Impact of anticoagulation/antiplatelet therapy on femoropopliteal bypass graft outcomes

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ABSTRACT

Background: Anticoagulant and antiplatelet (AC/AP) medications have been reported to improve bypass graft patency, however, the optimal AC/AP strategy remains unclear in the heterogenous peripheral artery disease population.

Methods: A multi-institutional retrospective review utilizing the Research Patient Data Registry database from 1995 to 2020 was performed for all patients who underwent femoropopliteal bypass procedures. Electronic medical records were used to obtain demographic information, comorbidities, smoking status, operative details (bypass target), postoperative AC/AP medications, postoperative complications, and long-term outcomes and were reviewed for the cohort. Cox proportional hazards model was used to determine independent risk factors for major adverse limb events (MALE) after bypass. MALE was defined as reintervention for patency or major amputation of index limb (above- or below-knee amputation).

Results: A total of 1421 patients underwent femoropopliteal bypass between 1995 and 2020 throughout five institutions included in this study. Complete data were available for 1292 of the 1421 patients (90.9%). The indications for bypass included intermittent claudication (21.4%), rest pain (30.3%), tissue loss (33.5%), and nonatherosclerotic disease (14.8%). Distal bypass targets comprised above-knee (38.6%) and below-knee (61.4%) popliteal arteries. Patients were divided into six groups based on postoperative AC/AP use including none (n = 57 [4.4%]), monoantiplatelet therapy (n = 587 [45.4%]), dual AP therapy (n = 214 [16.6%]), AC alone (n = 73 [5.7%]), AC + monoantiplatelet therapy (n = 319 [24.7%]), and AC + dual AP therapy (n = 42 [3.3%]). Postoperative bleeding complications were low for both hematoma (3.7%) and pseudoaneurysm (0.7%). There was no difference in bleeding complications across AC/AP groups (hematoma, $P = .61$; pseudoaneurysm, $P = .31$). After adjusting for patient factors, below-knee bypass target (hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.04-1.52; $P = .019$) and bypass for tissue loss (HR, 1.40; 95% CI, 1.04-1.88; $P = .028$) were independent predictors for MALE. Great saphenous vein conduit trended toward protection for MALE, compared with prosthetic grafts (HR, 0.84; 95% CI, 0.70-1.01; $P = .06$). No AC/AP regimen was associated with of MALE, even stratifying by above-knee and below-knee bypass cohorts. The median follow-up period was 2 years.

Conclusions: Among patients undergoing femoropopliteal bypass grafting, no combination of AC or AP medications was associated with improved graft patency; however, a below-knee target and tissue loss were associated with adverse limb events. AC and AP regimen may be individualized after bypass with regard to other concomitant medical comorbidities. (J Vasc Surg 2022;■:1-8.)

Keywords: Anticoagulation; Antiplatelets; Femoropopliteal bypass

More than 200 million people are diagnosed with lower extremity peripheral arterial disease (PAD) worldwide.[1] PAD is estimated to affect more than 20% of individuals over 80 years old, and the incidence of PAD is increasing as the population continues to age.[2] This atherosclerotic disease process frequently manifests through functional limitations, ranging from intermittent claudication to chronic limb-threatening ischemia. In addition to decreased functional capacity and impaired wound healing, PAD also serves as a marker for cardiovascular morbidity and mortality.[3-5] Despite these prognostic implications, PAD remains underdiagnosed and undertreated by primary care physicians.[6]

The femoral and popliteal arteries are the most common sites of atherosclerotic disease among patients with PAD.[7] Approximately 80% to 90% of patients with symptomatic PAD have some combination of femoropopliteal occlusive disease.[8] For patients with lifestyle-limiting claudication and chronic limb-threatening ischemia as a result of femoropopliteal disease, both endovascular and surgical bypass options are available. Although endovascular interventions have grown immensely in popularity over the past two decades, even for complex lesions, few randomized trials have

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compared surgical bypass with endovascular therapy. Two such trials include Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial and Bypass or Angioplasty in Severe Intermittent Claudication (BASIC) trial, both of which favor surgical bypass for long-term outcomes.[9,10] The Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial is currently ongoing.[11]

