From the Western Vascular Society

Safety and efficacy of antiplatelet/anticoagulation regimens after Viabahn stent graft treatment for femoropopliteal occlusive disease

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Objective: **We aimed to determine the safety and efficacy of antiplatelet/anticoagulation regimens after placement of Viabahn stent graft (W. L. Gore & Associates, Flagstaff, Ariz) for the treatment of femoropopliteal occlusive disease.**
Methods: **Clinical, angiographic, and procedural data for patients undergoing endovascular treatment of femoropopliteal occlusive disease using Viabahn covered stent grafts at a single institution between 2006 and 2013 were retrospectively reviewed. Graft patency and freedom from thrombolysis, major adverse limb event, and reintervention were determined by Kaplan-Meier analysis. The influence of relevant variables on clinical outcome was determined through univariate and multivariate Cox proportional hazards analyses.**
Results: **Viabahn stent grafts were placed in a total of 91 limbs in 61 patients (66% men; mean age, 69 ± 12 years) during the study period. Indication for intervention was either claudication (n = 59) or critical limb ischemia (n = 32), with the majority (70%) classified as TransAtlantic Inter-Society Consensus II C (n = 33) or D (n = 31) lesions. Mean follow-up was 38.3 months (range, 1-91 months). Postprocedural pharmacologic regimens included aspirin, clopidogrel, and warfarin (47%); indefinite aspirin and clopidogrel (46%); or aspirin and temporary clopidogrel (7%). Primary and secondary patency rates were 60%, 44%, and 36% and 95%, 82%, and 74% at 1 year, 3 years, and 5 years, respectively. Kaplan-Meier analysis demonstrated more aggressive antiplatelet/anticoagulation regimens to be associated with improved primary patency and freedom from reintervention. Cox proportional hazards analysis demonstrated TransAtlantic Inter-Society Consensus II D lesions, tobacco use, coronary artery disease, and smaller stent diameter to be independent risk factors for stent graft failure. Bleeding events were limited to those in the aspirin, clopidogrel, and warfarin group (11.6% [n = 5]; *P* = .052), although the majority of these events were not life-threatening, and only two cases required blood transfusion.**
Conclusions: **Increasingly aggressive antithrombotic regimens after Viabahn stent graft placement trended toward improved overall clinical outcomes, although the marginal patency benefit observed with the addition of warfarin to dual antiplatelet therapy was tempered by an observed increased risk of bleeding complications. Longer term follow-up and multicenter studies are needed to further define optimal type and duration of antithrombotic therapy after endovascular peripheral interventions. (J Vasc Surg 2015;61:1479-88.)**

Expanded polytetrafluoroethylene-covered Viabahn stent grafts (W. L. Gore & Associates, Flagstaff, Ariz) may have multiple potential advantages over bare-metal stents for the treatment of femoropopliteal occlusive disease. From a simple physical standpoint, stent grafts potentially improve technical success by permanently compressing atherosclerotic plaque, intimal injuries, and dissections and also facilitate inhibition of elastic recoil. Covered stent grafts are also noted to prevent tissue infiltration and thereby to hinder local remodeling and neointimal hyperplasia.[1,2] Heparin as a bioactive surface on these stent grafts provides additional thromboresistance and further ameliorates neointimal hyperplasia by a multitude of antiproliferative effects on smooth muscle cells.[3] The prospective, randomized, single-blind, multicenter VIASTAR trial[4] (Viabahn Endoprosthesis with PROPATEN Bioactive Surface [VIA] vs Bare Nitinol Stent in the Treatment of Long Lesions in Superficial Femoral Artery Occlusive Disease) recently demonstrated significant clinical and patency benefits for Viabahn stent grafts compared with bare-metal stents in patients with symptomatic peripheral arterial disease (PAD).

Despite increasing utilization of covered stent grafts in the femoropopliteal distribution, there is lack of consensus regarding the optimal type and duration of antiplatelet/anticoagulation regimen after endovascular treatment of PAD. Prescribing practices of peripheral interventionalists are frequently influenced by Level I data in the cardiology literature, using this as a surrogate for the treatment of

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PAD. Results of recent randomized controlled trials have favored dual antiplatelet therapy with aspirin and clopidogrel over aspirin and systemic anticoagulation with warfarin as the preferred antithrombotic regimen for patients with acute coronary syndromes.[5,6] However, there remains a select group of patients with PAD having indications for both dual antiplatelet therapy and oral anticoagulation because of a history of atrial fibrillation, prosthetic heart valves, arterial or venous thromboembolism, or other medical conditions. In this study, we aimed to explore the safety and efficacy of Viabahn stent graft placement for the treatment of femoropopliteal occlusive disease using three common antiplatelet/anticoagulation regimens.

METHODS

Study design

A retrospective chart and imaging review of a consecutive cohort of patients treated with Viabahn stent grafts for femoropopliteal occlusive disease at a single institution from 2006 to 2013 was performed. The study was approved by our local Institutional Review Board, but given the retrospective nature, informed consent was not obtained from each patient. Only patients with symptomatic PAD (Rutherford clinical stage 2 to 6, corresponding to moderate to severe claudication and critical limb ischemia) characterized by de novo atherosclerotic stenosis or occlusion of the superficial femoral artery (SFA) or proximal popliteal artery were included for analysis. All patients had patent or successfully treated aortoiliac inflow and a minimum of one tibial vessel runoff. Patients with a history of previous ipsilateral infrainguinal open bypass or stenting or those presenting with acute limb ischemia, regardless of etiology (ie, trauma, aneurysm, embolus), were excluded.

Medical charts were queried to identify and record patient demographics, cardiovascular risk factors, clinical characteristics, procedural details, and hospital course. Angiograms from the index procedure were reviewed for anatomic and device-related details, and postoperative duplex surveillance images were reviewed.

