

## Validation of the Global Limb Anatomic Staging System in first-time lower extremity revascularization

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### ABSTRACT

**Objective:** The Global Limb Anatomic Staging System (GLASS) was developed as a new anatomic classification scheme to grade the severity of chronic limb threatening ischemia. We evaluated the ability of this anatomic grading system to determine major adverse limb events after lower extremity revascularization.

**Methods:** We performed a single-institutional retrospective review of 1060 consecutive patients who had undergone 1180 first-time open or endovascular revascularization procedures for chronic limb threatening ischemia from 2005 to 2014. Using the review of angiographic images, the limbs were classified as GLASS stage 1, 2, or 3. The primary composite outcome was reintervention, major amputation (below- or above-the-knee amputation), and/or restenosis ( $>3.5\times$  step-up by duplex criteria) events (RAS). The secondary outcomes included all-cause mortality, failure to cross the lesion by endovascular methods, and a comparison between bypass vs endovascular intervention. Kaplan-Meier estimates were used to determine the event rates at 1 and 5 years, and Cox regression analysis was used to adjust for baseline differences among the GLASS stages.

**Results:** Of all patients undergoing first-time revascularization, imaging studies were available for 1180 procedures (91%) for GLASS grading. Of these procedures, 552 were open bypass (47%) and 628 were endovascular intervention (53%). Compared with GLASS stage 1 disease ( $n = 267$ ; 23%), stage 2 ( $n = 367$ ; 31%) and stage 3 ( $n = 546$ ; 42%) disease were associated with a greater risk of RAS at 1 year (stage 1, 33% vs stage 2, 48% vs stage 3, 53%) and 5 years (stage 1, 45% [reference]; stage 2, 65%; hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.3-2.2;  $P < .001$ ; stage 3, 69%; HR, 2.3; 95% CI, 1.7-2.9;  $P < .001$ ). These differences were mainly driven by reintervention and restenosis rather than by major amputation. The 5-year mortality was similar for stage 2 and 3 compared with stage 1 disease (stage 1, 40% [reference]; stage 2, 45%; HR, 1.1; 95% CI, 0.8-1.4;  $P = .69$ ; stage 3, 49%; HR, 1.2; 95% CI, 1.0-1.6;  $P = .11$ ). For all attempted endovascular interventions, failure to cross a target lesion increased with advancing GLASS stage (stage 1, 4.5% vs stage 2, 6.3% vs stage 3, 13.3%;  $P < .01$ ). Compared with open bypass ( $n = 552$ ; 46.8%), endovascular intervention ( $n = 628$ ; 53.3%) was associated with a higher rate of 5-year RAS for GLASS stage 1 (49% vs 34%; HR, 1.9; 95% CI, [1.1-3.5;  $P = .03$ ], stage 2 (69% vs 52%; HR, 1.7; 95% CI, 1.2-2.5;  $P < .01$ ), and stage 3 (83% vs 61%; HR, 1.5; 95% CI, 1.2-2.0;  $P < .01$ ) disease.

**Conclusions:** For patients undergoing first-time lower extremity revascularization, the GLASS can be used to predict for reintervention and restenosis. Bypass resulted in better long-term outcomes compared with endovascular intervention for all GLASS stages. (J Vasc Surg 2021;73:1683-91.)

**Keywords:** Chronic limb threatening ischemia; Global Limb Anatomic Staging System; Peripheral vascular disease; Lower extremity

The Global Vascular Guidelines were published in September 2019 as a joint effort among three vascular surgical societies to address the increasing prevalence of chronic limb threatening ischemia (CLTI) worldwide by increasing public awareness of CLTI and providing updated guidelines on the definition, evaluation, and

management of this disease entity.<sup>1,2</sup> The three vascular societies participating in the design of the Global Vascular Guidelines included the Society for Vascular Surgery (SVS), European Society for Vascular Surgery, and World Federation of Vascular Societies. Within these guidelines, a new anatomic lower extremity staging

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system was also introduced to provide a better assessment of limb ischemia and characterization of the anatomic distribution of peripheral arterial disease.

Several previous classification schemes for lower extremity vascular disease have been proposed for limb staging, including the Fontaine, Rutherford, Second European Consensus, Trans-Atlantic Inter-Society Consensus (TASC) I, and TASC II, but only the TASC guidelines provide a classification system based on the anatomic distribution of disease.<sup>3,4</sup> The TASC classification systems, however, have been subject to criticism for both their clinical and scientific applications, given the complexity of the grading systems, room for individual interpretation, and failure to address multilevel disease.<sup>5,6</sup> In response to these criticisms and to incorporate the rapid advancements of endovascular technology and better define infrapopliteal disease distribution, an update to TASC II was published. However, many of the major vascular societies originally present for TASC I and II were absent from this new consensus statement.<sup>7</sup>

The more recent Global Vascular Guidelines' Global Limb Anatomic Staging System (GLASS) was designed with the intent to provide an updated anatomic classification system using a more clinically focused method of classifying the patterns of peripheral vascular disease, but it has yet to be clinically validated. Therefore, we performed a retrospective review of patients who had undergone lower extremity open bypass or endovascular interventional procedures at our institution to determine the capability of this new anatomic grading system to predict major adverse limb events after first-time lower extremity revascularization.

