Does Oral Anticoagulation Give a Leg Up on Symptomatic Peripheral Artery Disease (PAD)?

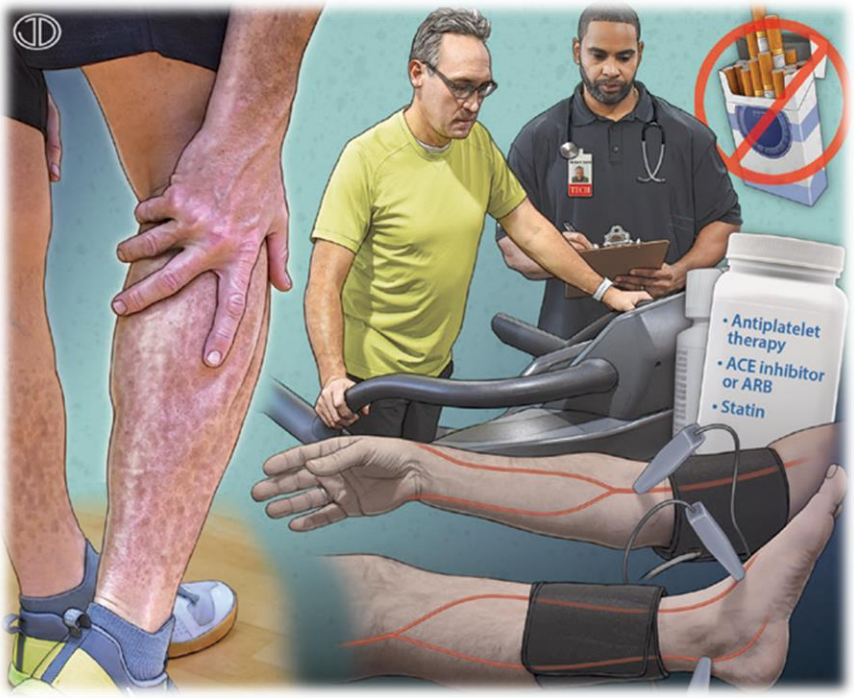

Figure 1. PAD[1]

Blake M. Wassom, PharmD, TTS
PGY-2 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy
November 12, 2021

Learning Objectives

Pharmacists

1. Discuss current guideline recommendations for the management of symptomatic PAD.
2. Summarize key clinical studies supporting the use of anticoagulation in the treatment of symptomatic PAD.
3. Assess a patient with symptomatic PAD to determine if the use of low-dose rivaroxaban is appropriate.

Technicians

1. Describe common risk factors for the development of PAD.
2. List agents or drug classes recommended in current guidelines for the management of symptomatic PAD.
3. Identify a patient with symptomatic PAD who may benefit from the use of low-dose rivaroxaban.

Abbreviations

AAA: abdominal aortic aneurism	GDMT: guideline-directed medical therapy
ABI: ankle-brachial index	GI: gastrointestinal
ACE-I: angiotensin converting enzyme inhibitor	HF: heart failure
ACS: acute coronary syndrome	HLD: hyperlipidemia
ASCVD: atherosclerotic cardiovascular disease	HTN: hypertension
BB: beta blocker	IC: intermittent claudication
BID: twice daily	ICH: intracranial hemorrhage
BMI: body mass index	LE: lower extremity
CABG: coronary artery bypass graft	LVEF: left ventricular ejection fraction
CAD: coronary artery disease	MACE: major adverse cardiovascular event
CKD: chronic kidney disease	MALE: major adverse limb event
CLI: critical limb ischemia	MI: myocardial infarction
CRNM: clinically relevant nonmajor (bleed)	PAD: peripheral artery disease
CV: cardiovascular	PSVR: peak systolic velocity ratio
CVA: cerebrovascular accident (stroke)	SBP: systolic blood pressure
CVD: cerebrovascular disease	SFA: superficial femoral artery
DAPT: dual antiplatelet therapy	T2DM: type-2 diabetes mellitus
DOAC: direct oral anticoagulant	TBI: toe-brachial index
DM: diabetes mellitus	TIA: transient ischemic attack
ESRD: end-stage renal disease	VKA: vitamin K antagonist
EVT: endovascular therapy	VTE: venous thromboembolism

Introduction

- Peripheral artery disease (PAD): manifestation of systemic atherosclerosis typically affecting arteries of the lower extremities[2]
  - Most common: femoropopliteal-tibial, aortoiliac
- PAD affects more than 8.5 million adults in the United States[3]
- Risk of major adverse cardiovascular events (MACE) is greatly increased in PAD
- Symptomatic PAD also concerning for major adverse limb events (MALE)
  - Need for revascularization, amputation

Risk Factors[4,5]

- Risk factors for PAD are similar to those of coronary artery disease (CAD) and cerebrovascular disease (CVD) and are directly correlated with atherogenesis
- Smoking increases the risk of developing PAD by 4-fold is associated with poorer outcomes

Table 1. Risk Factors for PAD

Nonmodifiable	Modifiable
Age >50	**Smoking (greatest risk)**
Male Gender	HLD
African American	T2DM
Family History of PAD	HTN
CKD	Hyperhomocysteinemia
	Sedentary Lifestyle
	Poor Diet
	Inflammation

Clinical Presentation[1]