Femoropopliteal intervention

Percutaneous access was obtained through a contralateral or antegrade femoral arterial approach under local anesthesia. Determination of hemodynamically significant lesions was made on the basis of the angiographic appearance of the vessel in combination with available preoperative noninvasive imaging studies. After confirmation of hemodynamically significant atherosclerotic disease in the femoropopliteal distribution, systemic heparin (100 units/kg) was administered to achieve an activated clotting time of >250 seconds. Through a 6F or 7F Pinnacle destination sheath (Terumo, Leuven, Belgium), atherosclerotic lesions were typically crossed with a 0.035-inch or 0.018-inch hydrophilic wire (Glidewire, Terumo) and support catheter (CXI; Cook Medical, Bloomington, Ind). Subintimal recanalization was performed, if necessary. Balloon angioplasty was performed with 4- to 7-mm-diameter balloons of varying lengths. Lesions with significant recoil, >30% residual stenosis, or dissection flaps compromising flow constituted failure of initial balloon angioplasty and prompted consideration of stent graft deployment. Stent diameter and length were determined by preintervention cross-sectional imaging or angiographic measurements. No stent grafts were placed across the knee joint. Each stent graft was deployed according to the manufacturer's instructions for use and postdilated to implant size. Post-balloon dilation was confined to the area within the covered stent graft. Patients were generally discharged after 23-hour observation.

Procedural characteristics and definitions

Lesion characteristics. TransAtlantic Inter-Society Consensus (TASC) II definitions[7] were applied on the basis of findings of the initial diagnostic arteriogram. Runoff was assessed by recording the number of patent or minimally diseased (<50% stenosis) infrapopliteal arteries present in the ipsilateral lower extremity. Review of angiographic images and classification of arterial lesions were performed by one of the authors (N.I.) qualified to interpret peripheral angiography.

Stent grafts. Location of stent graft implantation was the SFA or proximal popliteal artery. In September 2007, our inventory was updated to the heparin-bonded Viabahn stent graft. The number, length, and diameter of implanted stent grafts were recorded. Total length of implanted stent graft reflected the aggregate length of the individual devices and did not take into account stent graft overlap.

Clinical events. Loss of primary patency, or stent graft failure, was defined as the development of significant restenosis (peak systolic velocity ratio >2 or peak systolic velocity >300 cm/s) or occlusion of the treated arterial segment. Any subsequent infrainguinal open or endovascular procedure on the index lower extremity was deemed a reintervention. Major amputation included any amputation at the level of the ankle or above. Bypass was defined as any open autogenous or prosthetic infrainguinal or infrapopliteal bypass procedure. Thrombolysis included either catheter-directed percutaneous pharmacomechanical or open thrombectomy. In accordance with more recent reports and adherence to reporting guidelines,[8] major adverse limb event (MALE) was defined as the composite of thrombolysis, bypass procedure, or major amputation.

Clinical end points. Primary end points included primary, primary assisted, and secondary patency rates. Primary patency was defined as uninterrupted freedom from significant restenosis or occlusion within the treated vessel based on follow-up color duplex ultrasound. Primary assisted patency was defined as patency of the target lesion maintained by repeated intervention in an attempt to salvage the stent graft before significant restenosis or occlusion of the treated arterial segment. Secondary patency was defined as reintervention yielding restored graft patency after significant restenosis or occlusion of the treated arterial segment. Secondary end points included MALE, need for thrombolysis, need for reintervention, and

Table I. Patient characteristics of overall cohort and for each treated limb, stratified by drug regimen

Characteristic	*Overall cohort (N = 61), No. (%)*	*Treated limbs (N = 91)*			P[a]	P[b]
		Regimen A (n = 6), No. (%)	*Regimen B (n = 42), No. (%)*	*Regimen C (n = 43), No. (%)*		
Demographics						
Age, years, mean ± SD	69.1 ± 12.1	67.2 ± 12.8	72.9 ± 11.5	69.0 ± 8.9	.01	.10
Gender, male	40 (66)	2 (33)	33 (79)	22 (51)	.01	.01
Comorbidities						
Coronary artery disease	24 (39)	1 (17)	19 (45)	19 (44)	.41	1.0
Hypertension	50 (82)	5 (83)	36 (86)	26 (84)	.96	1.0
Diabetes mellitus	21 (34)	1 (17)	14 (33)	17 (40)	.52	.65
Renal insufficiency[c]	11 (18)	1 (17)	9 (21)	5 (12)	.48	.26
Tobacco use	19 (31)	2 (33)	9 (21)	17 (40)	.19	.10
Dyslipidemia	44 (72)	4 (67)	35 (83)	34 (79)	.61	.78
Statin use	75 (82)	4 (67)	38 (90)	33 (77)	.10	.08

SD, Standard deviation.
Regimen A: aspirin and temporary clopidogrel; regimen B: indefinite dual antiplatelet therapy (aspirin and clopidogrel); regimen C: indefinite triple therapy (dual antiplatelet and warfarin).
[a] *P* value comparing drug regimen A vs B vs C.
[b] *P* value comparing drug regimen B vs C.
[c] Defined as serum creatinine concentration ≥1.5 mg/dL.

bleeding complications. The incidence and severity of bleeding complications were recorded and classified as life-threatening, moderate, or minor on the basis of similar definitions used in previous reports.[9,10]