## METHODS

**Dataset.** We retrospectively identified all consecutive patients at Beth Israel Deaconess Medical Center (Boston, Mass) who had undergone first-time lower extremity open bypass surgery or endovascular revascularization for CLTI from January 1, 2005 to December 31, 2014. Patients were identified using Current Procedural Terminology codes for lower extremity bypass and endovascular revascularization. We excluded patients who had undergone any previous ipsilateral open or endovascular lower extremity intervention and patients who had undergone diagnostic arteriography without attempted open or endovascular revascularization. Patients without arteriograms available for review were also excluded from the present analysis (n = 119; 9.2%). The institutional review board at the Beth Israel Deaconess Medical Center approved the present study without the need for patient informed consent given the retrospective nature of the study design.

**Patients.** The patient demographics and comorbid conditions were obtained by medical record review by four of us (J.D.D., D.K., V.R., E.S.J.). Three of us (P.L., C.L.M.,

## ARTICLE HIGHLIGHTS

- **Type of Research:** A single-institution, retrospective cohort study
- **Key Findings:** Using the Global Limb Anatomic Staging System (GLASS) to arteriographically stage 1180 consecutive lower extremity first-time open or endovascular revascularization procedures for chronic limb threatening ischemia from 2005 to 2014, we found that a higher GLASS stage was associated with greater rates of reintervention and restenosis.
- **Take Home Message:** The GLASS can be used to predict reintervention and restenosis after first-time lower extremity revascularization.

M.L.S.) performed the arteriogram imaging review and GLASS classification assignments using the Centricity Universal Viewer Picture Archiving and Communications System (GE Healthcare, Chicago, Ill). The indications for intervention included tissue loss or rest pain. For patients presenting with more than one indication, the most severe indication was assigned (gangrene considered more severe than ulcer, which was considered more severe than rest pain). Because each limb was treated individually, patients were included in the analysis twice if both limbs had undergone first-time revascularization during the study period. Patients who had undergone a failed attempted endovascular revascularization procedure and later underwent ipsilateral open bypass were included in the first-time open bypass cohort. Patients undergoing lower extremity revascularization were routinely seen for follow-up at 1 month after the index procedure, every 3 to 4 months for 2 years, and every 6 months thereafter. During each visit, the patients were examined using noninvasive imaging modalities, including arterial duplex ultrasound imaging, ankle brachial index, and forefoot and/or toe pressure recordings. The last date of follow-up was August 31, 2018.

**GLASS classification.** Using the anatomic grading and staging criteria set forth by the Global Vascular Guidelines' GLASS,<sup>1,2</sup> each limb was assigned a femoropopliteal and infrapopliteal grade ranging from 0 to 4, which correlates with mild or no significant disease in the primary target artery path to an increasing severity of stenosis and disease length (Table I). The primary target artery path was defined as the optimal arterial pathway to restore inline (pulsatile) flow to the ankle and foot.<sup>1,2</sup> We determined the infrapopliteal target artery path as the tibial vessel intervened on with angioplasty and or stenting or the vessel to which a bypass was distally targeted. If more than one tibial vessel was intervened on for an endovascular procedure, we graded the vessel that had the most robust inline flow to the foot and pedal arch after intervention, determined by completion

**Table I.** Femoropopliteal and infrapopliteal disease grade using the Global Limb Anatomic Staging System (GLASS)

Grade	Description
<b>Femoropopliteal disease</b>	
0	Mild or no significant (<50%) disease
1	Total length of SFA disease less than one third (<10 cm); can include single focal CTO (<5 cm) as long as not flush occlusion; popliteal artery with mild or no significant disease
2	Total length of SFA disease one third to two thirds (10-20 cm); can include CTO totaling less than one third (10 cm) but not flush occlusion; focal popliteal artery stenosis <2 cm not involving trifurcation
3	Total length of SFA disease greater than two thirds (>20 cm) length; can include any flush occlusion <20 cm or nonflush CTO of 10-20 cm; short popliteal stenosis 2-5 cm not involving trifurcation
4	Total length of SFA occlusion >20 cm; popliteal disease >5 cm or extending into trifurcation; any popliteal CTO
<b>Infrapopliteal disease</b>	
0	Mild or no significant disease in primary target artery path
1	Stenosis involving one third of total vessel length; can include focal CTO (<3 cm); not including TP trunk or tibial vessel origin
2	Stenosis involving one third total vessel length; can include focal CTO (<3 cm); not including TP trunk or tibial vessel origin
3	Disease up to two thirds of vessel length; CTO up to one third length (can include tibial vessel origin but not tibioperoneal trunk)
4	Diffuse stenosis greater than two thirds total vessel length; CTO greater than one-third vessel length (can include vessel origin); any CTO of tibioperoneal trunk if AT is not the target artery
AT, Anterior tibial; CTO, chronic total occlusion; SFA, superficial femoral artery; TP, tibioperoneal. Adapted from Conte et al. <sup>1,2</sup>	

arteriography. Limb stages were then assigned using the GLASS femoropopliteal and infrapopliteal algorithm (Table II). The GLASS stages range from 1 to 3, with 3 the most severe stage. A GLASS inframalleolar/pedal descriptor modifier, which ranges from P0 to P2, was also assigned to grade the presence of the target artery crossing the ankle and into the foot. P0 and P1 are defined as a target artery that crossed the ankle into foot and P2 as no target artery crossing into the foot. This modifier also factors in the presence of an intact pedal arch, with P0 describing an intact pedal arch and P1 an absent or severely diseased pedal arch.