Leg Pain

- Intermittent claudication (IC): fatigue, discomfort, cramping, or pain in calves that is consistently induced by exercise and relieved within 10 minutes of rest
  - Hallmark sign of PAD
- Atypical leg pain: other pain syndrome not characterized by IC (e.g., pain not induced by exercise or relieved with rest, pain involving other muscle groups)
- Ischemic rest pain: burning and numbness in the forefoot, often relieved by hanging feet over side of bed
  - Associated with critical limb ischemia (CLI)

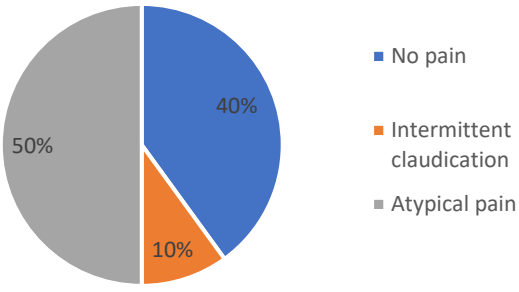

Figure 2. Pain Syndromes in Stable PAD

Other Signs/Symptoms

- Impaired walking function
- Diminished lower extremity (LE) pulses
- Vascular bruit
- Nonhealing LE wound
- Pallor on elevation of the legs or dependent rubor
- LE gangrene

Diagnosis[6]

- The Ankle-Brachial Index (ABI) is a simple, noninvasive test that has been shown to be highly sensitive and specific (≥90%) for PAD
  - Ratio of SBP at the ankle to SBP at the arm
- In patients with a history and/or physical exam findings suggestive of PAD, the diagnosis is established by measuring the resting ABI
  - ABI ≤0.90: abnormal
  - ABI 0.91-0.99: borderline
  - ABI 1.00-1.40: normal
  - ABI >1.40: noncompressible

Clinical Outcomes

- In the REACH registry, 40% of patients with PAD experienced an MI, stroke, vascular death, or hospitalization within 3 years[7]
  - Risk exceeds that of CAD (30%) or CVD (28%)
- Mortality increases as ABI decreases
- Up to 21% of patients with IC progress to CLI[1]
  - Risk of CV mortality and amputation are 25% each at 1 year[8]
- Mortality rates are nearly 50% at 1 year and 70% at 3 years after major amputation[9,10]

Antithrombotic Therapy in PAD

- Antiplatelet therapies are a cornerstone of treatment for patients with ASCVD[11]
  - Relative-odds reduction of 25% for subsequent MACE in a broad population
- Oral anticoagulation has had limited applications in PAD until recently

Table 3. Guideline Recommendations for Antithrombotic Therapy in PAD[6,12,13]			
	AHA/ACC 2016	**ESC 2017**	**SVS 2015**
Asymptomatic PAD	• Antiplatelet therapy is reasonable in ABI ≤0.90 (IIa) • Usefulness of antiplatelet therapy is uncertain in ABI 0.91-0.99 (IIb)	• Antiplatelets not routinely recommended (III)	• No recommendation
Symptomatic PAD	• Aspirin (75-325 mg) or clopidogrel (75 mg) monotherapy (I) • Usefulness of aspirin + clopidogrel DAPT is not well established (IIb) • **Anticoagulation should not be used to reduce ischemic events (III)**	• Aspirin or clopidogrel monotherapy (I) • Clopidogrel may be preferred over aspirin (IIb)	• Aspirin 75-325 mg (I) • Clopidogrel 75 mg is an effective alternative to aspirin (I) • **Warfarin should not be used to reduce cardiovascular events (I)**
Endovascular Therapy	• Aspirin + clopidogrel DAPT may be reasonable to reduce limb events (IIb)	• Aspirin + clopidogrel DAPT for ≥1 month after stent placement (IIb) followed by long-term aspirin or clopidogrel monotherapy (IIb)	• Aspirin + clopidogrel DAPT for ≥1 month (II)
Surgical Revascularization	• Aspirin + clopidogrel DAPT may be reasonable to reduce limb events (IIb) • **Usefulness of anticoagulation to improve bypass patency is uncertain (IIb)**	• Aspirin or clopidogrel monotherapy (I) • **VKA may be considered after vein bypass (IIb)** • Aspirin + clopidogrel DAPT may be considered after below-knee prosthetic bypass (IIb)	• Antiplatelet therapy (aspirin, clopidogrel, or aspirin + clopidogrel DAPT) for venous and prosthetic bypass (II)

ESC 2019: **Low-dose rivaroxaban (2.5 mg BID) plus aspirin may be considered in patients with T2DM and PAD (IIa)**[14]

ADA 2021: **Combination therapy with aspirin plus low-dose rivaroxaban should be considered for patients with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events**[15]