Two dreaded complications after femoropopliteal bypass include graft failure and major limb amputation. Graft surveillance protocols have been shown to be protective of these adverse limb events following bypass surgery, and are currently recommended by the Society for Vascular Surgery practice guidelines.[12] Several studies have purported that antithrombotic therapy may also be protective, however, results are conflicting and the optimal combination of anticoagulation (AC) and antiplatelet (AP) medications remains unclear.[13-15] In the present study, we investigated the impact of AC/AP medications on outcomes after femoropopliteal bypass. The primary composite outcomes were major adverse limb events (MALE) after surgical intervention.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter retrospective cohort study
- **Key Findings:** Among 1292 patients who underwent femoropopliteal bypass, no anticoagulation or antiplatelet regimen was associated with major adverse limb events, even after stratifying by above-knee and below-knee bypass cohorts.
- **Take Home Message:** An anticoagulation/antiplatelet regimen may be individualized after bypass with regard to other concomitant medical comorbidities.

METHODS

Study population. A multi-institutional retrospective cohort study using the Research Patient Data Registry (RPDR) database was performed for all patients who underwent femoropopliteal bypass procedures from 1995 to 2020. The RPDR is a centralized clinical data registry that is populated with patient-level data from multiple hospitals throughout the Mass General Brigham health system. The RPDR dataset was retrospectively queried using current procedural terminology and *International Classification of Diseases*, 9th edition codes. Medical records were queried for patient demographic information, medical comorbidities, date of operation, operative details, postoperative medications, and postoperative and long-term outcomes.

Variables defined. The following patient information was collected: date of birth, date of bypass, gender, race, and medical comorbidities. Racial/ethnic groups included White/Caucasian, Black/African-American, Hispanic/Latinx, Asian/Pacific Islander, other, and not reported. Medical comorbidities were determined by *International Classification of Diseases*, editions 9 and 10, diagnosis codes and included hypertension, hyperlipidemia, coronary artery disease, prior myocardial infarction (MI), prior coronary artery bypass graft, diabetes mellitus, active smoking, cancer, cerebrovascular accident, chronic kidney disease, end-stage renal disease, chronic obstructive pulmonary disease, congestive heart failure, deep venous thrombosis, pulmonary embolism, and cirrhosis.

Indications for surgery were obtained from operative reports and included intermittent claudication, ischemic rest pain, tissue loss, and nonatherosclerotic indications. Tissue loss encompassed ischemic ulcers, dry gangrene, and wet gangrene. Nonatherosclerotic indications for bypass included femoral artery aneurysms, popliteal artery aneurysms, malignancy (eg, sarcoma), and trauma. All concurrent interventions at the time of bypass were determined through review of operative reports. Endovascular interventions included angioplasty and/or stenting procedures at time of bypass. Completion angiograms were not included as endovascular interventions.

All bypass procedures included in the study are all index procedures. Any redo bypasses were excluded from analysis, and the initial bypass performed in the ipsilateral leg (not the redo) was included for analysis. If a redo procedure was performed for an index bypass performed at an outside institution, this was excluded from analysis. All bypasses for infections were also excluded from the analysis.

Bypass target was determined by reviewing operative reports and divided into supragenicular (above-knee) and infragenicular (below-knee) popliteal artery. Conduits were divided into great saphenous vein (GSV) and prosthetic grafts. Prosthetic grafts included polyethylene terephthalate (Dacron) and expanded polytetrafluoroethylene (PTFE) grafts. Patients who underwent bypass with arm vein, short saphenous vein, or experimental conduits were excluded from this analysis.

Perioperative medication was obtained through medication reconciliation records in the discharge summaries of the index hospital admission. All AC and AP medications were reviewed. AC medications included warfarin and direct oral anticoagulants (DOAC) such as apixaban and rivaroxaban. AP medications included aspirin (both 81 mg and 325 mg) and clopidogrel. Monoantiplatelet therapy (MAPT) was defined as use of either aspirin or clopidogrel but not both. Dual antiplatelet therapy (DAPT) was defined as the concurrent use of both aspirin and clopidogrel.