Antiplatelet/anticoagulation regimens

After the procedure, all patients were treated with dual antiplatelet therapy consisting of aspirin (81 mg/d) and clopidogrel (300 mg loading dose followed by 75 mg/d) unless specifically contraindicated. Dual antiplatelet therapy was intended to be indefinite on the basis of the surgeon's preference (J.T.L.). Patients with nonsevere hemorrhagic complications or complaints of easy bruising during the early follow-up period discontinued the use of clopidogrel after completing a 6-week course but remained on aspirin indefinitely. Those with severe hemorrhagic complications promptly discontinued clopidogrel. In case of associated medical comorbidities requiring oral anticoagulation, warfarin was added to the dual antiplatelet therapy. Select patients were initiated on warfarin after peripheral vascular intervention at the surgeon's discretion. As such, patients were maintained on one of three medication regimens in the postprocedural setting: regimen A, aspirin plus a temporary 6-week course of clopidogrel; regimen B, indefinite dual antiplatelet therapy; or regimen C, triple therapy (indefinite dual antiplatelet therapy plus warfarin [target international normalized ratio (INR), 2.0-3.0]).

Follow-up

Clinical assessment with color duplex ultrasound and resting ankle-brachial index (ABI) measurements was recommended at 1 month, 3 months, and 6 months, then annually thereafter. Compliance with the antiplatelet/anticoagulation regimen was assessed at each office visit and managed by the patient's primary care physician or cardiologist. In cases of restenosis or occlusion, repeated angiography was performed.

Statistical analyses

Descriptive statistics were used to assess study demographics, comorbidities, and outcomes variables as appropriate. Univariate predictors were calculated by Wilcoxon rank sum test and Pearson χ^2 test for continuous and categorical variables, respectively. Outcome event rates were estimated by Kaplan-Meier methods. Log-rank tests were applied to assess differences in event-free survival. Univariate Cox proportional hazards models were constructed to identify possible predictors of event-free survival. Univariate associations with $P < .10$ were subsequently analyzed within a multivariate model. A $P < .05$ was considered statistically significant for all analyses. All calculations were performed in Stata 12.0 (StataCorp LP, College Station, Tex).

RESULTS

Patient characteristics

During the study period, 91 limbs in 61 patients were treated with Viabahn stent grafts for femoropopliteal occlusive disease. Whereas there was no difference in the comorbid status between drug regimen groups, patients taking regimen A were noted to be slightly younger and had a smaller proportion of men (Table I). Previous open or endovascular peripheral interventions occurred in 21 patients (34%), including 6 patients (10%) with prior inflow, 14 patients (23%) with prior outflow, and 1 patient (2%) with both prior inflow and outflow procedures (Table II). Prior inflow or outflow procedures had no significant relationships to any primary or secondary end points.

After Viabahn stent graft placement, 48 patients were discharged on dual antiplatelet therapy and 43 were discharged on triple therapy with indefinite aspirin, clopidogrel, and warfarin. During the early follow-up period, six

Table II. Previous open and endovascular peripheral interventions

Type of procedure	*No. of patients*
Inflow	
Iliac angioplasty/stenting	3
Femoral endarterectomy	3
Aortobifemoral bypass	1
Outflow	
Tibial angioplasty	3
SFA atherectomy	5
SFA angioplasty	7

SFA, Superficial femoral artery.

patients ultimately discontinued clopidogrel because of easy bruising after completing a 6-week course of dual antiplatelet therapy. Postprocedural drug regimens included 6 patients in regimen A, 42 patients in regimen B, and 43 patients in regimen C. Five patients discontinued warfarin (gastrointestinal bleeding, n = 2; switch to different form of oral anticoagulant, n = 3) during the study period. All patients in regimen B and regimen C remained on indefinite dual antiplatelet therapy.

Anatomic and device-related characteristics

Review of angiographic studies indicated that the majority of femoropopliteal occlusive lesions were either TASC II C (36%) or D (34%). The number of patent or minimally diseased infrapopliteal runoff arteries varied widely across limbs, with 32%, 38%, and 30% having one, two, or three adequate runoff vessels, respectively. In total, 188 Viabahn stent grafts were implanted in the 91 limbs. The median number of stent grafts used per limb was two (range, 1-4). The median summed length of stent graft coverage in the femoropopliteal arterial distribution was 250 mm (range, 50-600 mm). Non-heparin-bonded stent grafts were deployed in 16 limbs (18%), most commonly in regimen B (11 grafts; 26%). The minimum stent graft diameter used was 5 mm in 20 limbs (22%), 6 mm in 70 limbs (77%), and 7 mm in 1 limb (1%). Technical success was 100%. There were no stent graft deployment failures. TASC II classification, number of runoff arteries, minimum stent graft size, number of stent grafts used, and summed length of stent graft coverage were not significantly different on the basis of the drug regimen (Table III).

Clinical results

The mean preintervention and postintervention ABIs were 0.59 and 0.91 (mean change, 0.32; $P < .0001$). Whereas no patients were lost to follow-up, 26 (42%) of the 61 patients had incomplete follow-up. In total, 46 (75%), 39 (63%), and 37 (60%) patients received at least 1 year, 2 years, and 3 years of follow-up. At a median follow-up period of 36.2 months (range, 1-91 months), loss of primary patency occurred in 48 (53%) of the 91 treated limbs as a result of stent graft failure (>50% in-stent restenosis, n = 17; occlusion, n = 31). Primary and primary assisted patency at longest follow-up were 47% and 71%, respectively. Median time to stent failure was 15.9 months (range, 0.70-50.0 months). Four occlusions and zero restenoses occurred early within 30 days of the procedure. Procedure indication did not significantly affect the risk of future MALEs (Table IV).