**Table II.** Global Limb Anatomic Staging System (GLASS) using femoropopliteal and infrapopliteal disease grades

Grade	Infringuinal GLASS stage				
<b>Femoropopliteal</b>					
4	3	3	3	3	3
3	2	2	2	3	3
2	1	2	2	2	3
1	1	1	2	2	3
0	NA	1	1	2	3
<b>Infrapopliteal</b>					
	0	1	2	3	4
NA, Not applicable. Adapted from Conte et al. <sup>1,2</sup>					

**Variable definition.** Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m<sup>2</sup> and was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.<sup>8</sup> The SVS lower extremity threatened limb (wound, ischemia, foot infection [WIFI]) classification system was used to stratify the severity of the presenting CLTI wound.<sup>9</sup> The wound extent, degree of ischemia, and extent of foot infection were individually graded on a scale of 0 to 3 using the WIFI classification system. The clinical WIFI stages were determined using the composite additive score or mean score. Previous studies using our first-time lower extremity revascularization institutional dataset have shown that the a WIFI mean score can be used to predict for amputation, major adverse events, and mortality according to the limb severity at presentation.<sup>10</sup>

**Outcomes.** The primary outcome was the composite endpoint of reintervention, major amputation (below- or above-the-knee amputation), or restenosis (RAS) at 1 and 5 years. Reintervention was defined as either endovascular or open lower extremity reoperation for restenosis, occlusion, or unresolved limb ischemia not compatible with wound healing. Major amputation was defined as below- or above-the-knee amputation. Restenosis was defined as a 3.5× peak-systolic velocity step-up or occlusion on surveillance duplex ultrasound scan or angiogram. The secondary outcomes included the individual outcomes of reintervention, major amputation, restenosis, all-cause mortality, amputation-free survival, and technical failure using endovascular methods. Technical failure was defined as an inability to cross or recanalize the target lesion and provide inline flow to the ankle and foot. Additionally, we compared the 1- and 5-year RAS outcomes and 1- and 5-year mortality between patients undergoing endovascular intervention and open bypass and stratified by GLASS stage.

**Statistical analysis.** Continuous variables are presented as the mean ± standard deviation or median and interquartile range. Categorical variables are presented as

**Table III.** Baseline patient characteristics stratified by Global Limb Anatomic Staging System (GLASS) stage

Characteristic	Stage 1 (n = 267; 22.6%)		Stage 2 (n = 367; 31.1%)		Stage 3 (n = 546; 42.3%)	
	No. (%)	P value	No. (%)	P value	No. (%)	P value
Mean age, years	69.2 ± 12.8	Ref	71.4 ± 12.1	.03	73.1 ± 12.3	<.001
Male gender	164 (61.7)	–	205 (55.9)	.14	325 (59.5)	.56
White race	204 (76.4)	–	279 (76.4)	.99	429 (79.0)	.40
Comorbidities						
Hypertension	225 (84.9)	–	321 (88.9)	.14	456 (84.3)	.82
Diabetes mellitus	215 (80.5)	–	284 (77.8)	.41	387 (71.4)	.005
Hyperlipidemia	167 (63.0)	–	220 (61.1)	.63	316 (58.7)	.24
Coronary artery disease	122 (46.2)	–	187 (51.9)	.16	291 (54.1)	.036
Previous myocardial infarction	67 (25.3)	–	100 (27.9)	.47	142 (26.4)	.72
Chronic kidney disease, eGFR <60 mL/min/1.73 m <sup>2</sup>	165 (62.5)	–	244 (67.4)	.20	333 (61.3)	.75
Dialysis dependence	61 (23.1)	–	81 (22.5)	.86	98 (18.2)	.10
Congestive heart failure	81 (30.7)	–	106 (29.4)	.74	171 (31.8)	.75
Previous stroke	29 (11.9)	–	34 (10.3)	.54	82 (16.6)	.19
COPD	32 (12.1)	–	35 (9.7)	.35	56 (10.4)	.49
Current or previous smoker	153 (57.7)	–	219 (61.0)	.41	314 (58.3)	.89
Mean BMI, kg/m <sup>2</sup>	28.0 ± 6.6	–	28.4 ± 6.3	.42	27.1 ± 6.2	.01
Indication for intervention		–		.56		.032
Rest pain	35 (13.1)		46 (12.5)		86 (15.8)	
Ulcer	170 (63.7)		222 (60.5)		295 (54.0)	
Gangrene	62 (23.2)		99 (27.0)		165 (30.2)	
Mean Wifl classification score						
Wound	1.5 ± 0.8	–	1.5 ± 0.8	.04	1.5 ± 0.8	.72
Ischemia	2.6 ± 0.7	–	2.6 ± 0.7	.98	2.7 ± 0.6	.05
Foot infection	0.6 ± 0.8	–	0.5 ± 0.7	.10	0.4 ± 0.7	<.01
Average	1.4 ± 0.5	–	1.4 ± 0.5	.25	1.4 ± 0.5	.27

