Peripheral Artery Disease, the Factor Xa Inhibitor Rivaroxaban, and the Role of the Podiatrist

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Abstract

Antithrombotic therapy with aspirin has been the mainstay in guideline-directed medical therapy to prevent major adverse limb events (MALEs) for individuals with peripheral artery disease (PAD). Despite years of experience with evidence-based management, and evolving interventional techniques, the rates of amputation and harmful sequalae remain unacceptably high. This review serves to introduce the most recent data with a factor Xa inhibitor as a novel antithrombotic strategy for PAD. Recent data from the COMPASS and VOYAGER PAD clinical trials demonstrate improved outcomes with low-dose rivaroxaban added to aspirin when administered to patients with PAD. Both trials resulted in superior reductions in cardiovascular and limb events with the dual-pathway inhibition approach over aspirin alone. While an increase in bleeding was seen in the combination arm, irreversible harm (as in fatal intracranial hemorrhage or bleeding into a critical organ) were not different. Knowledge of the current use of antithrombotic therapy in the treatment of PAD, along with emerging data regarding the efficacy and safety of low-dose rivaroxaban plus aspirin, presents an opportunity to impact the outcomes for appropriate individuals with this disease.

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Key words: anticoagulation, major adverse limb events, MALE, PAD, peripheral artery disease, podiatry, rivaroxaban

Background

The traditional belief that peripheral artery disease (PAD) is a disease state with an inevitable path toward amputation is an antiquated paradigm that needs to be reassessed. PAD refers to a medical diagnosis involving partial or complete blockage of at least 1 peripheral artery and affects more than 200 million people worldwide.[1] Geographically and demographically, it is widespread, afflicting patients across the spectrum of age, sex, race, and socioeconomic status. Patients with PAD are likely to also experience a wide range of comorbidities, such as diabetes, hypertension, obesity, and hyperlipidemia.[2] These comorbidities are often complicating factors that either speed the progression of PAD and/or worsen the outcomes. Left unchecked, the loss of proper blood circulation caused by PAD leads to a sequela involving skin necrosis, aggressive infections, foot and limb amputation, and ultimately death. Therefore, proper management to maintain the patency of the lower-extremity arteries is critical in reducing tissue death and maintaining skin health, thereby helping to prevent these potential outcomes.

Additionally, PAD is a tremendous financial burden on both the patients and the overall healthcare system. For example, assessing the individual health are-related expenditures in the United States from 2011 to 2014, Scully et al reported that the total average annual expenditures per individual for those with PAD was approximately $11,553 (95% confidence interval [CI], $8137-$14,968) compared with $4219 (95% CI, $4064-$4375; *P*<.001) for those without.[3] With over 8 million individuals in the United States that have lower-extremity PAD, the combined annual healthcare cost exceeds $21 billion.[4] Certainly, this represents a significant financial burden for both the individual and the healthcare system.

Considering the global impact and progressive nature of the disease, vigilant management and engaged healthcare providers and patients are needed, with podiatrists playing an ever-increasing and integral role in the identification and care of these individuals. As such, this manuscript is meant to review the

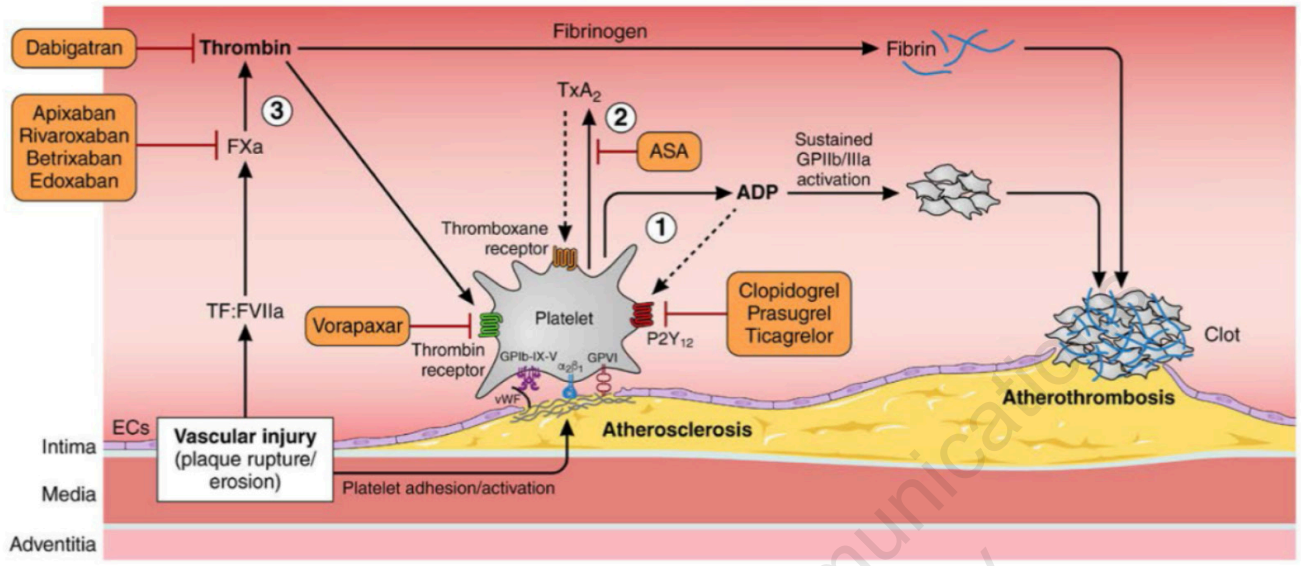


FIGURE 1. **Canonical mechanistic concept of atherothrombosis and potential therapeutic targets.** Platelet activation and coagulation are stimulated by the interaction of flowing blood with injured vessel wall. There are 3 major pathways amplifying platelet activation that are inhibited by currently available oral agents: (1) the COX-1 pathway; (2) the ADP-P2Y$_{12}$ pathway; and (3) the thrombin pathway. Activity of the thrombin pathway can be inhibited by direct inhibition of thrombin, inhibition of thrombin generation by targeting FXa, and inhibition of the platelet protease activated receptor (PAR)-1, the thrombin receptor. ASA = acetylsalicylic acid; EC = endothelial cell; FVIIa = factor VIIa; FXa = factor Xa; GP IIb/IIIa = glycoprotein IIb/IIIa; TF = tissue factor; TxA$_2$ = thromboxane A$_2$. Modified from Gurbel and Tantry[6] with permission. ©2010, Wolters Kluwer Health, Inc.

pathophysiology of PAD and inform the podiatry community of recent clinical trial data and a new pharmacologic treatment option available for these patients.