Reintervention occurred in 96% of cases involving stent graft failure. Two limbs (4%) with occluded stent grafts did not undergo any revascularization attempt as they were diagnosed incidentally on surveillance duplex ultrasound and were not associated with a significant decline in ABI or recurrence of symptoms. Twenty-four of the 31 occlusions underwent successful thrombolysis with return of stent graft patency. Open lower extremity bypass procedures were performed in 12 limbs (13.2%) during the follow-up period, including 8 procedures performed as primary treatment for initial stent graft occlusion or restenosis and 4 additional procedures performed following a second episode of stent graft failure after previous successful thrombolysis. Major amputation was required in seven limbs (7.7%). Primary amputation occurred in one limb after stent graft failure, whereas the remaining six amputations occurred after previous thrombolysis (n = 3) or bypass procedures (n = 4). The majority (five of seven) of these limbs requiring amputation initially presented with critical limb ischemia. There were no major perioperative complications or deaths in the cohort.

Clinical end points

Stent graft patency. Primary patency by Kaplan-Meier analysis was 89%, 77%, 60%, 44%, and 36% at 3 months, 6 months, 1 year, 3 years, and 5 years, respectively (Fig 1). There was a significant difference in primary patency in comparing the three drug regimens (Fig 2, *A*; log-rank, $P = .03$); however, the primary patency of drug regimen B and regimen C was not significantly different (log-rank, $P = .27$). A Cox proportional hazards model demonstrated TASC II D lesions (hazard ratio [HR], 2.7) and drug regimen (HR, 0.56) as independent significant factors affecting primary patency rates. Of note, whereas use of heparin-bonded stent grafts was associated with lower loss of patency rates in univariate analysis, this association was not significant within a multivariate model (Table V). Secondary patency rates were 97%, 97%, 95%, 82%, and 74% at 3 months, 6 months, 1 year, 3 years, and 5 years, respectively. There was no difference in secondary patency between the three drug regimens. In cases involving significant restenosis, both focal "edge" and diffuse in-stent restenosis were observed with roughly equal frequency.

MALE. The composite of thrombolysis, bypass procedure, or major amputation occurred in 33 limbs (36%). Freedom from MALE was 89%, 83%, 72%, 59%, and 56% at 3 months, 6 months, 1 year, 3 years, and 5 years, respectively (Fig 1, *B*). No difference in MALE was identified between the three drug regimens (Fig 2, *B*). Coronary artery disease (HR, 2.2) and tobacco use (HR, 2.9) were the only identified independent factors that increased the risk for development of MALE over time.

Table III. Anatomic and procedural characteristics for each treated limb (N = 91), stratified by drug regimen

Procedural variable	*Regimen A (n = 6), No. (%)*	*Regimen B (n = 42), No. (%)*	*Regimen C (n = 43), No. (%)*	*All (N = 91), No. (%)*	P[a]	P[b]
Indication					.02	.35
Claudication	1 (17)	31 (74)	27 (63)	59 (65)		
Critical limb ischemia	5 (83)	11 (26)	16 (37)	32 (35)		
TASC II classification					.45	.21
A	0 (0)	5 (12)	1 (2)	6 (7)		
B	1 (17)	7 (17)	13 (30)	21 (23)		
C	2 (33)	16 (38)	15 (35)	33 (36)		
D	3 (50)	14 (33)	14 (33)	31 (34)		
Number of infrapopliteal runoff arteries					.42	.72
1	2 (33)	13 (31)	14 (33)	29 (32)		
2	4 (67)	17 (40)	14 (33)	35 (38)		
3	0 (0)	12 (29)	15 (35)	27 (30)		
Minimum stent graft size, mm					.40	.17
5	2 (33)	12 (29)	6 (14)	20 (22)		
6	4 (67)	30 (71)	36 (84)	70 (77)		
7	0 (0)	0 (0)	1 (2)	1 (1)		
No. of stent grafts					.42	.29
1	1 (17)	17 (40)	10 (23)	28 (31)		
2	4 (67)	14 (33)	18 (42)	35 (38)		
3	1 (17)	7 (17)	12 (28)	20 (22)		
4	0 (0)	4 (10)	3 (7)	7 (8)		
Non-heparin-bonded grafts	1 (17)	11 (26)	4 (9)	16 (18)	.09	.04
Mean (±SD) summed length stent graft coverage, mm	250 ± 114	242 ± 149	270 ± 136	255 ± 140	.78	.37
Total length covered <200 mm	2 (33)	17 (40)	12 (28)	31 (34)	.47	.26

SD, Standard deviation; *TASC,* TransAtlantic Inter-Society Consensus.
Regimen A: aspirin and temporary clopidogrel; regimen B: indefinite dual antiplatelet therapy (aspirin and clopidogrel); regimen C: indefinite triple therapy (dual antiplatelet and warfarin).
[a] *P* value comparing drug regimen A vs B vs C.
[b] *P* value comparing drug regimen B vs C.

Thrombolysis. Freedom from thrombolysis was 90%, 87%, 78%, 70%, and 67% at 3 months, 6 months, 1 year, 3 years, and 5 years, respectively. There was no difference in the need for thrombolysis when stratified by drug regimens (Fig 2, *C*). Demographics, indication for intervention, lesion characteristics, arterial runoff, and stent size had no significant influence on thrombolysis rates.

Reintervention. Freedom from reintervention of any type was 89%, 79%, 54%, 43%, and 36% at 3 months, 6 months, 1 year, 3 years, and 5 years, respectively. There was a significant difference in the need for reintervention across the three drug regimens (log-rank, $P = .002$); however, the need for reintervention between drug regimens B and C was not significantly different (log-rank, $P = .28$; Fig 2, *D*). In a multivariate model, prior use of statins (HR, 3.2), smaller stent diameters (HR, 2.8), TASC II D lesions (HR, 3.4), and drug regimen (HR, 0.58) significantly influenced reintervention rates during the study period.