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Ref, reference; Wifl, wound, ischemia, foot infection.

counts and percentages. RAS event rates were estimated at 1 and 5 years using Kaplan-Meier life-table methods, and comparisons were performed using multivariable Cox proportional hazard models. Patients lost to follow-up during the study period were censored. For mortality of patients who had undergone bilateral lower extremity revascularization, censoring was performed for the first procedure at contralateral limb revascularization to avoid repeated measures. The proportional hazard model included the indication for intervention (rest pain, tissue loss, or gangrene), type of intervention (open bypass, endovascular intervention), age, diabetes, coronary artery disease, chronic kidney disease, smoking history, mean Wifl score, and GLASS inframalleolar/pedal modifier grade. The inframalleolar modifier was used in the adjusted Cox regression models because of the association found in the present study between the inframalleolar GLASS grade and the occurrence of major adverse events. *P* values <.05 were considered

statistically significant, and all tests were two-sided. Stata/SE, version 14.1 (StataCorp, College Station, Tex) was used for all analyses.

## RESULTS

**Patients.** We identified 1180 consecutive cases of first-time lower extremity revascularization in 1060 patients. Of the 1180 limbs, 267 limbs were anatomically classified as GLASS stage 1 (23%), 367 as GLASS stage 2 (31%), and 546 (42%) as GLASS stage 3. Compared with the patients with stage 1 limbs, patients with stage 2 limbs were older (age, 71.4 vs 69.2 years; *P* = .03). However, no statistically significant differences were found in medical comorbidities, indication for intervention, or average Wifl score (1.4 vs 1.4; *P* = .25; Table III). However, compared with patients with stage 1 limbs, patients with stage 3 limbs were more likely to be older (age, 73.1 vs 69.2 years; *P* < .001) and more likely to have diabetes mellitus (71.4%

**Table IV.** Global Limb Anatomic Staging System (GLASS) femoropopliteal and infrapopliteal grade distribution

Grade	Stage 1 (n = 267; 22.6%)		Stage 2 (n = 367; 31.1%)		Stage 3 (n = 546; 42.3%)	
	No. (%)	P value	No. (%)	P value	No. (%)	P value
Femoropopliteal		—		<.001		<.001
No disease	84 (31.8)		45 (12.3)		97 (17.8)	
Grade 1	109 (41.3)		72 (19.7)		47 (8.6)	
Grade 2	71 (26.9)		127 (34.7)		44 (8.1)	
Grade 3	0 (0.0)		121 (33.1)		39 (7.2)	
Grade 4	0 (0.0)		1 (0.3)		318 (58.3)	
Infrapopliteal		—		<.001		<.001
No disease	144 (53.9)		67 (18.3)		110 (20.2)	
Grade 1	80 (30.0)		89 (24.3)		37 (6.8)	
Grade 2	43 (16.1)		97 (26.4)		25 (4.6)	
Grade 3	0 (0.0)		114 (31.1)		55 (10.1)	
Grade 4	0 (0.0)		0 (0.0)		318 (58.3)	
GLASS inframalleolar/pedal modifier		—		.002		<.001
P0	119 (46.5)		115 (33.0)		163 (32.7)	
P1	110 (43.0)		196 (56.2)		263 (52.8)	
P2	27 (10.5)		38 (10.9)		72 (14.5)	