Outcomes. The primary outcomes of interest were adverse perioperative events and long-term freedom from MALE. Postoperative outcomes were obtained

Table I. Demographic information on all patients undergoing femoropopliteal bypass

	No. (%) or mean ± standard deviation
Total patients	1292
Age at BPG, years	68.4 ± 12.1
Sex	
Male	835 (64.6)
Female	457 (35.4)
Race	
White	1116 (86.4)
Black	72 (5.6)
Hispanic	34 (2.6)
Asian	7 (0.5)
Other/NR	63 (4.8)
Comorbidities	
HTN	1106 (85.9)
HLD	975 (75.8)
CAD	817 (63.5)
CABG	286 (22.2)
Prior MI	400 (31.1)
DM	621 (48.3)
Cancer	304 (23.6)
CVA	227 (17.6)
CKD	244 (19.0)
ESRD	47 (3.7)
COPD	367 (28.5)
CHF	390 (30.3)
DVT	150 (11.7)
PE	36 (2.8)
Cirrhosis	23 (1.8)

BPG, Bypass graft; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DM*, diabetes mellitus; *DVT*, deep vein thrombosis; *ESRD*, end-stage renal disease; *HLD*, hyperlipidemia; *HTN*, hypertension; *MI*, myocardial infarction; *NR*, not reported; *PE*, pulmonary embolism; *SD*, standard deviation.

through daily progress notes and discharge summaries of the index hospital admission. Complications included hematoma, pseudoaneurysm, wound infection, lymphocele, lymphocutaneous fistula, postoperative MI (within 30 days of procedure), and postoperative death (within 30 days of procedure). Long-term outcomes were obtained through a review of electronic medical records. MALE was defined as reintervention for patency or major amputation of index limb (above- or below-knee amputation). Toe amputations and transmetatarsal amputations were not considered MALE.

Statistical analyses. Categorical variables were described as frequency (n) and percentages (%). Continuous variables were described as means and standard deviation for normally distributed variables or median and interquartile range for non-normally distributed variables. Univariate analysis was performed using χ^2 tests, *t* tests, and Wilcoxon rank-sum tests where appropriate. Cox proportional hazards model was used to determine independent risk factors for MALE after bypass. A survival analysis was performed to plot freedom from MALE using Kaplan-Meier plots. A *P* value of less than .05 was used to designate statistical significance. Statistical analysis was performed using Stata 15 (StataCorp, College Station, TX). This study was approved by the Institutional Review Board at Mass General Brigham.

RESULTS

A total of 1421 patients underwent femoropopliteal bypass over the study period, throughout five institutions included in this study. There were 1292 of 1421 patients (90.9%) who met inclusion criteria and have data available. The median follow-up period was 2 years. A total of 111 of the 1292 patients (8.6%) were lost to follow-up, defined as last documented examination within 30 days after surgery not owing to postoperative mortality. Demographic information on all patients is listed in Table I. The mean patient age at time of bypass was 68.4 ± 12.1 years. The majority of patients were male (64.6%) and Caucasian (86.4%). Among this cohort, the indication for surgery was primarily tissue loss (33.5%) followed by ischemic rest pain (30.3%), claudication (21.4%), and nonatherosclerotic diseases (14.8%). The most common medical comorbidities included hypertension (85.9%), hyperlipidemia (75.8%), coronary artery disease (63.5%), and diabetes mellitus (48.3%).

Of the 1292 bypasses performed, 661 (51.1%) used a GSV conduit, whereas 631 (48.8%) were reconstructed using a prosthetic graft. The specific prosthetic conduits used included PTFE (575/631 [91.1%]), PTFE with a vein patch (20/631 [3.2%]), Dacron (35/631 [5.5%]), and Dacron with a vein patch (1/631 [0.2%]). Data regarding heparin-coated versus standard PTFE grafts were not available consistently based on operative reports. Of the available data, heparin-coated PTFE grafts comprised 36.3% (216/595) of all PTFE grafts, and standard grafts comprised 26.6% (158/595). Data regarding PTFE graft type was missing in 37.1% (221/595) of cases.

A total of 587 patients (45.4%) were on MAPT, which was the most prevalent postbypass AC/AP regimen. The DAPT group was comprised of 214 patients (16.6%). A total of 73 patients (5.7%) were in the AC only group, 319 (24.7%) in the AC+MAPT group, and 42 (3.3%) in the AC+DAPT group. Table II details demographic information by AC/AP grouping.