Literature Review

Table 4. Efficacy of Oral Anticoagulants Compared with Aspirin After Infrainguinal Bypass Surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): A Randomised Trial. *Lancet*. 2000;355(9201):346-51.[16]		
POPULATION		
Inclusion/ exclusion criteria	• Infrainguinal bypass surgery for PAD	• Contraindication or absolute indication for anticoagulation • High risk of bleeding • MI/CVA within 1 month • Inability to adhere to study protocol
Enrollment	• N=2650; 1326 in oral anticoagulants group, 1324 in aspirin group • Demographics: age 69, female 36% • PAD: IC 51%, ischemic rest pain 21%, ischemic ulceration 26%, gangrene 2% • Risk factors: DM 26%, HTN 39%, previous MI 18%, previous CVA/TIA 12%, current smoker 54% • Antithrombotic: any 64%, oral anticoagulant 22%, aspirin 28% • Graft material: vein 58%, prosthetic 42%	
INTERVENTION/COMPARATOR		
Interventions	• Patients randomized (open-label, 1:1) to receive oral anticoagulant (INR 3.0 to 4.5) or antiplatelet therapy, started within 5 days of surgery ○ Anticoagulant: phenprocoumon or acenocoumarol ○ Antiplatelet: carbasalate calcium 100 mg daily (aspirin 80 mg daily) ○ INR time in therapeutic range 50% • Graft patency determined by clinical examination and doppler/duplex scanning +/- arteriography • Follow-up conducted at 3 months and 6 months, then every 6 months	
OUTCOMES		
Primary (anti-coagulant vs antiplatelet)	• Graft occlusion: 23.2% vs 24.3 % (HR 0.95, 95% CI 0.82 to 1.11) ○ Venous (autogenous): 14.2% vs 20.3% (HR 0.69, 95% CI 0.54 to 0.88) ○ Non-venous (prosthetic): 36.2% vs 29.7% (HR 1.26, 95% CI 1.03 to 1.55)	
Secondary (anti-coagulant vs antiplatelet)	• CV death, nonfatal MI, nonfatal stroke, amputation: 18.7% vs 20.8% (HR 0.89, 95% CI 0.75 to 1.06) • All-cause mortality: 15.9% vs 15.5% (HR 1.02, 95% CI 0.85 to 1.24) • Vascular intervention: 32.4% vs 33.7% (HR 0.95, 95% CI 0.84 to 1.09) • Hemorrhage: 8.1% vs 4.2% (HR 1.96, 95% CI 1.42 to 2.71) • Hemorrhagic stroke: 1.1% vs 0.3% (HR 3.48, 95% CI 1.14 to 10.6)	
CONCLUSION		
Key Takeaway	• In patients who had undergone infrainguinal bypass surgery for PAD, oral anticoagulants (dosed to target INR 3.0 to 4.5) were superior to antiplatelets in preventing autogenous graft occlusion but inferior to antiplatelets in preventing prosthetic graft occlusion. • Hemorrhagic events were more frequent in the oral anticoagulant group.	

Table 5. Anand S, Yusuf S, Xie C, et al. Oral Anticoagulant and Antiplatelet Therapy and Peripheral Arterial Disease. *N Engl J Med.* 2007;357(3):217-27.[17]		
POPULATION		

Inclusion/ exclusion criteria	• Age 35-85
	• PAD
	  ○ LE: IC + ≥1 of the following: objective evidence of PAD, ischemic pain at rest, nonhealing ulcers/ focal gangrene, previous amputation, or revascularization
	  ○ Carotid artery: CVA/TIA >6 months, carotid endarterectomy, >50% stenosis
	  ○ Subclavian artery
		• Indication for oral anticoagulation
		• High risk of bleeding
		• CVA within 6 months
		• Requiring dialysis

Enrollment	• N=2161; 1080 in combined group, 1081 in antiplatelet only group ○ 256 (11%) patients screened were excluded following run-in phase (patient refusal, poor adherence, inability to maintain stable INR) • Demographics: age 64, female 26% • PAD: symptomatic PAD of LE 82%, other 18% • Risk factors: CAD 47% (45% combined, 49% aspirin), previous stroke 16%, current/former smoker 78% • Antiplatelet: aspirin 93%, ticlopidine 3%, clopidogrel 4% • Other medications: statin 44%, any lipid-lowering 55%, ACE-I 50%, BB 32%	
INTERVENTION/COMPARATOR		

Interventions	• Eligible patients entered 2- to 4-week run-in phase during which they received both an oral anticoagulant and antiplatelet therapy
	• Patients randomized (open-label, 1:1) to receive oral anticoagulant (INR 2.0 to 3.0) with antiplatelet therapy, or antiplatelet therapy alone
	  ○ Anticoagulants: warfarin, acenocoumarol
	  ○ Antiplatelets: aspirin 81-325 mg, ticlopidine, clopidogrel
	  ○ INR time in therapeutic range 62%
	• INR values obtained at least monthly
	• Follow-up conducted every 3 months over 2.5-3.5 years	

OUTCOMES		
Primary (combined vs antiplatelet only)	• MI, stroke, or CV death: 12.2% vs 13.3% (RR 0.92, 95% CI 0.73 to 1.16) • MI, stroke, severe ischemia of peripheral or coronary arteries, CV death: 15.9% vs 17.4% (RR 0.91, 95% CI 0.74 to 1.12)	
Secondary/ safety (combined vs antiplatelet only)	• No difference was seen in any efficacy outcome • Life-threatening bleeding: 4.0% vs 1.2% (RR 3.41, 95% CI 1.84 to 6.35) • Hemorrhagic stroke: 1.3% vs 0.0% (RR 15.2, 95% CI 2.0 to 115.6) • Fatal bleeding: 0.9% vs 0.3% (RR 3.34, 95% CI 0.92 to 12.1)	
CONCLUSION		
Key Takeaway	• In patients with stable PAD, the combination of a vitamin K antagonist (VKA) and an antiplatelet agent increased the risk of life-threatening bleeding without reducing MACE as compared to antiplatelet therapy alone.	