Pathophysiology. PAD encompasses atherosclerotic obstructions reducing blood flow to the lower extremities. This decrease in blood flow leads to deficiencies in oxygenation and a corresponding decrease in metabolic processes.[5] The combined ischemia and lack of perfusion results in endothelial dysfunction, oxidant stress, increased inflammatory processes, and metabolic changes within the muscles, which ultimately impair normal function. Normal blood-clotting mechanisms — specifically, thrombin and platelets — are key factors in the development and pathogenesis of atherosclerosis and thrombosis (Figure 1).[6] Given the already reduced lumen in peripheral arteries, any thrombus poses an increased ischemic risk to the PAD patient.

The continued ischemia results in claudication, the most common symptom of PAD. Claudication is characterized as pain in the calf muscles induced by exercise and generally relieved with rest. This condition is present in only 10% of patients with known PAD, while 40% have no pain-related symptoms and the remaining 50% have either lower levels of pain, pain that does not originate from the calves, or pain persisting beyond at least 10 minutes of rest.[7]

As previously noted, PAD is a progressive disease. As atherosclerotic lesions increase in size, so does the ischemic effect. Thrombi further increase the risk of critical limb ischemia (CLI). If left untreated, this situation often leads to amputation, spanning from minor to total. Limb preservation is one of the most critical aspects of PAD management, as data demonstrate that amputation adversely affects the patient's overall health, quality of life, and mortality.[8]

Current interventions. PAD is currently managed by either surgical or pharmacological interventions. In most cases, multiple modalities are required to relieve symptoms, improve function, preserve limbs, and attempt to slow the progression of the disease. Research into the physiological pathways that activate both thrombin and platelets offers insight into potential pharmacological treatment options for this disease. Current surgical options generally include angioplasty, stenting, and bypass grafts, all of which are then followed with dual-antiplatelet therapy. The duration of antiplatelet therapy varies based on current treatment guidelines for the specific surgical intervention that is applied.

As mentioned, pharmacological management of PAD has traditionally relied on the use of antiplatelet agents, alone or in combination, commonly using acetylsalicylic acid (ASA), a COX-2 Inhibitor, and/or clopidogrel (a P2Y$_{12}$ inhibitor).[9] This type of intervention is still considered a critical component of the overall strategy in the prevention of cardiovascular events in patients with PAD and is a strategy based on the pathophysiological development of atherothrombosis via platelet adhesion, activation, and aggregation at the site of injury. Other classes of medications have been developed, such

TABLE 1. General comparison of previous antiplatelet clinical trials to the use of rivaroxaban with aspirin (COMPASS trial) in patients at high cardiovascular risk.

Study	CAPRIE[12]	CHARISMA[13]	PEGASUS[14]	TRA 2°P-TIMI 50[15]	COMPASS[16]
Population	(n = 19,185) History of ischemic stroke, MI, symptomatic PAD	(n = 15,603) History of CV disease or risk factors	(n = 21,162) History of MI (prior 1 to 3 years), high CV risk	(n = 26,449) History of ischemic stroke, MI, symptomatic PAD	**(n = 27,395) Stable CAD and/or PAD**
Treatment arms	Clopidogrel vs aspirin	Clopidogrel + aspirin vs aspirin	Ticagrelor + aspirin vs aspirin	Vorapaxar vs aspirin ± thienopyridine	**Rivaroxaban + aspirin OR rivaroxaban alone vs aspirin**
Results	Significant reduction with clopidogrel in stroke, MI, and CV death, with PAD patients benefiting most. Higher GI bleeding seen with aspirin.	Non-significant reduction with the dual-antiplatelet arm in all participants. Benefit only seen in those with known CV. No increase in severe bleeding.	Significant reduction with combination treatment in CV death, MI, and stroke, with increased risk of major bleeding.	Reduction in peripheral revascularization CV death, MI, and stroke, with increased risk of moderate-severe bleeding with vorapaxar.	**Significant reduction with rivaroxaban + aspirin in CV death, MI, stroke, and limb events, with increased risk of bleeding leading to hospitalization.**
MACE	9% relative risk reduction	7% relative risk reduction (NS)	16% relative risk reduction	13% relative risk reduction	**24% relative risk reduction**
Mortality outcomes	No mortality benefit	No mortality benefit	No mortality benefit	No mortality benefit	**18% relative risk reduction**

CAD = coronary artery disease; CV = cardiovascular; GI = gastrointestinal; MACE = major adverse cardiovascular events; MI = myocardial infarction; NS = non-significant; PAD = peripheral artery disease.

as phosphodiesterase-2 (PDE2) inhibitors, including cilostazol and pentoxifylline, and protease activation receptor 4 (PAR4) inhibitors, including vorapaxar. However, they have not been widely adopted, likely due to their overall limited or mixed clinical efficacy.[10]