Bleeding complications. Bleeding events occurred in 0%, 0%, and 11.6% of patients in regimens A, B, and C, respectively ($P = .052$). In total, five patients, all of whom were taking drug regimen C, experienced some form of bleeding event at a median of 334 days (range, 2-870 days) after the procedure. Three episodes were classified as minor, including two cases that involved early readmission within 4 days of the index procedure. These two cases involved conservative management of mild bleeding from the puncture site in one patient and successful compression therapy for a femoral artery pseudoaneurysm in the other. Both patients had INR levels within therapeutic range, and neither required transfusion. The remaining mild bleeding episode involved a patient with recurrent episodes of self-limited epistaxis that increased in frequency nearly 20 months after the procedure. She discontinued warfarin and continued on dual antiplatelet therapy with full resolution of epistaxis. There was one moderate bleeding episode involving a patient presenting 29 months after the index procedure with hematemesis. Endoscopy demonstrated diffuse gastritis, and he was treated successfully with medical therapy and a total of 2 units of blood transfusion. Last, there was one life-threatening bleeding complication presenting as a lower gastrointestinal hemorrhage 11 months after the index procedure in the setting of a supratherapeutic INR level of 5.9. The patient underwent successful colonoscopic electrocautery and received 4 units of blood transfusion.

DISCUSSION

Despite a lack of definitive evidence or established practice guidelines, the use of antiplatelet therapy and anticoagulation after endovascular peripheral interventions is a common clinical practice. Allemang et al[11] recently surveyed a group of 51 vascular surgeons at a national meeting and noted significant variability in the prescribing practices

Table IV. Primary and secondary outcomes by indication

Indication	*Loss of patency, No. (%)*	*MALE, No. (%)*	*Thrombolysis, No. (%)*	*Reintervention, No. (%)*
Claudication (n = 59)	29 (49)	18 (31)	15 (25)	27 (46)
Critical limb ischemia (n = 32)	19 (59)	15 (47)	9 (28)	20 (63)
P value	.39	.17	.81	.19

MALE, Major adverse limb event.

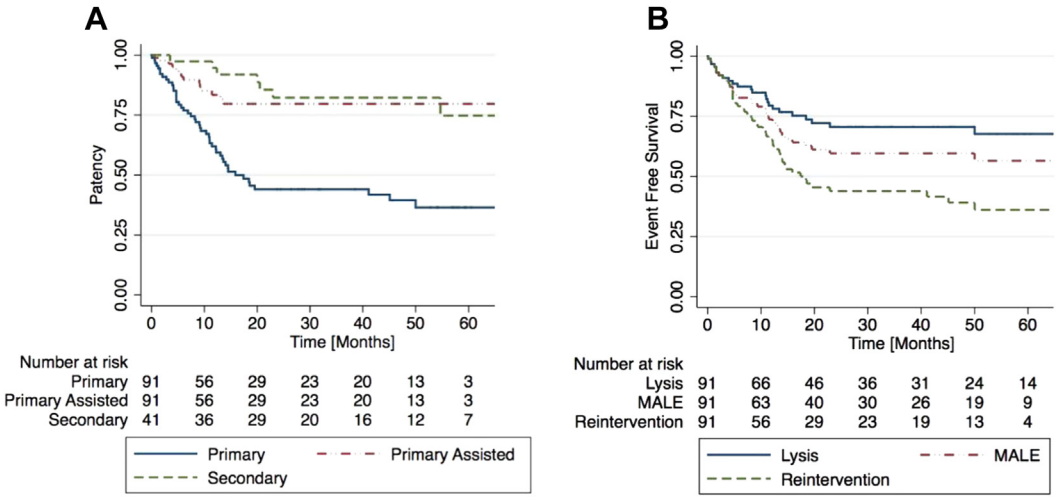

Fig 1. Kaplan-Meier time-to-event plots of the overall cohort (N = 91) for freedom from primary **(A)** and secondary **(B)** end points. *MALE,* Major adverse limb event.

of antiplatelet/anticoagulation agents after various lower extremity endovascular procedures. The majority of those surveyed reported the use of postprocedural dual antiplatelet therapy regardless of intervention type. After placement of an infrainguinal covered stent, 74% of respondents prescribed dual antiplatelet therapy, 9% aspirin alone, and 9% clopidogrel alone. Three respondents (2%) prescribed warfarin alone or in combination with antiplatelet agents. Notably, there was no clear consensus on the length of appropriate treatment for any procedure type.

The present study represents one of the largest series with covered stent grafts and is the only report to date examining the clinical outcomes of Viabahn stent grafts for the treatment of femoropopliteal occlusive disease stratified by postprocedural drug regimen. Despite no significant differences in overall patient, anatomic, or procedural characteristics, the 1-year primary patency was 33% higher (20% vs 53%) in regimen B relative to regimen A and 50% higher (20% vs 70%) in regimen C relative to regimen A. In addition, regimen A was associated with increased need for reinterventions over time compared with the other two drug regimens.

In the VIASTAR trial,[4] patients were treated with 100 mg of aspirin daily and at least 6 months of clopidogrel after intervention. The treatment per protocol analysis revealed 1-year primary and secondary patency rates for Viabahn stent grafts of 78% and 90%, respectively. The primary patency of 60% observed in our overall cohort was considerably lower, with only regimen C being able to more closely approximate this figure with a primary patency of 70%. In the VIBRANT trial (Viabahn vs Bare Nitinol Stent),[12] 148 patients with symptomatic complex lesions involving the SFA were randomly assigned to treatment with either the Viabahn stent graft or bare-metal stent. Postprocedural medical treatment included a minimum of 6 months of dual antiplatelet therapy. Midterm results were recently published and showed similarly low primary patency rates at the 3-year trial end point (24.2% for Viabahn and 25.9% for bare-metal stents). Despite the poor primary patency, 3-year primary assisted and secondary patency rates were 70% and 80%, respectively. These results reflect those from a select group of patients with complex SFA disease (all TASC C or D) using the non-heparin-bonded Viabahn stent graft, which included 61% of cases involving SFA occlusions and a mean lesion length of 19 cm.