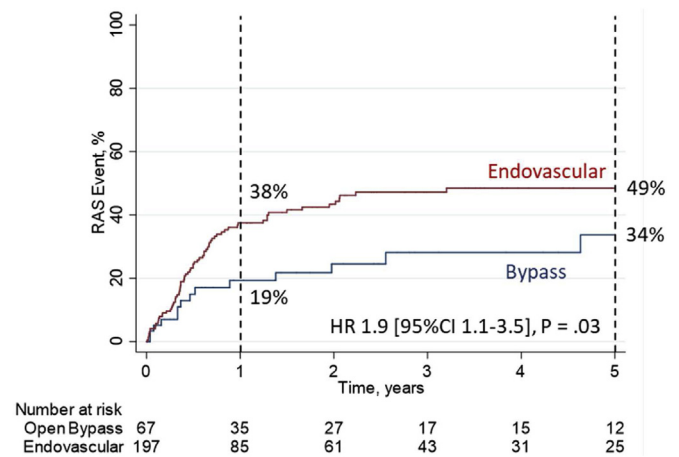
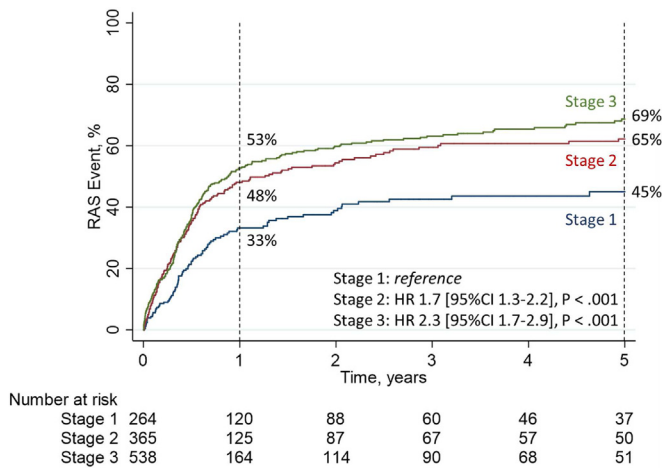
vs 77.8%;  $P = .005$ ) and coronary artery disease (54.1% vs 46.2%;  $P = .036$ ). Patients with stage 3 limbs were also more likely have a greater proportion of limbs treated for gangrene rather than ulcerative disease or rest pain (stage 3 vs stage 1: gangrene, 30.2% vs 23.3%; ulcer, 54.0% vs 63.7%; rest pain, 15.8% vs 13.1%;  $P = .003$ ). However, the mean Wifl score was similar between the stage 3 and stage 1 limbs (1.4 vs 1.4;  $P = .27$ ). The distribution of femoropopliteal and infrapopliteal grades and inframalleolar grades for each GLASS category is listed in Table IV. Increasing femoropopliteal and infrapopliteal grades were associated with higher GLASS stage.

**Overall outcomes.** The mean follow-up for the study population was 2.9 years. Compared with GLASS stage 1 disease, stage 2 and 3 disease were associated with a greater risk of RAS at 1 year (stage 1, 33% vs stage 2, 48% vs stage 3, 53%) and 5 years (stage 1, 45% [reference]; stage 2, 65%; hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.3-2.2;  $P < .001$ ; stage 3, 69%; HR, 2.3; 95% CI, 1.7-2.9;  $P < .001$ ; Fig 1). GLASS stage 2 and 3 disease was also associated with a significantly greater risk of the individual outcomes of reintervention at 1 year (stage 1, 21% vs stage 2, 32% vs stage 3, 33%) and 5 years (stage 1, 32% [reference]; stage 2, 46%; HR, 1.8; 95% CI, 1.2-2.5;  $P < .01$ ; stage 3, 47%; HR, 1.9; 95% CI, 1.3-2.7;  $P < .001$ ) and restenosis at 1 year (stage 1, 26% vs stage 2, 34% vs stage 3, 41%) and 5 years (stage 1, 35% [reference]; stage 2, 48%; HR, 1.6; 95% CI, 1.2-2.1;  $P < .01$ ; stage 3, 57%; HR, 2.3; 95% CI, 1.7-3.0;  $P < .001$ ). However, no statistically significant differences were found for major amputation at 1 year (stage 1, 7.6% vs stage 2, 11% vs stage 3, 12%), although at 5 years, a

trend was seen toward greater rates of amputation with a higher GLASS stage (stage 1, 11% [reference]; stage 2, 18%; HR, 1.7; 95% CI, 1.0-2.8;  $P = .06$ ; stage 3, 19%; HR, 1.7; 95% CI, 1.0-2.8;  $P = .05$ ).

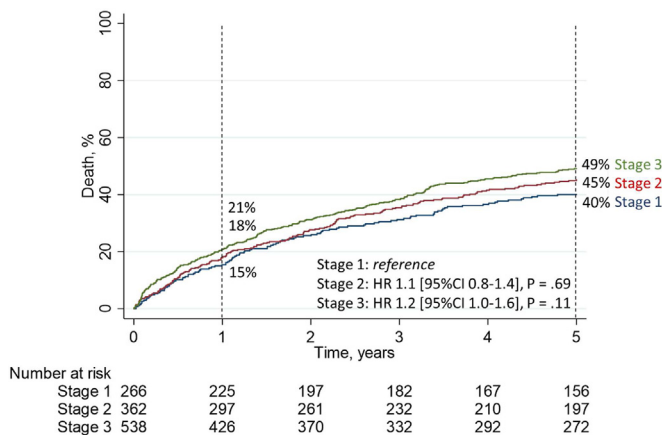
Also, among the GLASS stages, no statistically significant differences were seen in mortality at 1 year (stage 1, 15% vs stage 2, 18% vs stage 3, 21%) or 5 years (stage 1, 40% [reference]; stage 2, 45%; HR, 1.1; 95% CI, 0.8-1.4;  $P = .69$ ; stage 3, 49%; HR, 1.2; 95% CI, 1.0-1.6;  $P = .11$ ; Fig 2). No statistically significant difference was found for amputation-free survival among the GLASS stages at 1 year (stage 1, 78% vs stage 2, 74% vs stage 3, 70%). At 5 years, compared with patients treated for stage 1 disease, we also found no statistically significant difference in amputation-free survival for patients treated for stage 2 disease (39% vs 46%; HR, 1.1; 95% CI, 0.8-1.4;  $P = .59$ ) or stage 3 disease (37% vs 46%; HR, 1.2; 95% CI, 0.9-1.5;  $P = .13$ ). For all attempted endovascular interventions, failure to cross a target lesion increased with advancing GLASS stage (stage 1, 4.5% vs stage 2, 6.3% vs stage 3, 13.3%;  $P < .01$ ).