However, even with the relative success of antiplatelet therapy, given alone or in combination, the risk of vascular events remains high. Therefore, there has been interest in assessing the combination of antiplatelet and anticoagulant therapy as a possible enhancement to this traditional treatment paradigm.[6] This interest was not without merit, as previous trials assessing the use of warfarin dosed to an international normalized ratio of 2.0-3.0, in combination with ASA, reduced the risk of myocardial infarction (MI), ischemic stroke, and all-cause mortality by approximately 27% compared with ASA alone.[11] However, the efficacy of this regimen was accompanied by a more than 2-fold excess of major bleeding.[11] Likewise, other efforts in identifying a better treatment combination with warfarin, which typically focused on new antiplatelet therapies (terutroban [a platelet thromboxane receptor antagonist]; clopidogrel, prasugrel, and ticagrelor [$P2Y_{12}$ antagonists]; and vorapaxar [a PAR-1 receptor antagonist]), each resulted in either insufficient benefit to warrant a switch in treatment or was accompanied by a substantial excess of bleeding. Table 1 provides a general comparison of previous antiplatelet trials to the use of rivaroxaban, a factor Xa (FXa) inhibitor, in combination with ASA. Further details on the use of rivaroxaban in combination with ASA in these patient populations are provided in the subsequent sections (Table 1).[12-16]

Lastly, the combination of clopidogrel with ASA administered to PAD patients requiring below-the-knee bypass grafting, does not appear to improve the occurrence of limb or systemic outcomes as reported in the CASPAR (Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral ArteRial disease) trial.[17]

Over the last several years, a new class of anticoagulant agents, the direct oral anticoagulants (DOACs), have been developed. These agents affect the formation of thrombin, either directly or indirectly, through inhibiting the activation of prothrombin into thrombin. The factor Xa (FXa) inhibitors, a key agent in this class, have proven to be useful in the prevention and treatment of venous thromboembolic disease (deep vein thrombosis and pulmonary embolism), along with the prevention and treatment of stroke secondary to non-valvular atrial fibrillation. One of the many benefits of FXa inhibitors is that they are also orally administered, but have fewer drug-drug or dietary interactions, and do not require routine lab testing to monitor effective drug levels, compared with traditional vitamin K antagonists.

Recently, 2 pivotal clinical trials, COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[16] and VOYAGER-PAD (Vascular Outcomes Study of Aspirin Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD)[18] have demonstrated that when combined with ASA, the DOAC rivaroxaban significantly reduces both major adverse limb event (MALE) rate and major adverse cardiovascular event (MACE) rate in patients with PAD. While there is, in both cases, an increase in bleeding vs treating patients with ASA alone, the net clinical benefit still favors the use of rivaroxaban in

combination with ASA in this patient population.[16,18] The results of the COMPASS trial subsequently supported the currently approved labeling for the reduction of risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) and/or PAD.[19] The results from the VOYAGER-PAD study, reported earlier this year, will be submitted for regulatory consideration in the coming months; however, they do not yet support any labeling claim.

Rivaroxaban + ASA in combination as a pharmacologic intervention. Rivaroxaban is an extensively studied, potent, and clinically effective FXa inhibitor, and was the first of this class of compounds to receive approval from the United States Food and Drug Administration (FDA). As an FXa inhibitor, rivaroxaban acts at the convergence point of the intrinsic and extrinsic coagulation pathways. Inhibiting this enzyme pathway blocks the generation of thrombin, thereby effectively diminishing the thrombin-mediated activation of coagulation.[20] Rivaroxaban also displays some indirect effects on platelet aggregation via the inhibition of tissue-factor induced activity secondary to its primary mechanism of action.[21] However, these antiplatelet effects can be considered minor when compared to traditional $P2Y_{12}$ inhibitors or even ASA.

Rivaroxaban is currently approved for 8 therapeutic indications, and each has a specific regimen that involves different dosing strengths, frequency, and duration,[19] all of which are dependent on the condition being treated. Considering the recent success of rivaroxaban across many types of cardiovascular conditions, the concept of combining anticoagulant and antiplatelet therapies into a single regimen for CAD and/or PAD was targeted. Unlike other indications, where full-dose anticoagulation may be needed, a different approach was used. A very low dose of rivaroxaban (2.5 mg twice daily) was combined with ASA and assessed in the COMPASS trial.[16] It was believed, and later validated by the trial results, that this combination could act synergistically to inhibit thrombosis through these 2 pathways by both the direct effects of ASA on the actual clot via the effects mediated by the inhibition of platelet activation and the resultant inhibition of activated coagulation factor generation (FXa) with rivaroxaban.[6]

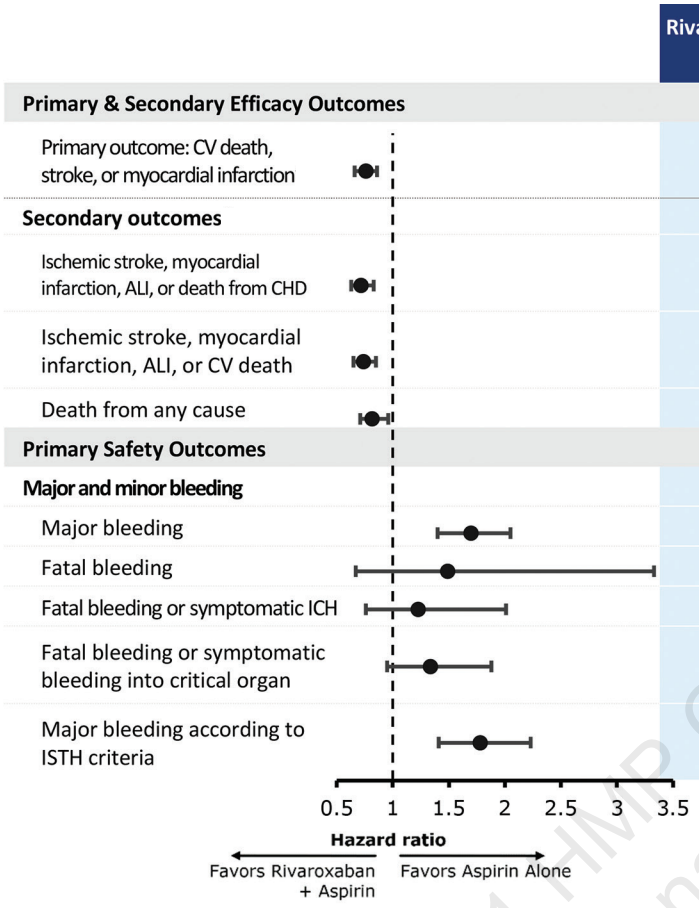
To date, rivaroxaban is the only FXa inhibitor to be successfully studied and later approved for use in this chronic disease state. The benefit of rivaroxaban in this patient population is further supported by multiple subgroup analyses in patients with comorbid conditions that include obesity, diabetes, and renal disease, across this and other approved indications.[22-24] Neither obesity nor diabetic comorbid states require the dose of rivaroxaban to be modified. While a dose modification for reduced renal function (creatinine clearance ≤50 mL/min) is required for the prevention of stroke in patients with non-valvular atrial fibrillation, such a modification is not required for patients with CAD and/or PAD.[19]