Table 6. Moll F, Baumgartner I, Jaff M, et al. Edoxaban plus Aspirin vs Dual Antiplatelet Therapy in Endovascular Treatment of Patients with Peripheral Artery Disease: Results of the ePAD Trial. *J Endovasc Ther*. 2018;25(2):158-68.[18]		
STUDY OVERVIEW		
Objective	• To compare edoxaban plus aspirin to clopidogrel plus aspirin with respect to rates of major bleeding and restenosis in patients with symptomatic PAD following endovascular therapy (EVT).	
METHODS		
Overview	• Multicenter, randomized, open-label trial	
Inclusion/ exclusion criteria	• Symptomatic PAD (Rutherford categories 2-5) without ulceration of heel • Superficial femoral or above-knee popliteal lesion and ≥50% stenosis at baseline • Successful EVT (≤30% residual stenosis) • ≥1 runoff vessel to foot	• CrCl <30 mL/min • Poorly controlled HTN (at discretion of investigator) • High risk of bleeding • CVA or ACS within 3 months • Other indications for DAPT or anticoagulation
Interventions	• Patients randomized (1:1) to receive edoxaban 60 mg daily or clopidogrel 300 mg x1, then 75 mg daily after successful EVT within 4 hours of achieving hemostasis ○ Edoxaban dose reduced (30 mg) in patients with CrCl 30-50 mL/min, body weight ≤60 kg, and/or concurrent use of strong P-glycoprotein inhibitors • Patients in both arms received aspirin 100 mg daily • Follow-up conducted at 1, 2, 3, 4, and 6 months	
Outcomes	• **Primary safety outcome:** clinically relevant bleeding (major bleeding or clinically relevant nonmajor bleeding) based on ISTH and TIMI definitions • **Primary efficacy outcome:** restenosis or reocclusion at 6 months (PSVR ≥2.4) • **Secondary outcomes:** MACE, CV death, all-cause mortality, amputation, subsequent revascularizations, ABI, Rutherford category	
Statistical analysis	• Aimed to enroll 200 patients to detect a 6% incidence of clinically relevant bleeding +/- 6.6% with 95% confidence • Kaplan-Meier method: estimate event risk over time • Normal approximation to binomial distribution: compare risk of events • Modified intention-to-treat analysis performed	
RESULTS		
Enrollment	• N=203; 101 in edoxaban group, 102 in clopidogrel group • Demographics: age 67, female 29%, BMI 27 • PAD: Rutherford 2 29%, Rutherford 3 57%, ABI 0.68, SFA lesion 92%, popliteal lesion 8% • Risk factors: DM 40%, HTN 83%, current/former smoker 86%, LDL 100 mg/dL • Renal function (mL/min): CrCl ≤50 9%, 51-79 26%, ≥80 65% (>95 34%) • Antithrombotic medications: aspirin 52% (86% routinely), heparin 11%, none 35% • Edoxaban dose (intervention arm): 60 mg/day 78%, 30 mg/day 22%	
Primary safety outcome (edoxaban vs clopidogrel)	• TIMI major bleeding: 0.0% vs 2.0% • ISTH major/CRNM bleeding: 11.0% vs 7.9% (RR 1.39, 95% CI 0.58 to 3.31)	

Primary efficacy outcome (edoxaban vs clopidogrel)	• Restenosis/reocclusion: 30.9% vs 34.7% (RR 0.89, 95% CI 0.59 to 1.34)
Secondary outcomes (edoxaban vs clopidogrel)	• No differences seen in any secondary outcomes; most occurred infrequently (<5 events in either group) • Target lesion revascularization: 11.0% vs 9.9% (RR 1.11, 95% CI 0.49 to 2.50)
Adherence	• Edoxaban more frequently interrupted (27% vs 15%) and permanently discontinued (22% vs 7%) as compared to clopidogrel
AUTHOR CONCLUSIONS	
Author's conclusions	"These results suggest that patients who have undergone EVT have similar risks for major and life-threatening bleeding events with edoxaban and aspirin compared with clopidogrel and aspirin. The incidence of restenosis/reocclusion events, while not statistically different, was lower with edoxaban and aspirin, but an adequately sized trial will be needed to confirm these findings."
CRITIQUE	
Study strengths	• Primary analysis based on (modified) intention-to-treat principle • Risk of bleeding established using two common scoring systems • Clinical events adjudicated by an independent committee
Study limitations	• Underpowered with respect to all outcomes • Open-label study • Weak primary efficacy outcome • Thrombotic reocclusion and restenosis not differentiated in study • Bleeding events may be underestimated as edoxaban was interrupted and discontinued more frequently • GDMT usage among study participants not reported (exception: aspirin) • High degree of selective reporting bias
Applicability	• Only study to assess a DOAC other than rivaroxaban in PAD • Shorter courses of DAPT (30 to 60 days) becoming increasingly more common after EVT • Results unlikely to change clinical practice given similar rates of MACE and major adverse limb events (MALE)
Key Takeaway	• Rates of clinically relevant bleeding and restenosis may be comparable between edoxaban plus aspirin and clopidogrel plus aspirin in patients with symptomatic PAD after EVT.

Table 7.

Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017;377(14):1319-30.[19]

Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without Aspirin in Patients with Stable Peripheral or Carotid Artery Disease: an International, Randomised, Double-Blind, Placebo-Controlled Trial. *Lancet*. 2018;391(10117):219-29.[20]

STUDY OVERVIEW		
Objective	• To determine whether rivaroxaban improves cardiovascular and limb outcomes in patients with high-risk CAD or symptomatic PAD when used either alone or in combination with aspirin	
METHODS		
Overview	• Multicenter, randomized, double-blind, placebo-controlled trial	

Inclusion/ exclusion criteria	• Presence of CAD or PAD
	  ○ CAD: MI within past 20 years; or history of stable or unstable angina
	  ○ PAD: history of claudication with ABI <0.9 or ≥50% stenosis of peripheral artery; previous peripheral revascularization or amputation for vascular causes; or previous carotid revascularization or ≥50% stenosis of carotid artery
	• If included for CAD, must be age >65 or age <65 with either multivessel disease or ≥2 of the following: current smoker, DM, CKD III/IV, HF, non-lacunar CVA
		• High risk of bleeding
		• CKD V
		• CVA within 1 month or history of hemorrhagic or symptomatic lacunar CVA
		• Severe HF (LVEF <30% or NYHA III/IV)
		• Need for DAPT, other non-aspirin antiplatelet therapy, or oral anticoagulant
		• Non-cardiovascular disease with poor prognosis

Interventions	• Eligible patients entered 30-day run-in phase during which they received aspirin with rivaroxaban-matched placebo
	• Patients that completed run-in phase were randomized (1:1:1) to receive rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone
	  ○ Rivaroxaban 2.5 mg BID + aspirin 100 mg daily
	  ○ Rivaroxaban 5 mg BID + aspirin-matched placebo
	  ○ Aspirin 100 mg daily + rivaroxaban-matched placebo
	• Follow-up conducted at 1 and 6 months, then every 6 months	

Outcomes	• **Primary:** composite of CV death, stroke, or MI • **Secondary/tertiary:** hospitalizations for CV causes, acute limb ischemia, limb amputation • **Safety:** major bleeding (modified ISTH) • **Net benefit:** composite of CV death, stroke, MI, major adverse limb events, major amputation, fatal bleeding, critical organ bleeding	
Statistical analysis	• Aimed to enroll 27,400 patients to provide the trial with 90% power to attain an estimated 2,200 events using HR of 0.80 in each of the comparator arms and two-sided alpha of 0.05 • Planned interim analyses at 50% and 75% of total events • Kaplan-Meier method: estimate event risk over time • Cox proportional-hazards model: compare risk of events • Intention-to-treat analysis performed	

<table>
<tr><th colspan="6">RESULTS</th></tr>
<tr><td>Enrollment (PAD subset)</td><td colspan="5">• N=7470 (N=27,395; 27%); 2492 in combined group, 2474 in rivaroxaban group, and 2504 in aspirin group
○ 447 (5.5%) patients screened were excluded for failing run-in phase (adherence <80%)
• Demographics: age 68, female 28%, BMI 28
• PAD: symptomatic PAD of LE 55%, carotid artery disease 26%, CAD and asymptomatic PAD 19%, previous revascularization for PAD 27%, previous limb/foot amputation 4.5%
• Risk factors: CAD 66%, previous stroke 6.7%, current/former smoker 73%
• Medications: antiplatelet 87%, lipid-lowering 83%, ACE-I/ARB 70%, BB 59%</td></tr>
<tr><td>Primary outcome</td><td colspan="5">• PAD subset (N=7470): 5.1% vs 6.0% vs 6.9%
○ Combined vs aspirin: HR 0.72, 95% CI 0.57 to 0.90, NNT=56
○ Rivaroxaban vs aspirin: HR 0.86, 95% CI 0.69 to 1.08
• Overall (N=27,395): 4.1% vs 4.9% vs 5.4%
○ Combined vs aspirin: HR 0.76, 95% CI 0.66 to 0.86, NNT=77
○ Rivaroxaban vs aspirin: HR 0.90, 95% CI 0.79 to 1.03
○ Mean follow-up: 23 months (stopped early for superiority)</td></tr>
<tr><td rowspan="5">Secondary/ tertiary outcomes</td><td>Component</td><td>Combined</td><td>Aspirin</td><td>HR (95% CI)</td><td>NNT</td></tr>
<tr><td>CV death</td><td>2.6%</td><td>3.1%</td><td>0.82 (0.59 to 1.14)</td><td>--</td></tr>
<tr><td>Stroke</td><td>1.0%</td><td>1.9%</td><td>0.54 (0.33 to 0.87)</td><td>115</td></tr>
<tr><td>MI</td><td>2.0%</td><td>2.7%</td><td>0.76 (0.53 to 1.09)</td><td>--</td></tr>
<tr><td colspan="5">• Acute limb ischemia: 0.8% vs 1.4% (HR 0.56, 95% CI 0.32 to 0.99, NNT=167)
• Major adverse limb event: 1.2% vs 2.2% (HR 0.54, 95% CI 0.35 to 0.84, NNT=100)
• Major amputation: 0.2% vs 0.7% (HR 0.30, 95% CI 0.11 to 0.80, NNT=210)</td></tr>
<tr><td>Safety (combined vs rivaroxaban vs aspirin)</td><td colspan="5">• Modified ISTH major bleeding: 3.1% vs 3.2% vs 1.9%
○ Combined vs aspirin: HR 1.61, 95% CI 1.12 to 2.31, NNH=83
○ Rivaroxaban vs aspirin: HR 1.68, 95% CI 1.17 to 2.40, NNH=76
• GI tract most common site of major bleeding (1.6% in combined group)
• No significant difference in risk of ICH, fatal bleeding, or symptomatic bleeding into a critical organ</td></tr>
<tr><td>Net Risk/ Benefit</td><td colspan="5">• Combined rivaroxaban-aspirin favored over aspirin alone: 6.8% vs 9.3% (HR 0.72, 95% CI 0.59 to 0.87)</td></tr>
<tr><th colspan="6">AUTHOR CONCLUSIONS</th></tr>
<tr><td>Author's conclusions</td><td colspan="5">• "Low-dose rivaroxaban taken twice a day plus aspirin taken once a day reduced major adverse cardiovascular and limb events when compared with aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not. This combination therapy represents an important advance in the management of patients with peripheral artery disease."</td></tr>
<tr><th colspan="6">CRITIQUE</th></tr>
<tr><td>Study strengths</td><td colspan="5">• Clinical outcomes assessed include both cardiovascular- and limb-related risk factors
• Primary analysis based on intention-to-treat principle
• Baseline characteristics well-matched between study arms
• High rates of GDMT usage among study participants
• Outcomes prespecified for PAD subgroup analysis
• Net clinical benefit analysis performed
• Clinical events adjudicated by a vascular disease expert as needed</td></tr>
</table>