In terms of concurrent procedures, 447 patients (34.6%) underwent femoral endarterectomy and 159 (12.3%) underwent retrograde iliac endovascular intervention at time of bypass. Patients who underwent concurrent

Table II. Demographic information on patients undergoing femoropopliteal bypass, grouped by anticoagulation/antiplatelet (*AC/AP*) regimen

	None	MAPT	DAPT	AC	AC+MAPT	AC+DAPT	*P* value
Total patients	57	587	214	73	319	42	
Age at BPG, years	67.4 ± 14.8	67.4 ± 13.0	68.0 ± 10.3	70.6 ± 11.0	70.0 ± 11.3	68.5 ± 10.0	**.027**
Sex							.51
Male	40 (70.2)	386 (65.8)	130 (60.7)	42 (57.5)	209 (65.5)	28 (66.7)	
Female	17 (29.8)	201 (34.2)	84 (39.3)	31 (42.5)	110 (34.5)	14 (33.3)	
Race							.71
White	45 (78.9)	498 (84.8)	190 (88.8)	65 (89.0)	281 (88.1)	37 (88.1)	
Black	3 (5.3)	38 (6.5)	8 (3.7)	4 (5.5)	15 (4.7)	4 (9.5)	
Hispanic	3 (5.3)	14 (2.4)	6 (2.8)	1 (1.4)	10 (3.1)	0 (0.0)	
Asian	0 (0.0)	3 (0.5)	2 (0.9)	0 (0.0)	2 (0.6)	0 (0.0)	
Other/NR	6 (10.6)	34 (5.8)	8 (3.7)	3 (4.1)	11 (3.4)	1 (2.4)	
Comorbidities							
HTN	43 (75.4)	491 (84.1)	194 (90.7)	57 (78.1)	285 (89.9)	36 (85.7)	**.002**
HLD	40 (70.2)	425 (72.8)	178 (83.2)	47 (64.4)	253 (79.8)	32 (76.2)	**.003**
CAD	26 (45.6)	334 (57.2)	154 (72.0)	44 (60.3)	227 (71.6)	32 (76.2)	**<.001**
CABG	11 (19.3)	84 (14.4)	62 (29.0)	17 (23.3)	96 (30.3)	16 (38.1)	**<.001**
Prior MI	10 (17.5)	157 (26.9)	95 (44.4)	13 (17.8)	108 (34.1)	17 (40.5)	**<.001**
DM	24 (42.1)	270 (46.2)	110 (51.4)	36 (49.3)	156 (49.2)	25 (59.5)	.42
Cancer	14 (24.6)	141 (24.1)	49 (22.9)	22 (30.1)	73 (23.0)	5 (11.9)	.40
Active smoker	30 (52.6)	329 (56.3)	131 (61.2)	33 (45.2)	182 (57.4)	27 (64.3)	.21
CVA	7 (12.3)	81 (13.9)	55 (25.7)	14 (19.2)	61 (19.2)	9 (21.4)	**.004**
CKD	5 (8.8)	107 (18.3)	40 (18.7)	11 (15.1)	71 (22.4)	10 (23.8)	.17
ESRD	3 (5.3)	20 (3.4)	9 (4.2)	1 (1.4)	12 (3.8)	2 (4.8)	.86
COPD	20 (35.1)	164 (28.1)	59 (27.6)	22 (30.1)	87 (27.4)	15 (35.7)	.75
CHF	12 (21.1)	145 (24.8)	76 (35.5)	22 (30.1)	118 (37.2)	17 (40.5)	**<.001**
DVT	6 (10.5)	61 (10.4)	5 (2.3)	11 (15.1)	62 (19.6)	5 (11.9)	**<.001**
PE	4 (7.0)	14 (2.4)	2 (0.9)	4 (5.5)	9 (2.8)	3 (7.1)	**.04**
Cirrhosis	3 (5.3)	10 (1.7)	2 (0.9)	1 (1.4)	5 (1.6)	2 (4.8)	.21

AC, Anticoagulation; *BPG*, bypass graft; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DAPT*, dual antiplatelet therapy; *DM*, diabetes mellitus; *DVT*, deep vein thrombosis; *ESRD*, end stage renal disease; *HLD*, hyperlipidemia; *HTN*, hypertension; *MAPT*, monoantiplatelet therapy; *MI*, myocardial infarction; *NR*, not reported; *PE*, pulmonary embolism; *SD*, standard deviation.
Values are mean ± standard deviation or number (%).
Boldface entries indicate statistical significance.

endarterectomy were most frequently prescribed AC+DAPT (45.2%) and AC+MAPT (36.1%) ($P = .049$). Patients who underwent simultaneous endovascular intervention were most frequently prescribed DAPT (19.2%) and AC+DAPT (31.0%). In terms of conduit type, patients who were bypassed with prosthetic conduit were more frequently prescribed AC alone (64.4%), AC+MAPT (64.9%), or AC+DAPT (57.1%), compared with a non-AC medication regimen ($P < .001$). Further operative details are described in Table III.