This is a targeted review of the DOAC rivaroxaban in patients with PAD, the objective of which is to review the phase 3 randomized clinical trial results from both the COMPASS and VOYAGER-PAD trials. The results from the COMPASS trial ultimately support the current drug labeling for the reduction of risk of major cardiovascular events in patients with CAD or PAD. The results from the VOYAGER-PAD trial, published in March 2020, will be filed for regulatory consideration in the coming months. Rivaroxaban is not currently approved for use in patients with PAD who have recently undergone a lower-extremity revascularization procedure. The data from the VOYAGER-PAD trial are felt to be relevant for this review to better inform the medical community of the latest research in this important patient population.

The COMPASS Trial

The COMPASS trial was a multicenter, international, double-blind, double-dummy, randomized, phase 3 trial conducted in 27,395 participants with stable atherosclerotic vascular disease, CAD (91%) and/or PAD (27%), who were at high risk for ischemic events.[16] CAD was defined as a history of MI or history of angina with evidence of multivessel disease, or multivessel revascularization. PAD was classified as claudication with documented arterial disease, previous amputation or revascularization, carotid revascularization, or asymptomatic carotid disease with at least 50% stenosis.[25] The primary efficacy outcome of the trial was a reduction in MACE, which was defined as the composite of cardiovascular death, stroke, or MI. The main safety outcome was bleeding that met the International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding and also included all bleeding that led to presentation to an acute-care facility.[26] Participants were randomized in a 1:1:1 ratio to receive either ASA 100 mg daily, rivaroxaban 5 mg twice daily, or rivaroxaban 2.5 mg twice daily + ASA 100 mg daily. Before the planned number of 2200 events had occurred during the trial, an independent data safety monitoring board recommended early termination after 50% of the efficacy events were reached, due to clear evidence of efficacy in favor of the rivaroxaban + ASA treatment arm. As such, this review will focus on the results obtained when comparing the 2.5 mg twice daily + ASA 100 mg daily treatment arm with the ASA 100 mg treatment arm, which ultimately supported its regulatory approval for use in the United States.[19]

Upon early study termination, the primary efficacy outcome occurred in 379 patients (4.1%) randomized to rivaroxaban + ASA and 496 patients (5.4%) randomized to ASA alone (hazard ratio [HR], 0.76; 95% CI, 0.66-0.86; $P<.001$) (Figure 1). The primary safety outcome occurred in 288 patients (3.1%) in the rivaroxaban + ASA group vs 170 patients (1.9%) in the ASA alone group (HR, 1.7; 95% CI, 1.40-2.05; $P<.001$) (Figure 2). Important to note, there was no significant difference between the 2 treatments when it came to fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ. A prespecified net clinical benefit



	Rivaroxaban + Aspirin (N = 9152)	Aspirin Alone (N = 9126)	Rivaroxaban + Aspirin vs. Aspirin Alone HR (95% CI)
Primary & Secondary Efficacy Outcomes			
Primary outcome: CV death, stroke, or myocardial infarction	379 (4.1)	496 (5.4)	0.76 (0.66-0.86)
Secondary outcomes			
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	450 (4.9)	0.72 (0.63-0.83)
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	516 (5.7)	0.74 (0.65-0.85)
Death from any cause	313 (3.4)	378 (4.1)	0.82 (0.71-0.96)
Primary Safety Outcomes			
Major and minor bleeding			
Major bleeding	288 (3.1)	170 (1.9)	1.70 (1.40-2.05)
Fatal bleeding	15 (0.2)	10 (0.1)	1.49 (0.67-3.33)
Fatal bleeding or symptomatic ICH	36 (0.4)	29 (0.3)	1.23 (0.76-2.01)
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	58 (0.6)	1.34 (0.95-1.88)
Major bleeding according to ISTH criteria	206 (2.3)	116 (1.3)	1.78 (1.41-2.23)

FIGURE 2. COMPASS efficacy and safety overall study outcomes.[16]

outcome of cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ significantly favored the rivaroxaban + ASA arm over ASA alone, with a lower risk of the combination regimen (4.7% vs 5.9%, respectively; HR, 0.80; 95% CI, 0.70-0.91; P<.001).

Diabetes mellitus is a commonly occurring major risk amplifier in patients with established atherosclerosis. In particular, those with polyvascular disease — a marker of significant clinical atherosclerotic burden — and concomitant diabetes mellitus, which frequently coexist, constitute a very high-risk group of patients, subject to coronary, cerebral, and peripheral ischemic events. There was a consistent and similar relative risk reduction for benefit of rivaroxaban + ASA vs ASA alone in patients both with and without diabetes for the primary efficacy endpoint and the secondary endpoints, including mortality. However, due to their higher baseline risk, although the absolute risk reduction (ARR) appeared larger in patients with vs without diabetes, both subgroups derived similar benefit. As in the trial overall, there was a significant increase in major bleeding with the dual-pathway regimen in the subgroups with and without diabetes, with a similar degree of risk increase.[23]