Study limitations	• Patients with symptomatic PAD of the LE represented a small subset of the overall study population (15%) • Treatment effect may be overestimated as trial was stopped early for efficacy • No adjustments made for multiple comparisons in the PAD subgroup analysis • No reporting of patient lipid profile • PAD subcommittee analysts aware that primary outcome was met in overall study population • Moderate potential for funding bias
Applicability	• Benefit of study drug seen against a background of GDMT • Bleeding risk and nonadherence are necessary considerations prior to initiating low-dose rivaroxaban • Patients with prior stroke poorly represented • Net clinical benefit favors low-dose rivaroxaban in patients with low bleeding risk
Key Takeaway	• In patients with stable CAD, PAD or carotid artery disease, low-dose rivaroxaban reduced the risk of MACE and limb events in patients with low bleeding risk already receiving standard GDMT.

Table 8. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. *N Engl J Med*. 2020;382(21):1994-2004.[21]		
STUDY OVERVIEW		
Objective	• To determine whether low-dose rivaroxaban further preserves lower extremities and improves CV outcomes in patients with symptomatic PAD who have undergone peripheral revascularization when used in combination with aspirin	
METHODS		
Overview	• Multicenter, randomized, double-blind, placebo-controlled trial	
Inclusion/ exclusion criteria	• Age ≥50 • LE PAD (ABI ≤0.8 or toe-brachial index [TBI] ≤0.6 w/functional limitation, imaging evidence of occlusive disease) • Revascularization within 10 days prior to randomization	• Planned long-term use (>6 months) of clopidogrel • Significant ulceration/gangrene in either leg • High risk of major bleeding • CKD V • History of ICH, CVA/TIA • ACS within 30 days • Poorly controlled HTN, DM (at discretion of investigator) • Clinical condition requiring systemic anticoagulation
Interventions	• Patients randomized (1:1) to receive rivaroxaban 2.5 mg BID or matching placebo in combination with aspirin 100 mg daily ○ Clopidogrel use at discretion of investigator • Follow-up conducted every 6 months	
Outcomes	• **Primary outcome:** composite of acute limb ischemia, major amputation for CV causes, MI, ischemic stroke, and death from CV causes • **Secondary outcomes:** unplanned index-limb revascularization for recurrent limb ischemia; hospitalization for coronary or peripheral event of thrombotic nature; all-cause mortality;	

<table>
<tr><td></td><td>VTE
• Safety: TIMI major bleeding; other definitions of bleeding (ISTH, BARC); ICH; fatal bleeding</td></tr>
<tr><td>Statistical analysis</td><td>• Aimed to enroll 6,500 patients to provide the trial with 90% power to attain an estimated 1,015 events using HR of 0.80 and one-sided alpha of 0.025
• Kaplan-Meier method: estimate event risk over time
• Cox proportional-hazards model: compare risk of events
• Secondary outcomes tested in hierarchical fashion
• Intention-to-treat analysis performed for primary and secondary outcomes; modified intention-to-treat analysis performed for safety outcomes</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Enrollment</td><td>• N=6564; 3286 in rivaroxaban group, 3278 in placebo group
• Demographics: age 67, female 26%, white 81%
• Risk factors: HTN 81%, DM 40%, previous MI 11%, current smoker 35%
• PAD: mean ABI 0.56, previous amputation 5.9%, claudication 95%, CLI 30%, previous peripheral revascularization 36%
• Qualifying event: endovascular 65%, surgical 35%
• Medications: statin 80%, ACE inhibitor/ARB 63%, clopidogrel 51%</td></tr>
<tr><td>Primary outcome (rivaroxaban vs placebo)</td><td>• 15.5% vs 17.8% (HR 0.85, 95% CI 0.76 to 0.96, NNT=44)
○ Median follow-up: 28 months (IQR 22 to 34 months)
<table>
<tr><th>Component</th><th>Rivaroxaban</th><th>Placebo</th><th>HR (95% CI)</th><th>NNT</th></tr>
<tr><td>Acute limb ischemia</td><td>4.7%</td><td>6.9%</td><td>0.67 (0.55 to 0.82)</td><td>46</td></tr>
<tr><td>Major amputation for CV causes</td><td>3.1%</td><td>3.5%</td><td>0.89 (0.68 to 1.16)</td><td>--</td></tr>
<tr><td>MI</td><td>4.0%</td><td>4.5%</td><td>0.88 (0.70 to 1.12)</td><td>--</td></tr>
<tr><td>Ischemic stroke</td><td>2.2%</td><td>2.5%</td><td>0.87 (0.63 to 1.19)</td><td>--</td></tr>
<tr><td>CV death</td><td>6.1%</td><td>5.3%</td><td>1.14 (0.93 to 1.40)</td><td>--</td></tr>
</table></td></tr>
<tr><td>Secondary outcomes (rivaroxaban vs placebo)</td><td>• Unplanned index-limb revascularization for recurrent limb ischemia: 17.8% vs 20.0% (p=0.03, NNT=46)
• Hospitalizations for coronary or peripheral events of thrombotic nature: 8.0% vs 10.9% (p<0.001, NNT=35)
• No difference observed in all-cause mortality (9.8% vs 9.1%, p=0.34)</td></tr>
<tr><td>Safety (rivaroxaban vs placebo)</td><td>• Similar rates of TIMI major bleeding (1.90% vs 1.35%, HR 1.43, 95% CI 0.97 to 2.10)
• ISTH major bleeding: 4.30% vs 3.08% (HR 1.42, 95% CI 1.10 to 1.84, NNH=82)
• No differences in ICH or fatal bleeding observed</td></tr>
<tr><td colspan="2">AUTHOR CONCLUSIONS</td></tr>
<tr><td>Author's conclusions</td><td>• "In patients with peripheral artery disease who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone."</td></tr>
</table>