On univariate analysis, there were no differences in postoperative hematomas, pseudoaneurysm, wound infection, lymphocele, lymphocutaneous fistula, or postoperative MI between the AC/AP groups ($P =$ NS each). Perioperative complications are listed in the Supplementary Table (online only). No specific AC/AP regimen was associated with MALE after femoropopliteal bypass ($P =$ NS each). After adjusting for patient factors, a below-knee target was associated with MALE with a hazard ratio (HR) of 1.25 (95% confidence interval [CI], 1.04-1.52; $P = .019$). The GSV conduit trended toward lower MALE with a HR or 0.84 (95% CI, 0.70-1.01) but was not statistically significant ($P = .06$). With regard to surgical indication, using nonatherosclerotic indications as a reference, neither intermittent claudication (HR, 1.18; 95% CI, 0.85-1.64; $P = .0317$) nor ischemic reset pain (HR, 1.34; 95% CI, 0.99-1.81; $P = .058$) were associated with MALE. Bypass for tissue loss, in contrast, was significantly associated with increased MALE (HR, 1.40; 95% CI, 1.04-1.88) compared with nonatherosclerotic diseases

Table III. Operative information on patients undergoing femoropopliteal bypass, grouped by anticoagulation/antiplatelet (*AC/AP*) regimen

	None	MAPT	DAPT	AC	AC+MAPT	AC+DAPT	*P* value
Total patients	57	587	214	73	319	42	
Indication							**<.001**
Nonatherosclerotic	14 (24.6)	92 (15.7)	12 (5.6)	15 (20.5)	51 (16.0)	7 (16.7)	
Claudication	14 (24.6)	149 (25.4)	66 (30.8)	10 (13.7)	34 (10.7)	4 (9.5)	
Rest pain	12 (21.1)	168 (28.6)	68 (31.8)	18 (24.7)	108 (33.9)	17 (40.5)	
Tissue loss	17 (29.8)	178 (30.3)	68 (31.8)	30 (41.1)	126 (39.5)	14 (33.3)	
Bypass target							**<.001**
Above knee	21 (36.8)	229 (39.0)	110 (51.4)	24 (32.9)	102 (32.0)	13 (31.0)	
Below knee	36 (63.2)	358 (61.0)	104 (48.6)	49 (67.1)	217 (68.0)	29 (69.0)	
Conduit type							**<.001**
GSV	27 (47.4)	379 (64.6)	99 (46.3)	26 (35.6)	112 (35.1)	18 (42.9)	
Prosthetic	30 (52.6)	208 (35.4)	115 (53.7)	47 (64.4)	207 (64.9)	24 (57.1)	
Concurrent intervention							
Endarterectomy	16 (28.1)	187 (31.9)	89 (41.6)	21 (28.8)	115 (36.1)	19 (45.2)	**.049**
Endovascular	5 (8.8)	51 (8.7)	41 (19.2)	5 (6.8)	44 (13.8)	13 (31.0)	**<.001**
AC/AP regimen							
Aspirin	0 (0.0)	564 (96.1)	214 (100)	0 (0.0)	298 (93.4)	42 (100)	**<.001**
Clopidogrel	0 (0.0)	23 (3.9)	214 (100)	0 (0.0)	21 (6.6)	42 (100)	**<.001**
Coumadin	0 (0.0)	0 (0.0)	0 (0.0)	66 (90.4)	285 (89.3)	39 (92.9)	**<.001**
DOAC	0 (0.0)	0 (0.0)	0 (0.0)	7 (9.6)	34 (10.6)	3 (7.2)	**<.001**

DAPT, Dual antiplatelet therapy; *DOAC*, direct oral anticoagulant; *GSV*, great saphenous vein; *MAPT*, monoantiplatelet therapy.
Nonatherosclerotic indications for bypass include femoral artery aneurysms, popliteal artery aneurysms, malignancy, and trauma.
Values are number (%).
Boldface entries indicate statistical significance.

($P = .028$). Other risk factors for adverse limb events are described in Table IV.

Kaplan-Meier curves detailing freedom from MALE after femoropopliteal bypass are depicted in Fig 1 with six separate AC/AP groups, and Fig 2 separated by AP regimen only. With regard to MALE categories at 5 years, major index limb amputation comprised three-quarters of cases (74.6%); loss of graft patency comprised the remaining 25.3%. There was a statistically significant difference in the AC/AP groups on Kaplan-Meier curves ($P = .018$); however, after adjusting for patient factors in multivariable modeling, there were no differences in MALE between groups. No difference was noted between AP groups with regard to long-term outcomes ($P = .18$).