The prespecified subpopulation analysis in participants with diabetes at baseline suggests a greater absolute reduction of the outcome of MACE and MALE including amputation with rivaroxaban + ASA vs ASA alone (9.4% vs 12.1%, respectively; HR, 0.73; 95% CI, 0.61-0.88; ARR, 2.7%).[27] For comparison, participants without diabetes experienced rates of 6.1% vs 7.8%, respectively (HR, 0.74; 95% CI, 0.62-0.89; ARR, 1.7%; Gail-Simon qualitative $P_{interaction}$<.001).[27]

COMPASS PAD subgroup analysis. Patients with CAD and/or PAD are at a high risk for MACE. However, patients with PAD are also at a higher risk for MALE, such as severe limb ischemia and amputation. Considering this risk, a prespecified subgroup analysis of the COMPASS trial was conducted, consisting of the 7470 participants diagnosed with PAD. From this PAD patient pool, 2492 patients were randomized to rivaroxaban 2.5 mg twice daily + ASA 100 mg daily, 2474 patients were randomized to rivaroxaban 5 mg twice daily, and 2504 patients were randomized to ASA 100 mg daily. Similar to the review of the overall COMPASS trial, only the results from the rivaroxaban 2.5 mg twice daily + ASA 100 mg daily and ASA 100 mg daily treatment arms will be discussed.

	Low-dose Rivaroxaban + Aspirin (N = 2492)	Aspirin Alone (N = 2504)	Low-dose Rivaroxaban + Aspirin vs. Aspirin Alone [HR (95% CI)]
Primary & Secondary Efficacy Outcomes			
Cardiovascular death, stroke, myocardial infarction*	126 (5%)	174 (7%)	0.72 (0.57-0.90)
Coronary heart disease death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	115 (5%)	169 (7%)	0.68 (0.53-0.86)
Cardiovascular death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	142 (6%)	198 (8%)	0.71 (0.57-0.88)
Myocardial infarction	51 (2%)	67 (3%)	0.76 (0.53-1.09)
Stroke	25 (1%)	47 (2%)	0.54 (0.33-0.87)
Cardiovascular death	64 (3%)	78 (3%)	0.82 (0.59-1.14)
Death	129 (5%)	142 (6%)	0.91 (0.72-1.16)
Prespecified limb outcomes			
Acute limb ischaemia‡	19 (1%)	34 (1%)	0.56 (0.32-0.99)
Chronic ischaemia‡	16 (1%)	24 (1%)	0.67 (0.35-1.26)
Major adverse limb event‡	30 (1%)	56 (2%)	0.54 (0.35-0.84)
All vascular amputations	11 (<1%)	28 (1%)	0.40 (0.20-0.79)
Major amputation‡	5 (<1%)	17 (1%)	0.30 (0.11-0.80)
Major adverse limb event plus major amputations§	32 (1%)	60 (2%)	0.54 (0.35-0.82)
Key composite outcomes for PAD			
Cardiovascular death, stroke, myocardial infarction or major adverse limb event	155 (6%)	222 (9%)	0.69 (0.56-0.85)
Cardiovascular death, stroke, myocardial infarction or major adverse limb event including major amputation	157 (6%)	225 (9%)	0.69 (0.56-0.85)
Primary Safety Outcomes			
Major bleeding*	77 (3%)	48 (2%)	1.61 (1.12-2.31)
Fatal bleeding	4 (<1%)	3 (<1%)	-
Non-fatal symptomatic intracranial heamorrhage	4 (<1%)	8 (<1%)	-
Non-fatal, non-intracranial haemorrhage symptomatic bleeding into a critical organ	13 (1%)	8 (<1%)	1.55 (0.64-3.74)
Other major bleeding (surgical site bleeding requiring reoperation or bleeding leading to hospitalization)	56 (2%)	29 (1%)	1.94 (1.24-3.04)
Fatal or symptomatic bleeding into critical organ	21 (1%)	19 (1%)	1.10 (0.59-2.05)
Fatal or symptomatic bleeding into critical organ or surgical site bleeding leading to re-operation	25 (1%)	22 (1%)	1.13 (0.64-2.01)
ISTH major bleeding	64 (3%)	40 (2%)	1.61 (1.08-2.39)
Sites of bleeding			
Gastrointestinal	41 (2%)	18 (1%)	2.28 (1.31-3.96)
Intracranial	5 (<1%)	9 (<1%)	0.56 (0.19-1.66)
Genitourinary	3 (<1%)	2 (<1%)	-
Ocular	7 (<1%)	3 (<1%)	-
Skin	5 (<1%)	8 (<1%)	-
Respiratory	4 (<1%)	0	-
Other	15 (1%)	10 (<1%)	-
Minor bleeding	198 (8%)	141 (6%)	1.43 (1.15-1.77)

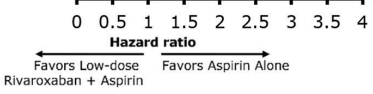


FIGURE 3. COMPASS efficacy and safety — analysis of patients with peripheral artery disease.[28]
Data are presented as number (%) or HR with 95% CI.
Efficacy outcomes: *Prespecified primary outcome of the overall trial. †Prespecified secondary outcomes of the overall trial. ‡Prespecified PAD outcomes. §An additional 11 major amputations of a vascular cause were done that were unlinked to acute or chronic limb ischemia (2 in the low-dose rivaroxaban + aspirin group, 5 in the rivaroxaban alone group, and 4 in the aspirin alone group).
Safety outcomes: *Includes 4 components of prespecified major bleeding definition summarized hierarchically.
CI = confidence interval; HR = hazard ratio; ISTH=International Society of Thrombosis and Hemostasis; PAD = peripheral artery disease.