CRITIQUE	
Study strengths	• Clinical outcomes assessed include both cardiovascular- and limb-related risk factors • Risk of bleeding well-established using three common scoring systems • Clinical events adjudicated by an independent committee • Baseline characteristics well-matched between study arms • Intention-to-treat analysis performed for efficacy endpoints • Triple therapy with aspirin, clopidogrel, and rivaroxaban allowed for up to six months
Study limitations	• High discontinuation rate • Stringent exclusion criteria (prior CVA, uncontrolled HTN/DM) • No reporting of graft type in patients that underwent surgical intervention • No reporting of patient lipid profile or adherence to trial regimen • Choice of TIMI major bleeding as primary safety outcome may downplay associated bleeding risk
Applicability	• VOYAGER PAD provides further evidence to support the use of low-dose rivaroxaban in patients with high-risk PAD • Evidence for reduction in MACE is most compelling in patients with concomitant CAD
Key Takeaway	• Low-dose rivaroxaban, in combination with aspirin, further reduces the risk of MACE and subsequent limb events in patients with PAD following peripheral revascularization.

Summary and Recommendations

- Evidence from recent studies demonstrate that low-dose oral anticoagulation (rivaroxaban 2.5 mg BID) in combination with aspirin reduces MACE and MALE in select patients with symptomatic PAD.
- Recommendations to support the use of oral anticoagulation for CV risk reduction can now be made in settings where ischemic risk is high and bleeding risk is low.
- The combination of rivaroxaban 2.5 mg BID + aspirin 81 mg daily should be considered in all patients with symptomatic PAD except for the following:
  - Full-dose anticoagulation
  - Compelling indication for DAPT (e.g., recent coronary stent or acute coronary syndrome)
  - Aspirin allergy or preference for non-aspirin antiplatelet agent
  - Poorly controlled HTN or history of stroke
  - High bleed risk (e.g., prior major bleed or predisposition to bleeding)
  - ESRD
  - Moderate-severe liver impairment (i.e., Child-Pugh B or C)
  - Poor adherence to BID medications
- In patients with symptomatic PAD not deemed to be good candidates for combined low-dose rivaroxaban plus aspirin, consider aspirin and/or clopidogrel as clinically appropriate.

Appendix A: Screening Criteria[6]

- Per AHA/ACC recommendations, the following should be screened for PAD:
  - Age ≥65 years
  - Age 50–64 years, with risk factors for atherosclerosis (e.g., DM, history of smoking, HLD, HTN) or family history of PAD
  - Age <50 years, with DM and 1 additional risk factor for atherosclerosis
  - Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)

Table A1. History and/or Physical Exam Findings Suggestive of PAD

History	Physical Exam
Claudication	Abnormal LE pulse examination
Other non-joint-related exertional LE symptoms	Vascular bruit
Impaired walking function	Nonhealing LE wound
Ischemic rest pain	LE gangrene
	Other suggestive LE physical findings

Appendix B: PAD Classification Systems[22]

Table B1. PAD Classification Systems					
Fontaine Classification			Rutherford Classification		
Stage	Symptoms	Proposed Universal Criteria	Grade	Category	Symptoms
I	Asymptomatic	Asymptomatic	0	0	Asymptomatic
II	IC/other exertional limb symptoms	Mild claudication/limb symptoms (no limitation in walking)	0	1	Mild claudication
IIa		Moderate claudication/limb symptoms (able to walk without stopping >2 blocks or 200 m or 4 min)	1	2	Moderate claudication
IIb		Severe claudication/limb symptoms (only able to walk without stopping <2 blocks or 200 m or 4 min)	1	3	Severe claudication
III	Ischemic rest pain	Ischemic rest pain (pain in the distal limb at rest felt to be due to limited arterial perfusion)	II	4	Ischemic rest pain
IV	Ulceration or gangrene	Ischemic ulcers on distal leg Ischemic gangrene	III III	5 6	Ischemic ulceration Ischemic gangrene

Appendix C: Revascularization Procedures[23]