DISCUSSION

Patients who undergo femoropopliteal bypass are at risk for impaired graft patency and major index limb amputation. In this retrospective study, we investigated the impact of antithrombotic medication strategies on outcomes after femoropopliteal bypass. Among patients undergoing bypass surgery, no combination of antithrombotic therapy was superior to others with regard to adverse limb events; however, a below-knee bypass target and tissue loss were both associated with MALE after bypass.

The Society for Vascular Surgery guidelines currently recommend AP monotherapy with aspirin in patients with symptomatic PAD (grade 1A). Alternatively, clopidogrel monotherapy may be substituted for aspirin in this patient population (grade 1B). Warfarin is not recommended for the sole indication of decreasing vascular occlusions or adverse cardiovascular events (grade 1C). Finally, patients undergoing infrainguinal bypass are recommended to be treated with either MAPT or DAPT after surgery (grade 2B).[16] Similarly, current American College of Cardiology/American Heart Association clinical practice guidelines recommend MAPT (either aspirin or clopidogrel) in the heterogeneous population of patients with symptomatic PAD.[17]

For PAD patients who have undergone lower extremity revascularization, studies investigating AC/AP therapy have reported conflicting results.[13-15] In 2000, the authors of the Dutch BOA trial performed a multicenter, randomized, open study in which 2690 patients were randomized to aspirin (80 mg) or coumadin (target international normalized ratio of 3.0-4.5) after infrainguinal bypass grafting. The primary outcome was graft occlusion, and the mean follow-up period was 21 months. The authors reported that coumadin was more effective

Table IV. Risks factors for adverse limb events after femoropopliteal bypass

	HR	95% CI	*P* value
Indication			
Nonatherosclerotic	*Ref.*		
Claudication	1.18	(0.85-1.64)	.317
Rest pain	1.34	(0.99-1.81)	.058
Tissue loss	1.40	(1.04-1.88)	**.028**
Hematoma	1.46	(0.99-2.14)	.055
CKD	1.26	(1.01-1.58)	**.043**
Bypass target			
Above knee	*Ref.*		
Below knee	1.25	(1.04-1.52)	**.019**
Conduit type			
GSV	0.84	(0.70-1.01)	.06
Prosthetic	*Ref.*		
AC/AP regimen			
None	*Ref.*		
MAPT	0.82	(0.53-1.29)	.403
DAPT	0.94	(0.58-1.51)	.79
AC	1.09	(0.64-1.87)	.747
AC+MAPT	0.97	(0.61-1.55)	.906
AC+DAPT	0.97	(0.52-1.80)	.924

AC, Anticoagulation; *AP*, antiplatelet; *CI*, confidence interval; *CKD*, chronic kidney disease; *DAPT*, dual antiplatelet therapy; *GSV*, great saphenous vein; *HR*, hazard ratio; *MAPT*, monoantiplatelet therapy.
Nonatherosclerotic indications for bypass include femoral artery aneurysms, popliteal artery aneurysms, malignancy, and trauma.
Boldface entries indicate statistical significance.

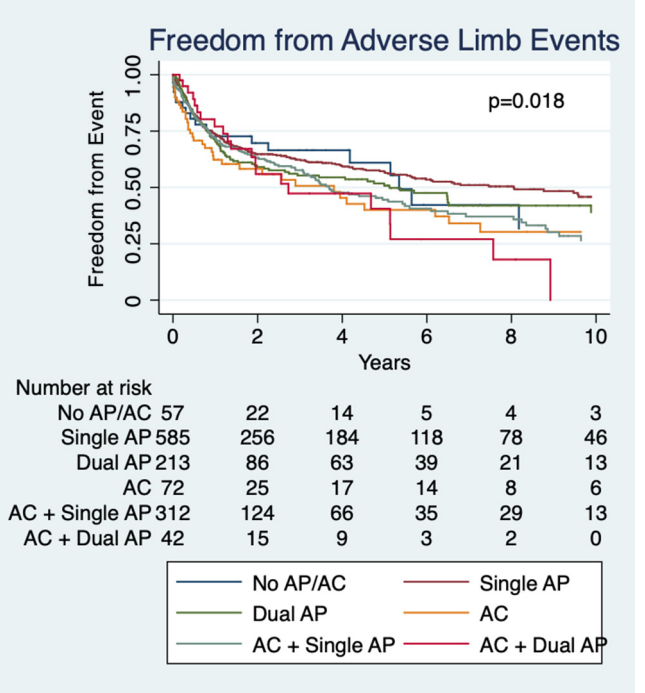

Fig 1. Kaplan-Meier curve detailing freedom from adverse limb events after femoropopliteal bypass, comparing different antiplatelet/anticoagulation (*AP/AC*) regimen. The standard error is greater than 10% at 4.7 years.