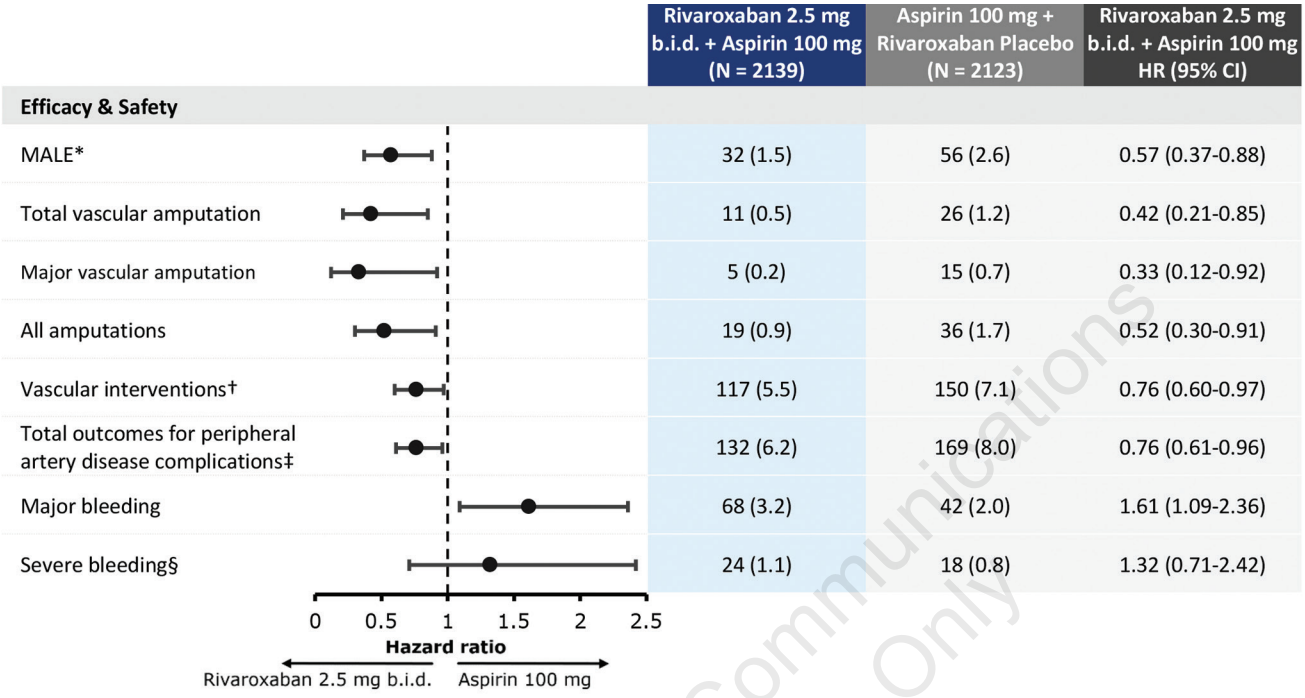


FIGURE 4. COMPASS efficacy and safety — analysis of patients with peripheral artery disease and a major adverse limb event (MALE).[29]
Data are presented as number (%) or HR with 95% CI.
*Acute or chronic limb ischemia; includes all major amputations. †Defined as any vascular interventions of the lower extremity, including bypass surgery, peripheral angioplasty/stenting, amputation, or revision; not captured in acute or chronic limb ischemia leading to an intervention. ‡Defined as a composite of acute or chronic limb ischemia, a peripheral vascular intervention, or hospitalization for other vascular reason. §Bleeding leading to death or symptomatic bleeding into a critical organ or surgical site bleeding requiring reoperation.

The primary efficacy analysis included the assessment of MACE (eg, composite of cardiovascular death, stroke, or MI) outcomes between these 2 treatment groups. However, considering the increased risk of major limb events, an assessment of MALE outcomes that included acute limb ischemia, CLI, and amputation was also included.[28] The primary safety analysis was the assessment of ISTH major bleeding. Both primary efficacy and safety endpoints were consistent with those assessed in the overall COMPASS trial.

For the primary efficacy analysis, a 28% relative risk reduction of the primary MACE outcome was observed in patients who received the combination of rivaroxaban + ASA (126/2492 [5.1% of patients]) compared with those who received ASA alone (174/2504 [6.9% of patients])[28] (Figure 3). MALE outcomes were also significantly lower in the rivaroxaban + ASA group when compared with the ASA alone group, with a 46% relative risk reduction (30/2492 [1.2% of patients] vs 56/2504 [2.2% of patients]) observed (Figure 3). Similarly, both acute limb ischemia (ALI) and major amputations were lower in the rivaroxaban + ASA group when compared with the ASA alone group, with a relative risk reduction of 44% and 70%, respectively (Figure 3).[28]

Compared with ASA alone, the combination of rivaroxaban and ASA significantly reduced the combination of MALE + all major amputations by 46% (Figure 3). Additionally, the composite of MACE or MALE outcomes was significantly lower in the rivaroxaban + ASA group vs the ASA alone group (155/2492 [6.2% of patients] vs 222/2504 [8.9% of patients]), leading to a 31% relative risk reduction (Figure 3). Lastly, the composite of MACE or MALE including major amputation led to a 31% relative risk reduction with rivaroxaban + ASA vs ASA alone (Figure 3).[28]

Major bleeding outcomes were similar to what was seen in the overall COMPASS population and occurred in 77 patients (3%) in the rivaroxaban + ASA group vs 48 patients (2%) in the ASA alone group (HR, 1.61) (Figure 2). Although there was an increase in both major and minor bleeding in the rivaroxaban + ASA group when compared with the ASA alone group, most were gastrointestinal in nature, and there was no difference in either fatal bleeding, intracranial hemorrhage, or symptomatic bleeding into a critical organ (Figure 3).[28]

COMPASS PAD — MALE subgroup analysis. A *posthoc* subgroup analysis of the COMPASS trial was performed solely in patients with lower-extremity PAD to assess the prognosis after a MALE (ostensibly, how dangerous is it to have an MALE?) and the impact of the combination of rivaroxaban + ASA on the outcomes of these and other vascular outcomes.[29] A total of 6391 participants met

the definition for lower-extremity PAD. Of those, 128 participants (2.0%) suffered a MALE during the trial. When evaluating the 1-year cumulative incidence, a MALE significantly increased the risk for subsequent hospitalizations (61.5%), total vascular amputation (20.5%), MACE (3.7%), and death (8.3%). After experiencing an initial (index) MALE, the risk of a subsequent hospitalization increased by approximately 7 times (HR, 7.2), total vascular amputations increased by approximately 200 times (HR, 197.5), the composite of MACE or total vascular amputations increased by approximately 8 times (HR, 7.6), and death increased by approximately 3 times (HR, 3.2); it is important to note that these results were not adjusted for multiplicity.[29]