**Inframalleolar/pedal descriptor modifier.** Using the GLASS inframalleolar/pedal descriptor modifier classification system, 397 limbs underwent revascularization for P0 (34%), 569 for P1 (48%), and 137 for P2 (12%) disease. Seventy-seven limbs (6.5%) did not have adequate angiographic imaging of the foot to grade the target vessel runoff into the foot and were, therefore, excluded from this assessment. Compared with P0 disease at the 1-year follow-up examination, P2 disease was associated with significantly higher rates of RAS (P2, 58% vs P0, 42%;  $P < .01$ ) and major amputation (18.4% vs 8.1%;  $P < .01$ ) but



**Fig 1.** Kaplan-Meier estimated reintervention, major amputation, and restenosis (RAS) rates for patients undergoing first-time lower extremity revascularization stratified by the Global Limb Anatomic Staging System (GLASS) stage. *CI*, Confidence interval; *HR*, hazard ratio.

**Fig 3.** Kaplan-Meier estimated reintervention, major amputation, and restenosis (RAS) rates stratified by endovascular or open bypass intervention for first-time lower extremity revascularization for Global Limb Anatomic Staging System (GLASS) stage 1 (a), stage 2 (b), and stage 3 (c). *CI*, Confidence interval; *HR*, hazard ratio.



**Fig 2.** Kaplan-Meier estimated mortality rates for patients undergoing first-time lower extremity revascularization stratified by the Global Limb Anatomic Staging System (GLASS) stage. *CI*, Confidence interval; *HR*, hazard ratio.

**Open vs endovascular treatment.** Of all patients undergoing first-time lower extremity revascularization, 552 limbs were treated with open bypass (47%) and 628 with endovascular intervention (53%). Of the patients undergoing endovascular intervention, 49% underwent angioplasty with stenting and 51% underwent angioplasty alone. Of those undergoing open bypass, 12% underwent bypass with a prosthetic bypass and 88% with a vein conduit. The baseline characteristics are reported in the [Supplementary Table](#) (online only). Patients treated with endovascular intervention were more likely to have a history of hypertension (89.1% vs 82.2%;  $P < .001$ ) and chronic kidney disease (68.3% vs 58.0%;  $P < .001$ ) but were less likely to be male (56.2% vs 61.9%;  $P = .048$ ), white (74.7% vs 80.9%;  $P = .01$ ), or have a smoking history (52.9% vs 65.8%;  $P < .001$ ). Higher GLASS stages were more likely to be treated with open revascularization (stage 1, 25%; stage 2, 40%; stage 3, 62%) than with endovascular intervention (stage 1, 75%; stage 2, 61%; stage 3, 38%;  $P < .001$ ).

Overall, endovascular intervention was associated with a greater rate of 1-year RAS for GLASS stage 1 (38% vs 19%;  $P = .02$ ), stage 2 (55% vs 37%;  $P < .01$ ), and stage 3 (61% vs 48%;  $P < .01$ ) disease. These differences persisted, because endovascular intervention was also associated with a greater rate of 5-year RAS for GLASS stage 1 (49% vs 34%;  $HR, 1.9; 95\% CI, 1.1-3.5; P = .03$ ), stage 2 (69% vs 52%;  $HR, 1.7; 95\% CI, 1.2-2.5; P < .01$ ), and stage 3 (83% vs 61%;  $HR, 1.5; 95\% CI, 1.2-2.0; P < .01$ ; [Fig 3](#)). At 5 years, the differences in RAS were primarily driven by differences in reintervention for stage 2 disease (stage 1:  $HR, 1.5; 95\% CI, 0.8-3.1; P = .24$ ; stage 2:  $HR, 1.5; 95\% CI, 1.0-2.3; P = .04$ ; stage 3:  $HR, 1.3; 95\% CI, 0.9-1.8; P = .11$ ) and restenosis for stage 2 and 3 disease (stage 1:  $HR, 1.6$ ;

only a trend toward increased rates of reintervention (37% vs 28%;  $P = .08$ ) and restenosis (45% vs 35%;  $P = .05$ ). No statistically significant differences were found at 1 year between P1 and P0 disease for RAS (P1 vs P0, 46% vs 42%;  $P = .15$ ), reintervention (30% vs 28%;  $P = .37$ ), major amputation (10% vs 8.1%;  $P = .32$ ), or restenosis (32% vs 35%;  $P = .48$ ). However, at 5 years, both P2 and P1 disease were associated with higher rates of RAS (P2 vs P0, 70% vs 55%;  $P < .001$ ; P1 vs P0, 64% vs 55%;  $P = .03$ ) and major amputation (P2 vs P0, 23% vs 11%;  $P < .01$ ; P1 vs P0, 20% vs 11%;  $P = .01$ ). However, again, no statistically significant differences were found for the rates of reintervention (P2 vs P0, 50% vs 39%;  $P = .06$ ; P1 vs P0, 45% vs 39%;  $P = .16$ ) or restenosis (P2 vs P0, 55% vs 47%;  $P = .06$ ; P1 vs P0, 49% vs 47%;  $P = .82$ ).