in preventing vein graft occlusion after bypass (HR, 0.69; 95% CI, 0.54-0.88), at the expense of increased major bleeding events.[13] Conversely, aspirin was better for prosthetic conduit patency (HR, 1.26; 95% CI, 1.03-1.55). In 2011, the CASPAR trial investigated aspirin monotherapy versus DAPT in patients undergoing below-knee bypass grafting. A total of 851 patients were randomized with a primary composite end point of graft occlusion, graft revascularization, major amputation, and death. The authors found that the addition of clopidogrel (75 mg) did not improve outcomes in this heterogeneous patient population, and also noted that there was no significant increase in bleeding risk with the addition of clopidogrel (2.1% vs 1.2%).[14] The recent VOYAGER PAD trial, published in the *New England Journal of Medicine*, investigated the impact of aspirin plus rivaroxaban versus placebo in 6564 patients undergoing lower extremity revascularization.[15] Two-thirds of patients underwent endovascular intervention and one-third underwent open surgical revascularization. The authors found that the addition of rivaroxaban significantly decreased the risk of the primary composite end point of acute limb ischemia, major limb amputation, MI, ischemic stroke, and death from cardiovascular causes.

The rationale for our study in the setting of these randomized controlled trials are three-fold. First, as with other highly powered, randomized controlled trials, the need for real-world, confirmatory data is imperative. Second, the VOYAGER PAD trial is limited in that Bayer and Janssen (trial sponsors and makers of rivaroxaban [Xarelto]) were involved in development of study protocol, conduct, and oversight of the study. We have no such disclosures. Third, antithrombotic trials in PAD patients after invasive therapy remain relatively scarce. Given these factors, we believe that there is value to our multi-institutional, retrospective analysis on the impact of antithrombotic regimen on postbypass outcomes.

In this retrospective analysis, AP monotherapy was the most frequently prescribed medication after femoropopliteal bypass, followed by AC with MAPT. No specific combination of antithrombotic medications was associated with freedom from MALE on multivariate analyses. Even after grouping patients by AP type (none, MAPT, DAPT), no differences were noted in MALE between subgroups, complementing results from the CASPAR trial.[14] Reassuringly, our findings confirm other well-defined risk factors for MALE after bypass, including a below-knee (vs above-knee) bypass target, prosthetic conduit, and surgical indication.[18-22]

In the present study, DOAC medications were prescribed uncommonly after femoropopliteal bypass. Coumadin was more commonly prescribed for AC (30.2%)

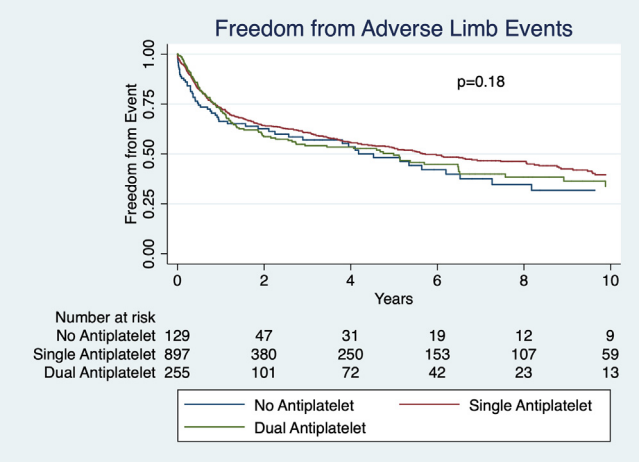

Fig 2. Kaplan-Meier curve detailing freedom from adverse limb events after femoropopliteal bypass, comparing different single versus dual versus no antiplatelet (AP) medications. The standard error is greater than 10% for all displayed data.

within our patient cohort, whereas only 3.4% of patients (44 of 1292) were transitioned to a DOAC at discharge. We observed an increasing use of DOAC after bypass over the past several years compared with previous decades, including both apixaban and rivaroxaban. With the results of the recent VOYAGER PAD trial demonstrating the benefits of rivaroxaban after revascularization, it would be interesting to see future trends in AC prescription after bypass.