Importantly, when further assessing these risks following a MALE between treatment arms, the risk of death did not change in participants receiving the combination of rivaroxaban + ASA; however, there was a 6 times greater risk of death (HR, 6.0) for participants randomized to receive ASA alone. Similarly, the risk for the composite of MACE or total vascular amputation in participants receiving rivaroxaban + ASA did not change. However, the risk in those randomized to receive ASA alone increased by approximately 10 times (HR, 10.2).

Much like the overall COMPASS population, participants with lower-extremity PAD in the rivaroxaban + ASA group were less likely to experience either a MALE, total vascular amputation, or major vascular amputation, or to require a vascular intervention.[29] To better understand the relationship between comorbid conditions and residual risk, a *posthoc* analysis of the COMPASS data identified features that contributed to the definition of a high-risk patient as polyvascular disease, diabetes mellitus, heart failure, and estimated glomerular filtration rate <60 mL/min. Patients with several or all of these high-risk features experience reduced thrombotic risk compared with those who have fewer or none of the high-risk features (Figure 4).[30] As expected, the risk for major bleeding was approximately 1.6 fold greater in the rivaroxaban + ASA group when compared with the ASA alone group (HR, 1.6).

VOYAGER-PAD Trial

Up until recently, there have been no proven antithrombotic pharmacologic strategies that have demonstrated efficacy for reducing major adverse events after peripheral interventions for ischemia. VOYAGER-PAD was a multicenter, international, double-blind, double-dummy, randomized trial conducted in 6564 patients.[18] In contrast with the COMPASS trial, which looked at the chronic stable patients with CAD and/or PAD, the VOYAGER-PAD trial (also assessing the same rivaroxaban 2.5 mg + ASA vs ASA alone regimens) focused on outcomes from symptomatic PAD patients randomized within 10 days after a successful revascularization. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition.[18,31] The rivaroxaban + ASA regimen significantly reduced the primary outcome when compared with ASA alone, with the primary composite outcome occurring in 508 patients (15.5%) vs 584 patients (17.8%), respectively; the Kaplan-Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (HR, 0.85; 95% CI, 0.76-0.96; $P<.01$).[18] Specifically, for acute limb ischemia, a 33% relative risk reduction was observed in the rivaroxaban + ASA arm vs ASA alone.[18]

While showing no difference in mortality, there was significant lowering of several other prespecified secondary outcomes, including unplanned index-limb revascularization (relative risk reduction of 12%), hospitalization for coronary or peripheral thrombosis (relative risk reduction of 28%), and various composites of cardiovascular and limb outcomes in the rivaroxaban + ASA group. There was no statistically significant increase in the principal safety outcome of TIMI major bleeding during follow-up, which occurred in 62 patients (1.9%) in the rivaroxaban group and 44 patients (1.35%) in the placebo group, with Kaplan-Meier estimates of the incidence at 3 years of 2.65% and 1.87%, respectively (HR, 1.43; 95% CI, 0.97-2.10; $P=.07$). There was also no increase in intracranial or fatal bleeding between the 2 arms (HR, 0.91; 95% CI, 0.47-1.76; $P=.10$).

Discussion

As podiatrists, we are aware of the complications of PAD, with over 8.5 million people within the United States afflicted by this disease.[32] With a significant number of these individuals being asymptomatic, awareness of this disease is paramount to all lower-extremity physicians. PAD is often diagnosed only when it reaches a symptomatic or critical stage, at which point treatment tends to focus on endovascular or surgical procedures.[33] While these techniques have evolved and innovative treatments continue to be developed, these options do not address the underlying pathophysiologic development of PAD.

Atherosclerotic disease includes PAD, CAD, and cerebrovascular disease (CVD). These disease states have significant overlap, as evidenced in the REACH registry where 3 out of 5 patients with PAD also had CAD and/or CVD. REACH was a large, global, observational registry of ~68,000 patients in 44 countries who were at high risk of atherothrombosis.[34] Nearly 1 in 5 patients from the REACH registry with symptomatic atherosclerosis in the United States had polyvascular disease, with documented symptomatic disease in 2 or more arterial beds. Patients with symptomatic polyvascular atherosclerosis had significantly higher risk for CV events at 3 years vs patients with single vascular bed disease. Over the 3-year course of REACH, patients with PAD only at baseline had the highest risk of progressing to atherosclerosis in other vascular beds. Nearly 10% of PAD patients progressed to polyvascular disease over 3 years, compared with approximately

4% of patients with either CAD or CVD at baseline. And PAD is a progressive disease worsening over time. Five years after clinical diagnosis of PAD, 20% of patients will suffer a non-fatal MI or stroke, while up to 30% will die (75% from cardiovascular causes).[35,36] The importance of developing therapeutic options affecting the pathophysiologic development of this disease is key to temporal and anatomic progression of PAD.