95% CI, 0.8-3.1;  $P = .18$ ; stage 2: HR, 1.7; 95% CI, 1.2-2.5;  $P = .01$ ; stage 3: HR, 1.3; 95% CI, 1.0-1.8;  $P = .06$ ), rather than by major amputation (stage 1: HR, 1.3; 95% CI, 0.5-3.6;  $P = .63$ ; stage 2: HR, 0.9; 95% CI, 0.5-1.8;  $P = .83$ ; stage 3: HR, 1.0; 95% CI, 0.5-1.7;  $P = .86$ ).

Endovascular intervention was associated with greater rates of 1-year RAS for patients with P2 inframalleolar disease (71% vs 41%;  $P < .01$ ). However, similar rates of RAS were found for the treatment of patients with P0 (43% vs 40%;  $P = .58$ ) or P1 (49% vs 43%;  $P = .20$ ) disease. Similarly, at 5 years, higher rates of RAS were only found for patients with P2 disease (79% vs 59%;  $P < .01$ ) and not for P0 disease (58% vs 51%;  $P = .33$ ) or P1 disease (68% vs 59%;  $P = .11$ ). These RAS differences in P2 disease were primarily driven by restenosis and reintervention rather than by major amputation.

## DISCUSSION

In the present single-institution retrospective review of consecutive first-time lower extremity endovascular or open revascularization procedures, we found that the Global Vascular Guidelines' GLASS can be used to predict for reintervention and restenosis. Increasing GLASS stage was also associated with an increased risk of major amputation; however, these findings did not reach statistical significance. However, the degree of inframalleolar disease, as specified by the GLASS inframalleolar modifier, was strongly associated with major amputation. Higher GLASS stage was also associated with a greater rate of technical failure after endovascular procedures. Across all GLASS stages and for patients with severe inframalleolar disease, bypass resulted in better long-term outcomes compared with endovascular intervention.

The previously popularized TASC lower extremity arterial grading system consisted of multiple distinct classification schemes for each level of disease (aortoiliac vs femoropopliteal vs infrapopliteal segments), without any overarching assessment of the entire limb or method for multilevel disease classification. In a previous study, we demonstrated that a higher infrapopliteal TASC classification was associated with a greater risk of restenosis and reintervention after endovascular intervention.<sup>11</sup> Although TASC II was developed to adapt to the innovation of newer endovascular techniques by downgrading lesions, it still failed to provide an overarching system for grading multilevel segments. As much as 67% of patients presenting with CLTI will have concomitant femoropopliteal and infrapopliteal disease and will require multilevel endovascular interventions or open bypass surgery to a distal target to restore inline blood flow to the foot.<sup>12,13</sup> Therefore, it is clinically important to have a grading system that combines the assessment of both femoropopliteal and infrapopliteal segments and provides a universal language that can be used to describe the overall limb burden of arterial disease.

The GLASS bridges this gap between the femoropopliteal and infrapopliteal disease classifications by assigning limb "stages," which are determined by an algorithm that combines the burden of disease between the two segments. In the present study, we found that the GLASS multilevel combined staging system can be used in two clinically important ways: first, to preoperatively determine which limbs are likely to be successfully treated with endovascular methods; and, second, to postoperatively determine which limbs have the greatest risk of restenosis and the need for future reintervention. However, we found that more advanced GLASS stages were not significantly associated statistically with greater rates of major amputation, although this might have been limited by our sample size. Inadequate runoff to the ankle or the lack of an intact pedal arch appeared to be an important factor associated with major amputation.

The Global Vascular Guidelines' inframalleolar modifier in the GLASS describes three patterns of disease for target arteries crossing the ankle: an artery that crosses the ankle into the foot with an intact pedal arch, an artery that crosses the ankle into the foot but without an intact pedal arch (or a severely diseased pedal arch), and an artery that does not cross the ankle into the foot. However, the Global Vascular Guidelines state that this "inframalleolar modifier is not considered within the primary assignment of limb stages in GLASS, given the absence of strong evidence on how it affects treatment outcomes."<sup>1,2</sup> In our analysis, the inframalleolar modifier was the only Global Vascular Guidelines descriptor significantly associated with major amputation. Thus, we believe that the inframalleolar modifier should be considered an important addition to the overall limb disease assessment and should be factored into the decision-making for lower extremity revascularization vs primary amputation.