Comparative analysis of clinical outcomes across multiple other studies[4,12-17] is greatly limited by the aforementioned heterogeneity in the type and duration of periprocedural antiplatelet/anticoagulation therapy as well as by the wide variability in lesion characteristics, patient demographics, concomitant inflow/outflow occlusive disease, and evolution in stent graft technology during the course of the study periods. Those limitations notwithstanding, primary patency in our single-institution series of Viabahn stent grafts mostly approached or slightly exceeded that observed in other reports, and our secondary

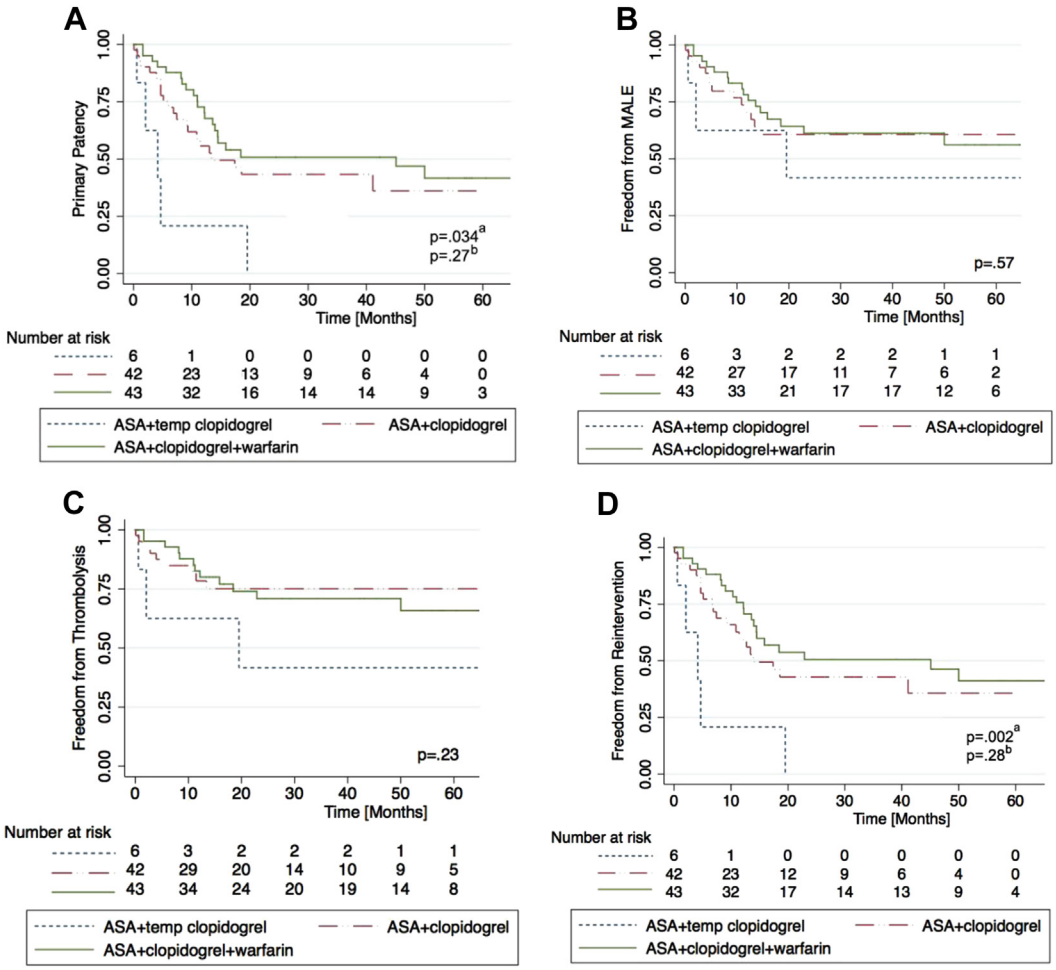

Fig 2. Kaplan-Meier time-to-event plots stratified by drug regimen for freedom from loss of patency **(A)**, major adverse limb event (*MALE*, **B**), thrombolysis **(C)**, and reintervention **(D)**. Unless otherwise indicated, log-rank *P* value corresponds to comparison between all three drug regimen groups. **A** and **D**, [a]Regimen A vs B vs C; [b]Regimen B vs C. *ASA*, Aspirin.

patency was greater at nearly every time point compared with other reports, particularly among those in our cohort with more aggressive drug regimens. Although our data are limited by a small number of patients in drug regimen A, there was a nonsignificant trend toward improved primary and secondary patency across drug regimen groups.

Details about additional clinical outcomes and reinterventions after Viabahn stent graft placement are not consistently reported but are in line with our results. In a retrospective review of 87 limbs in 77 patients treated with Viabahn stent grafts and indefinite dual antiplatelet therapy, Johnston et al[16] recorded 26 primary reinterventions, including 7 angioplasty or stenting procedures, 5 with placement of additional Viabahn stent grafts, 7 thrombolysis procedures, 1 thrombectomy, and 6 open bypass procedures. There was a total of 20 MALEs in 18 limbs in their series. Freedom from reintervention, MALE, and thrombolysis at 1 year was 57%, 72%, and 83%, respectively. Our results similarly note that reintervention is commonly required after Viabahn stent placement and included a 36% incidence of MALE in our experience. Freedom from reintervention, MALE, and thrombolysis in our series compares favorably to that reported by Johnson et al and, similar to patency, demonstrates a trend toward improved results with more aggressive anticoagulation regimens B and C.

