event; PVI, peripheral endovascular intervention; RAO, reintervention or amputation.

**Table 6.** Outcomes at 1-Year Follow-up in All Patients, With Univariate Analysis by Primary Versus Secondary LEB and Inverse Propensity Weighting

Variable	Unweighted Data			Inverse Propensity-Weighted Analysis		
	Primary LEB (n=2350)	Secondary LEB (n=1154)	P Value*	Primary LEB (n=2350)	Secondary LEB (n=1154)	P Value*
Overall survival	86.6%	88.2%	0.183	87.4%	86.8%	0.667
Amputation-free survival	77.0%	75.6%	0.459	78.0%	75.5%	0.198
RAO-free survival	64.1%	58.9%	0.017	64.7%	58.3%	0.003
Overall survival	86.6%	88.2%	0.183	87.4%	86.8%	0.667
Freedom from amputation	91.5%	88.0%	0.028	91.7%	89.9%	0.239
Freedom from any reintervention	73.5%	66.1%	0.001	73.6%	66.3%	0.002
MALE-free survival	67.5%	61.6%	0.007	67.9%	61.0%	0.002
Overall survival	86.6%	88.2%	0.183	87.4%	86.8%	0.667
Freedom from amputation	91.5%	88.0%	0.028	91.7%	89.9%	0.239
Freedom from major reintervention <sup>†</sup>	78.2%	69.9%	<0.001	78.0%	70.3%	<0.001

LEB indicates lower extremity bypass; MALE, freedom from death, amputation, or major reintervention; RAO, freedom from death, amputation, or any reintervention.

\*P value from asymptotically  $\chi^2$  test with 1 *df* at 1 year for unweighted and weighted outcomes.

<sup>†</sup>Major reintervention, new bypass graft, a jump/interposition graft placed during a revision, or thrombectomy/thrombolysis.

performed after an initial failed PVI had notably inferior outcomes compared with bypass performed as the initial strategy in BASIL. While a major criticism of BASIL has been whether the protocol-mandated use of balloon angioplasty alone represents current best endovascular practice, our contemporary study suggests broadly similar implications in the present era of PVI.

Are the regional results reported in our dataset broadly generalizable? We believe the answer is yes. Our study is based on risk-adjusted, clinically detailed data from real-world practice, and we used inverse propensity weighting to account for differences in patient characteristics as well as surgical variables such as type of conduit used and distal target. And, given that our study cohort is composed of peripheral vascular operations, many, but not all, of the contributors to our dataset are vascular surgeons. In fact, of those physicians who contribute to the VSGNE and report board certification, >40% are interventional cardiologists, radiologists, or procedure-based specialists other than vascular surgeons. Specialty issues aside, the optimal manner by which to assess the extended impact of initial treatment selections in patients with advanced PAD would be a randomized trial, comparing the clinical and functional outcomes for differing initial treatment strategies with long-term follow-up including secondary interventions. However, given current cost constraints, no such trials are on the immediate horizon.

How, then, should we proceed? Disease-based registries, used in cooperation across a variety of provider specialties, may provide a practical method to gain insight into this complex problem. Using detailed risk adjustment algorithms, patient-level risk for adverse outcomes can be assessed for a

variety of treatment strategies—conservative care, endovascular first, primary LEB, and secondary interventions (both PVI and LEB). While a disease-based registry would share several of the limitations inherent to our procedure-based registry, it would add the benefit of insight from other treatment strategies to detect marginal differences in outcomes across treatment types. Given that procedure-based registries are becoming more common in the vascular community, construction of disease-based registries, which include phenotypic information as it becomes widely available, would be a straightforward path to follow.

These findings build on previous work by our group,<sup>5,8</sup> in which we examined the adverse effect of a prior failed endovascular intervention on outcomes in subsequent lower extremity bypass and found a rising proportion of LEBs being performed for claudication in recent years. The present analysis adds additional insights to this work. First, we demonstrate that the overall incidence of secondary LEB has dramatically increased during the past decade. In patients with claudication, this provides evidence, albeit indirect, of a “treatment trap.” Patients, who may have foregone open surgery for claudication initially but chose to undergo PVI, are now presenting for bypass surgery in increasing numbers following failure of their PVI.<sup>1,5</sup> Although it is generally understood that repeat procedures will have inferior outcomes compared with an index procedure, this study also serves to delineate the real-world extent of this effect. As a result, clinicians can use these results to counsel patients regarding realistic expectations of outcomes following a secondary LEB, thereby better informing discussions of risks and benefits of intervention. Most important, the current data

show that the mid-term outcomes of LEBs are inferior in the setting of prior treatment failure and that the deleterious effects of restenosis appear to transcend the nature of the initial intervention (surgical or endovascular).

Our study has important limitations. First, while we examined traditional outcomes such as mortality and amputation-free survival,<sup>9,12,20,21</sup> we did not directly examine patient-centered outcomes, such as symptom recurrence, quality-adjusted life years, or pain-free walking distance. Second, our study lacks data on genetic biomarkers, defined hypercoagulable states, and other phenotypic data associated with treatment failure,<sup>22–24</sup> and, thus, the impact of these variables is impossible to assess for primary or secondary bypass. Furthermore, unlike randomized controlled trials, the technique of inverse propensity weighting can only account for measured variables, and it is therefore possible that the weighted cohorts differ from each other by an unmeasured factor that is biasing the results of the model. Third, our dataset does not contain cost-related data. There is an unmet need in understanding how this apparent “epidemic of restenosis” in PAD fits into the national discussion around cost-effectiveness and cost saving, particularly because the long-term implications (and costs) of an “endovascular first” strategy are not well understood. Additionally, given the demographics of the hospitals in our region, our dataset contains few nonwhite patients, limiting our generalizability in high-risk subgroups such as African American patients.<sup>16</sup> Our study also underestimates the true overall impact of restenosis on surgical practice, because we only considered 1 limb per subject and only the first LEB that was recorded in the database. Fourth, data within our registry are self-reported, and while audits of our prior work have yet to reveal systematic underreporting of adverse events, this potential exists.<sup>5,25</sup> Finally, given the observational nature of our dataset, we are obviously unable to discern if those patients treated with secondary LEB following a failed PVI would have achieved better outcomes if they were treated initially with LEB. Although we used inverse propensity weighting to account for differences between groups, confounding by indication and anatomic distributions of disease undoubtedly represents a significant limitation to the inferences allowable by our findings.

In conclusion, the rate of secondary bypass operations for infrainguinal PAD has increased dramatically in recent years, as patients with both claudication and CLI are more likely to receive LEB following a failed prior PVI or LEB in that limb. Our data indicate that nearly 1 of 2 LEBs currently performed is in the setting of a prior failed infrainguinal revascularization in the same limb. Patients undergoing secondary LEB have poorer outcomes than patients who undergo LEB as a primary procedure, regardless of the nature of the first intervention. Efforts to reduce this rising burden of restenosis in the periphery should focus on the development of evidence-based

algorithms to guide patient selection for initial treatment, developing new technologies to improve the durability of both endovascular and surgical interventions, and closer examination of the impact of failed revascularizations on functional and quality of life outcomes to improve both the quality and value of PAD care.

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## Disclosures

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