Since 2001, percutaneous endovascular intervention using angioplasty and/or stenting has become the predominant modality for treating peripheral vascular disease compared with open bypass in the United States.<sup>14</sup> However, data supporting the use of endovascular therapy compared with open bypass have been lacking. At present, the only reported randomized, prospective trial comparing bypass first or angioplasty first is the BASIL (bypass vs angioplasty in severe ischaemia of the leg) trial. This trial found that in the short term, no statistically significant differences were found in terms of amputation-free survival; however, after 2 years, bypass was associated with a significantly reduced risk of future amputation.<sup>15</sup> Despite the lower periprocedural morbidity achieved with endovascular intervention, the risk of reintervention, which was not factored into the BASIL trial's primary endpoint, should also be considered an important marker when comparing revascularization strategies.<sup>16</sup> Therefore, in

accordance with SVS outcome reporting standard guidelines for lower extremity revascularization, we factored reintervention into the composite primary endpoint of RAS.<sup>17</sup>

In a previous study evaluating the outcomes after first-time lower extremity revascularization, we found that bypass was associated with greater freedom from restenosis, improved patency rates, and significantly fewer reinterventions compared with endovascular therapy.<sup>18</sup> Furthermore, TASC C and D lesions were associated with a greater risk of reintervention. The results from our present study, with longer term follow-up than the previously reported study, similarly suggest that patients undergoing open bypass will have better long-term outcomes in terms of the composite endpoint of RAS, regardless of the GLASS classification. However, these findings must be interpreted in the context of an observational, nonrandomized study. The forthcoming results from the BEST-CLI (best endovascular vs best surgical therapy for patients with critical limb ischemia) trial, a randomized prospective trial comparing bypass and endovascular intervention, will better establish the optimal revascularization strategies for CLTI.<sup>19,20</sup> Irrespective of the findings, it will be critical to examine the effect of the anatomic distribution of disease on the outcomes for patients enrolled in the BEST-CLI trial.

The present study had several limitations. Given the nonrandomized retrospective design of the present study, a risk of selection bias was present because the treating provider determined whether a patient would undergo open bypass or endovascular intervention. In addition, as a single-institutional tertiary referral center, our experience might not be generalizable to a typical vascular surgery practice. Furthermore, given our small group of surgeons with similar training background during the study period, we were not able to further investigate the differences between the various bypass or endovascular techniques, given the limited variability in practice. Finally, the present study evaluated only patients undergoing first-time revascularization and did not provide an evaluation of all comers with CLTI. Future studies evaluating all comers with CLTI using GLASS stages will be important in clarifying the natural history of peripheral vascular disease.

## CONCLUSIONS

The SVS GLASS can be used to predict for reintervention and restenosis in patients undergoing first-time lower extremity revascularization. The severity of inframalleolar and pedal arterial disease is an important indicator for the risk of major amputation and should be factored into the assessment of overall anatomic disease. In our experience, open bypass was associated with a lower risk of RAS compared with endovascular intervention across all GLASS stages.

## AUTHOR CONTRIBUTIONS

Conception and design: PL, CM, JD, DK, VR, ES, MW, AH, MS

Analysis and interpretation: PL, CM, JD, MW, AH, MS

Data collection: PL, CM, JD, DK, VR, ES

Writing the article: PL

Critical revision of the article: PL, CM, JD, DK, VR, ES, MW, AH, MS

Final approval of the article: PL, CM, JD, DK, VR, ES, MW, AH, MS

Statistical analysis: PL

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Overall responsibility: MS

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**Supplementary Table (online only).** Baseline patient characteristics stratified by treatment type

Characteristic	Open bypass (n = 552; 46.8%)	Endovascular (n = 628; 53.2%)	P value
Mean age, years	71.0 ± 12.2	72.3 ± 12.6	.07
Male gender	341 (61.9)	353 (56.2)	.048
White race	446 (80.9)	466 (74.7)	.01
Comorbidities			
Hypertension	452 (82.2)	550 (89.1)	<.001
Diabetes mellitus	408 (73.9)	478 (76.8)	.24
Hyperlipidemia	319 (58.1)	384 (62.5)	.12
Coronary artery disease	292 (53.3)	308 (50.2)	.29
Previous myocardial infarction	155 (28.3)	154 (25.1)	.22
Chronic kidney disease, eGFR < 60 mL/min/1.73 m <sup>2</sup>	319 (58.0)	423 (68.3)	<.001
Dialysis dependence	100 (18.2)	140 (22.8)	.05
Congestive heart failure	162 (29.6)	196 (31.9)	.38
Previous Stroke	70 (14.3)	75 (12.9)	.50
COPD	68 (12.4)	55 (9.0)	.06
Current or previous smoker	361 (65.8)	325 (52.9)	<.001
Mean BMI, kg/m <sup>2</sup>	27.4 ± 6.2	28.0 ± 6.4	.22
Indication for intervention			
Rest pain	86 (15.6)	81 (12.9)	
Ulcer	304 (55.1)	383 (61.0)	
Gangrene	162 (29.3)	164 (26.1)	
Mean Wifl classification score			
Wound	1.5 ± 0.9	1.5 ± 0.8	.85
Ischemia	2.7 ± 0.6	2.6 ± 0.7	.021
Foot infection	0.4 ± 0.7	0.5 ± 0.8	.006
Average	1.4 ± 0.5	1.4 ± 0.5	.042

*BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *Ref*, reference; *Wifl*, wound, ischemia, foot infection.