The selection of an appropriate drug regimen after endovascular treatment of PAD and its duration is one of clinical judgment based on the physician's perceived balance between the individual patient's risk for thromboembolic events and atherosclerotic disease progression, the presence of a concomitant indication for anticoagulation, and the patient's risk for bleeding complications. In the only randomized trial reported to date, the Warfarin Antiplatelet Vascular Evaluation (WAVE) investigators[10] sought to determine whether triple antithrombotic therapy was superior to dual antiplatelet therapy in patients with PAD and either acute coronary syndrome or intracoronary stent placement. No significant difference was observed across any clinical end points, including severe ischemia of the peripheral or coronary arteries; however, a significant increase

Table V. Univariate and multivariate Cox proportional hazards models for clinical outcomes

		Characteristic	*HR*	*95% CI*	P *value*
Primary patency	Univariate associations	CAD	1.71	0.96-3.02	.0641
		Statin use	2.95	1.06-8.24	.038
		Runoff	0.670	0.46-0.97	.033
		Stent <6 mm	2.43	1.30-4.56	.008
		TASC D	2.12	1.20-3.77	.011
		Drug regimen	0.557	0.34-0.91	.020
		Heparin	0.504	0.26-0.97	.042
	Multivariate model	CAD	1.50	0.81-2.76	.190
		Statin use	2.80	0.92-8.52	.069
		Runoff	0.94	0.62-1.43	.778
		Stent <6 mm	2.47	0.94-6.52	.067
		TASC D	2.70	1.31-5.55	.007
		Drug regimen	0.56	0.33-0.935	.027
		Heparin	1.93	0.64-5.74	.236
MALE	Univariate associations	CAD	1.86	0.93-3.72	.078
		Tobacco	2.28	1.14-4.57	.019
		CRI	0.289	0.07-1.21	.089
		Indication	1.95	0.98-3.89	.057
		Runoff	0.626	0.40-0.98	.042
		Stent <6 mm	1.90	0.90-4.02	.091
		TASC D	2.13	1.07-4.25	.030
	Multivariate model	CAD	2.17	1.05-4.44	.035
		Tobacco	2.89	1.31-6.32	.008
		CRI	0.31	0.06-1.35	.118
		Indication	1.89	0.79-4.48	.148
		Runoff	0.68	0.40-1.13	.140
		Stent <6 mm	1.30	0.57-2.98	.530
		TASC D	1.53	0.67-3.47	.312
Thrombolysis	Univariate associations	Tobacco	2.06	0.92-4.67	.080
	Multivariate model	—	—	—	—
Reintervention	Univariate associations	Statin use	2.85	1.02-7.96	.045
		Indication	2.07	1.15-3.72	.015
		Runoff	0.69	0.48-1.0	.050
		Stent <6 mm	2.29	1.20-4.35	.011
		TASC D	2.40	1.35-4.29	.003
		Drug regimen	0.55	0.34-0.89	.016
		Heparin	0.55	0.28-1.09	.09
	Multivariate model	Statin use	3.24	1.11-9.38	.030
		Indication	1.17	0.58-2.37	.650
		Runoff	0.99	0.63-1.53	.965
		Stent <6 mm	2.85	1.08-7.49	.033
		TASC D	3.37	1.55-7.29	.002
		Drug regimen	0.58	0.34-0.97	.038
		Heparin	2.73	0.92-8.11	.069

CAD, Coronary artery disease; *CI,* confidence interval; *CRI,* chronic renal insufficiency; *HR,* hazard ratio; *MALE,* major adverse limb event; *TASC,* TransAtlantic Inter-Society Consensus.
Only univariate associations with a $P < .10$ are reported.

in the risk of life-threatening hemorrhage in patients randomized to triple antithrombotic therapy was observed (4.0% vs 1.2%). Similarly, bleeding events in our study were confined to the subgroup of patients taking triple therapy, although the majority of these events were not life-threatening and only two cases required blood transfusion.

Additional comparative information can be gathered from select studies investigating the efficacy of antithrombotic regimens after peripheral bypass surgery. In a randomized prospective study, Monaco et al[9] examined outcomes in patients undergoing bypass procedures using prosthetic conduits for above-knee bypasses and autogenous vein conduits for below-knee bypasses. Combination therapy with clopidogrel plus warfarin resulted in significantly higher 3-year, 5-year, and 8-year patency rates compared with dual antiplatelet therapy alone (86.7% vs 80.8%, 77.3% vs 63.3%, and 44.4% vs 30.4%, respectively; $P = .026$). However, this patency benefit was achieved at the expense of increased minor bleeding complications (2.9% vs 1.4% patient-years; $P = .03$). In a separate analysis, Suckow et al[18] compared graft patency, limb salvage, and antithrombotic therapy in a propensity-matched cohort undergoing prosthetic and autogenous below-knee bypass for critical limb ischemia. Overall 1-year prosthetic graft patency was noted to vary from 51% (aspirin plus clopidogrel) to 78% (aspirin plus warfarin), but no significant

differences were noted in primary patency or major amputation rates by antithrombotic regimen. Neither bleeding complications nor 1-year mortality differed by either conduit type or antithrombotic regimen.