Table C1. Revascularization of Advanced PAD			
	Techniques	Advantages	Limitations
Endovascular Revascularization	• Balloon angioplasty • Drug-coated balloon • Bare-metal stents • Drug-eluting stents • Covered stents • Atherectomy	• Minimally invasive • Low morbidity • Often repeatable • Favorable outcomes in large arteries, short lesions, and stenosis (vs occlusion)	• Long lesion length, small vessel diameter, and severe calcification • Common femoral artery and popliteal artery disease is unfavorable • Reduced anatomic durability for femoropopliteal and infrapopliteal interventions • In-stent restenosis is difficult to treat

Open Surgical Revascularization	• Endarterectomy
	• Open bypass
	  ○ Prosthetic graft
	  ○ Autogenous graft
		• Flexibility to address diverse anatomic patterns and lesions
		• Can be combined with endovascular revascularization in hybrid approaches
		• Improved anatomical durability
			• Invasive and increased risk for patient
			• Wound morbidity and systemic complications
			• Adequate-quality autogenous vein is absent in 20-40% of patients who require a distal bypass
			• Poor outcomes for non-autogenous conduits in below-knee bypass

Appendix D: Bleeding Definitions[24,25]

TIMI

- Major
  - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
  - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
  - Fatal bleeding (bleeding that directly results in death within 7 d)
- Minor
  - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

ISTH

- Major
  - Fatal bleeding
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome
  - Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells
- Minor: all nonmajor bleeds
  - Clinically Relevant Nonmajor/Minor
    - An acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:
      - A hospital admission for bleeding
      - A physician guided medical or surgical treatment for bleeding
      - A change in antithrombotic therapy (including interruption or discontinuation of study drug)

BARC

- Type 0
  - No bleeding
- Type 1
  - Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- Type 2
  - Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
    - Requiring nonsurgical, medical intervention by a healthcare professional
    - Leading to hospitalization or increased level of care
    - Prompting evaluation
- Type 3
  - Type 3a

        - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed)
        - Any transfusion with overt bleeding
    - Type 3b
        - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed)
        - Cardiac tamponade
        - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/ hemorrhoid)
        - Bleeding requiring intravenous vasoactive agents
    - Type 3c
        - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
        - Subcategories confirmed by autopsy or imaging or lumbar puncture
        - Intraocular bleed compromising vision
- Type 4: CABG-related bleeding
    - Perioperative intracranial bleeding within 48 h
    - Reoperation after sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period
    - Chest tube output ≥2L within a 24-h period
- Type 5: fatal bleeding
    - Type 5a
        - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b
        - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

References

1. Firnhaber JM, Powell CS. Lower extremity peripheral artery disease: diagnosis and treatment. *Am Fam Physician*. 2019;99(6)362-9.
2. Rueda CA, Nehler MR, Perry DJ, et al. Patterns of artery disease in 450 patients undergoing revascularization for critical limb ischemia: implications for clinical trial design. *J Vasc Surg*. 2008;47(5):995-1000.
3. Criqui MH, Matsushita K, Aboyans V, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e171-e191.
4. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110(6):738-43.
5. Ridker PM, Stampfer MJ, Rifai N, et al. A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral artery disease. *JAMA*. 2001;285(19):2481-85.
6. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation. 2017 Mar 21;135(12):e790]. *Circulation*. 2017;135(12):e686-e725.
7. Alberts MJ, Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international Reduction of Atherothrombosis for Continued Health Registry. *Eur Heart J*. 2009;30(19):2318-26.
8. Violi F, Basili S, Berger JS, Hiatt WR. Antiplatelet therapy in peripheral artery disease. *Handb Exp Pharmacol*. 2012;(210):547-563.
9. Jones WS, Patel MR, Dai D, et al. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000-2008. *J Am Coll Cardiol*. 2012;60(21):2230-6.
10. Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J*. 2013;165(5):809-815.e1.
11. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in BMJ 2002 Jan 19;324(7330):141]. *BMJ*. 2002;324(7329):71-86.
12. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39(9):763-816.
13. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication [published correction appears in J Vasc Surg. 2015 May;61(5):1382]. *J Vasc Surg*. 2015;61(3 Suppl):2S-41S.

14. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [published correction appears in Eur Heart J. 2020 Dec 1;41(45):4317]. *Eur Heart J*. 2020;41(2):255-323.
15. American Diabetes Association. 10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes-2021* [published correction appears in Diabetes Care. 2021 Sep;44(9):2183-2185]. *Diabetes Care*. 2021;44(Suppl 1):S125-S150.
16. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial [published correction appears in Lancet 2000 Mar 25;355(9209):1104]. *Lancet*. 2000;355(9201):346-51.
17. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med.* 2007;357(3):217-27.
18. Moll F, Baumgartner I, Jaff M, et al. Edoxaban plus aspirin vs dual antiplatelet therapy in endovascular treatment of patients with peripheral artery disease: results of the ePAD trial. *J Endovasc Ther*. 2018;25(2):158-68.
19. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-30.
20. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):219-29.
21. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382(21):1994-2004.
22. Stacy Z, Chow S. Peripheral Arterial Disease. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e*. McGraw Hill; 2020. Accessed October 30, 2021.
23. Hiramota JS, Teraa M, de Borst GJ, Conte MS. Interventions for lower extremity peripheral artery disease. *Nature Reviews Cardiology*. 2018;15:332-50.
24. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736-2747.
25. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.