Our findings signal the need for alternative markers of AC/AP efficacy and compliance in the heterogeneous PAD population. Many of the studies investigating AC/AP medications (ours included) control for the type and dosage of medications taken; however, they do not address the heterogeneity in patient responsiveness to such medications. First, many patients are either medication noncompliant or cannot afford their medications. Second, it is imperative not to subject the diverse PAD population to oversimplification in terms of individual coagulation dynamics. Many patients are hypercoagulable at baseline[23]; other studies suggest that PAD is itself a hypercoagulable disease process.[24-26] Third, significant heterogeneity exists in terms of AP resistance and AP responders.[27] In fact, clopidogrel resistance may impact up to 44% of people worldwide.[28] The use of thromboelastography (TEG) or other viscoelastic assays can account for these many limitations and provide individualized data on their coagulation parameters. TEG can detect patient-level variability in hypercoagulability, AC/AP efficacy, and medication compliance; and may help to guide antithrombotic strategies in bypass patients.[29-31] The usefulness of TEG to help to direct antithrombotic therapy in patients with PAD is currently under investigation in ongoing clinical trials.

The results of this study must be interpreted in the context of several major limitations. First, this is a retrospective analysis and is subject to confounding and bias. For instance, the 30-day mortality rates were higher among patients who were not prescribed AC/AP medications after bypass, likely representing in-hospital mortality rather than medication effect. Second, postbypass angiography images were not available for review, so the number of outflow vessels were not included in our statistical analysis. Graft duplex studies were also not routinely available. Third, postbypass medication data were obtained via discharge summaries, and we cannot account for several factors, including medication noncompliance, duration of therapy, and medication responsiveness (such as clopidogrel resistance or a subtherapeutic international normalized ratio). Fourth, our findings on femoropopliteal bypasses should not be generalized to bypasses performed distal to the infrageniculate popliteal artery. Finally, the heterogeneity of the patient population with PAD contributes directly to the difficulty of drawing any firm conclusion with regard to AC/AP medications and bypass graft outcomes.

CONCLUSIONS

Patients who undergo femoropopliteal bypass are at risk for impaired graft patency and major index limb amputation. In this retrospective study, no combination of AC/AP therapy was superior to others with regard to MALE after femoropopliteal bypass surgery. Future investigations may elucidate the optimal antithrombotic medication regimen in this heterogeneous patient population.

AUTHOR CONTRIBUTIONS

Conception and design: YK, AM, AD
Analysis and interpretation: YK, CSD, SSP, IEM, MM, SJ, SL, AM, AD
Data collection: YK, CSD, SSP, SL
Writing the article: YK, CSD, AD
Critical revision of the article: YK, CSD, SSP, IEM, MM, SJ, SL, AM, AD
Final approval of the article: YK, CSD, SSP, IEM, MM, SJ, SL, AM, AD
Statistical analysis: YK, CSD
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Overall responsibility: AD

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Supplementary Table (online only). Perioperative complications in patients undergoing femoropopliteal bypass, grouped by anticoagulation/antiplatelet (*AC/AP*) regimen

	None	MAPT	DAPT	AC	AC+MAPT	AC+DAPT	*P* value
Total patients	57	587	214	73	319	42	
Hematoma	1 (1.8)	18 (3.1)	9 (4.2)	4 (5.5)	13 (4.1)	3 (7.1)	.61
PSA	0 (0.0)	2 (0.3)	2 (0.9)	0 (0.0)	5 (1.6)	0 (0.0)	.31
Wound infection	8 (14.0)	109 (18.6)	46 (21.5)	6 (8.2)	67 (21.0)	10 (23.8)	.12
Lymphocele/LCF	0 (0.0)	16 (2.7)	5 (2.3)	0 (0.0)	6 (1.9)	0 (0.0)	.42
MI (30 d)	3 (5.3)	13 (2.2)	6 (2.8)	1 (1.4)	4 (1.3)	0 (0.0)	.35
Death (30 d)	9 (15.8)	12 (2.0)	2 (0.9)	2 (2.7)	4 (1.3)	1 (2.4)	**<.001**

DAPT, Dual antiplatelet therapy; *LCF*, lymphocutaneous fistula; *MAPT*, monoantiplatelet therapy; *MI*, myocardial infarction; *PSA*, pseudoaneurysm.
Values are number (%).
Boldface entries indicate statistical significance.