The present study has several important limitations. These include its retrospective nature and modest size, evolution of stent graft technology during the study period, and variable compliance with postoperative follow-up, surveillance ultrasound, and antiplatelet/anticoagulation regimen. Lesion length was not calculated in this series because of the infrequent use of angiographic distance markers. Similar to that used in a previous report,[16] total summed length of stent graft coverage was used as a surrogate for both disease severity and intraoperative decision-making, which commonly differs from the length of the occlusive or stenotic lesion. In addition, our analysis does not take into account additional anatomic factors that may significantly affect clinical outcome, such as presence of collaterals, frequency of collateral coverage, presence of occlusion, presence and degree of lesion calcification, and target vessel diameter. Determination of the efficacy of triple therapy is also limited by lack of laboratory information (eg, INR) at the time of stent graft failure.

CONCLUSIONS

Our data demonstrate that select patients with indications for both dual antiplatelet therapy and anticoagulation who undergo endovascular treatment of femoropopliteal occlusive disease with Viabahn stent grafts achieve outcomes that trend toward a nonsignificant patency benefit compared with those taking indefinite dual antiplatelet therapy and significantly improved outcomes relative to those taking temporary (6 weeks) dual antiplatelet therapy. We have moved toward recommending lifelong dual antiplatelet therapy after these peripheral interventions. For those already receiving warfarin for other reasons, we assess the individual patient's risk/benefit profile before introduction of triple therapy. Careful consideration must be given to those with indications for both dual antiplatelet therapy and anticoagulation, given that triple therapy is associated with increased risk for bleeding complications, albeit mostly mild in severity. Longer term follow-up and potential multicenter randomized clinical trials are needed to further define optimal antithrombotic therapy and treatment length after endovascular peripheral interventions to better elucidate much needed evidence-based practice guidelines.

AUTHOR CONTRIBUTIONS

Conception and design: BU, KT, NI, KC, RD, JL
Analysis and interpretation: BU, KT, NI
Data collection: BU, KT, NI
Writing the article: BU, KT
Critical revision of the article: BU, KT, NI, KC, RD, JL
Final approval of the article: BU, KT, NI, KC, RD, JL
Statistical analysis: KT
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Overall responsibility: JL

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DISCUSSION

Dr Joseph L. Mills Sr (*Seattle, Wash*). I have the following questions for the authors:

1. In this well presented series from the Stanford group, 91 limbs in 61 patients were treated with Viabahn covered stent grafts and in 65% of the limbs (59), the indication for intervention was claudication. Given this distribution of indications, it is sobering that the median time to stent failure was 15.9 months and primary patency at 3 years for the entire group was only 44%. There were seven limbs amputated during follow-up and it is also sobering to learn that two of these patients were treated initially for claudication. Given these less than stellar results, have your indications for placing covered stents for TransAtlantic Inter-Society Consensus (TASC) C and D lesions changed?
2. Previous work by our group presented by Daniel Ihnat at this meeting and by others elsewhere suggests that runoff strongly influences outcomes after superficial femoral artery (SFA) stenting and that runoff suffers after stent occlusion (both for bare metal and covered). Did you analyze patency versus SVS runoff score and did you examine the runoff in patients I whom you had to reintervene?
3. With regard to optimal antiplatelet therapy, the limitations of the study relate to lack of randomization, small sample size (patient n = 61) and event frequency.
4. So, the final question: How can we select patients at highest risk for stent complications in whom this increased bleeding risk might be acceptable?

Dr Brant W. Ullery. To answer your questions:

1. Long-term patency for percutaneous revascularization in the SFA distribution remains a rather sobering field in general. Indeed, SFA revascularization remains one of the most active areas of research and we are optimistic that better results are on the horizon with the newly developing drug eluting balloon technology. Regarding the current results, we found no difference in any of the primary outcomes, including major adverse limb events, loss of patency, or need for reintervention, based on indication (claudication vs. critical limb ischemia). Given this lack of apparent difference in outcomes between groups, as well as the significant baseline comorbid burden in those with TASC C and D lesions, we have not at this time chanced our indications for placing Viabahn stent grafts.
2. In our study, runoff was assessed by recording the number of patent or minimally diseased (<50% stenosis) infrapopliteal arteries in the ipsilateral lower extremity. We noted relatively equal distribution regarding number of runoff vessels, with 32%, 38%, and 30% having one, two, or three adequate runoff vessels, respectively. While the SVS runoff score certainly represents a more rigorous evaluation of runoff, patency and need for thrombolysis did not vary based on number of runoff vessels in our analysis.
3. In large series, bleeding is a significant risk of dual antiplatelet therapy. For example in asymptomatic peripheral arterial disease patients, while the CHARISMA trial did demonstrate a modest reduction in subsequent thrombotic events in a subset analysis of patients with stable, pre-existing vascular disease, the bottom line was that dual antiplatelet therapy was associated with a 4% risk of moderate to severe bleeding and that there were strong correlations between moderate bleeding and all-cause mortality (hazard ratio [HR], 2.55), myocardial infarction (HR, 2.92) and stroke (HR, 4.25). The bleeding risk of dual antiplatelet therapy thus seems to outweigh the benefits.
4. This represents perhaps the most important questions of all. As you note, multiple trials have demonstrated reduction in thrombotic events but at the expense of variable risk for concomitant bleeding events. Subgroup analysis in the CASPAR trial suggests that clopidogrel plus ASA confers benefit in patients receiving prosthetic grafts without significantly increasing major bleeding risk. When it comes to selecting patients for appropriate antithrombotic regimens, clearly those with additional indications for anticoagulation/antiplatelet therapy (eg, mechanical value, atrial fibrillation, deep vein thrombosis/pulmonary embolism) have a risk/benefit ration favoring the use of a more aggressive regimen. For the remainder, however, this is obviously less clear. We believe those with more extensive disease (TASC C and D), limited arterial runoff, or a history of prior arterial thrombotic event represents a good starting point in the identification of patients at high risk for stent failure and where the possible increased risk for bleeding events may be justified.