In patients with diabetes, PAD creates an even greater concern. One out of 3 diabetic individuals over the age of 50 years is likely to have PAD, and more than 60% of all lower-limb amputations are performed on diabetic patients. With the rate of diabetes increasing in our society, and the projection that 1 in 3 Americans will have diabetes by 2050, the need for closer observation of the arterial supply to the extremities becomes even more vital. Individuals with diabetes have a greater incidence of PAD, with an acceleration of the disease progression, an increased disease severity, and higher risk of lower-extremity amputation than either disease alone. According to the American Heart Association, people with diabetes and PAD are up to 5 times more likely to lose a limb, and 3 times more likely to die at a younger age.[37-39] To further underscore the importance of optimal medical management of patients with diabetes, the American Diabetes Association (ADA) recently updated the Standards of Medical Care in Diabetes in 2021, wherein recommendation 10:38 states that "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," with level of evidence grade A.[40]

Most individuals with lower-extremity PAD do not present with classic ischemic symptoms, such as claudication, non-healing wounds, or gangrene. In fact, classic claudication is often absent in PAD, as was observed in the Rotterdam study, which showed that only 6% of PAD patients had claudication.[41] The 2001 PARTNERS study found that patients already diagnosed with PAD had classic claudication symptoms <15% of the time, but those recently diagnosed with PAD exhibited this symptom only 6% of the time. Physicians who depend on classic claudication symptoms to detect PAD will miss up to 90% of these patients.[42]

Of major concern to lower-extremity physicians is the development of MALEs, defined as acute or chronic limb ischemia requiring vascular intervention or amputation. The COMPASS PAD subgroup analyses investigated the complications associated with a MALE. After a MALE occurs, the cumulative risk of amputation increases approximately 200 times, with subsequent hospitalization risk increasing approximately 7 times and risk of death increasing approximately 3 times.[29] With such dire prognoses, treatments aimed at avoiding MALEs would be extremely beneficial to both the individual and the healthcare system in direct and indirect physical, socioeconomic, and psychological aspects.

The results of the COMPASS trial have important implications for our patients with PAD. The combination of low-dose rivaroxaban + ASA shows a reduction in MALE risk by 46%, need for perivascular interventions by 24%, reduction in major amputation risk by 67%, with reduction in acute limb ischemia of 44% and CLI by 33%.[28] This needs to be balanced with the bleeding risk, which cannot be ignored, although the benefit appears to favor use of low-dose rivaroxaban with ASA therapy. While this was a global study, non-White patients were under-represented and thus conclusions regarding their treatment cannot be drawn. Further research is necessary to better understand how Asian, Black, and Latino patients would benefit. As expected, regarding patients >75 years vs <75 years of age, there were numerically more bleeding events but there was not a statistically significant difference between the groups in terms of either efficacy or bleeding.[16,18] It is also of note that metastatic cancers were excluded from COMPASS and VOYAGER due to poor patient prognosis. This exclusion is not based on a lack of efficacy in cancer patients, but rather avoidance of confounding from a poor prognosis due to malignancy.[16,18]

The second article discussed in this review is the VOYAGER trial, which addresses the use of low-dose rivaroxaban + ASA in patients who have undergone vascular intervention.[18] At the more severe end of PAD, symptoms develop such as severe claudication (which can limit function) and CLI (which may lead to chronic wounds or gangrene). These severe complications are often treated by vascular intervention, but these patients continue to have a higher risk of vascular pathology. Acute limb ischemia is a serious situation often associated with long hospitalizations and high incidences of limb loss, disability, and death. Patients who have had a peripheral revascularization have approximately 4 times greater risk of developing acute limb ischemia compared with those who have never undergone revascularization.[43-45] Also, individuals who have undergone lower-extremity revascularization are at high risk of developing MALE and other cardiovascular problems. This is evident when assessing the VOYAGER trial, wherein nearly 1 in 5 patients in the placebo (ASA alone) group developed the primary composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes at 3 years.[18]

The major concern of using low-dose rivaroxaban + ASA therapy is the bleeding risk. This is important and should be seriously considered in a risk-benefit ratio. But in the Voyager trial, results implied that for every 10,000 patients treated, the low-dose rivaroxaban + ASA therapy would prevent 181 primary efficacy outcome events at the cost of 29 principal safety (bleeding) outcome events.[18] These 2 studies remind us that PAD is a progressive and dangerous disease even after successful interventions have been performed. Addressing the physiologic development of atherosclerosis may be beneficial to these individuals throughout the course of this disease. The medications discussed in this article are well known to our cardiovascular colleagues, but possibly less so to podiatric physicians. As new research emerges that affects our patients, awareness of these potentially beneficial therapeutic

options is of vital benefit. Therapies that significantly reduce the risk of limb ischemia, which may lead to gangrene or non-healing wounds, should be considered within our knowledge base and may affect our treatment protocols and recommendations. It is important we follow the research in these areas that so directly affect our ability to treat these patients.

Given the pharmacokinetic and pharmacodynamic nuances of the DOACs, there are several practical considerations for use. Routine monitoring is not required or recommended for rivaroxaban or other DOACs. If levels are needed to determine patient compliance or drug presence prior to procedure, there are several commercially available assays that may be considered. Dose-dependent inhibition of FXa activity was observed in humans, and the neoplastin prothrombin time, activated partial thromboplastin time, and HepTest are prolonged dose dependently. Anti-FXa activity is also influenced by rivaroxaban.[19]

Regarding initiation and periprocedural management of rivaroxaban, treatment may be started in patients with PAD at any time, provided they are not receiving dual-antiplatelet therapy, do not have active bleeding at the time of initiation, and are not allergic to rivaroxaban or any of its components. If a patient requires anticoagulation and needs a surgical procedure, according to labeling, doses of rivaroxaban should be held at least 24 hours prior to a procedure and restarted as soon as adequate hemostasis has been achieved.[19] Additionally, if rivaroxaban + ASA is determined to be the appropriate treatment option for a patient with PAD post limb-preserving podiatric procedure or if the patient is already being treated with rivaroxaban, it may be initiated as soon as adequate hemostasis has been achieved.[19]

The podiatrist is well positioned to diagnose PAD and understands that symptoms are often absent or atypical. They are skilled in determining whether adequate blood flow is present and are familiar with diagnostic technology that quantifies blood flow to the legs and feet. They develop referral networks connecting patients with vascular surgeons and interventionists to improve vascular flow to the limbs and understand the behavioral changes necessary to reduce the development of PAD, including smoking cessation, glycemic control, obesity, hypertension, and dyslipidemia. However, research that may affect the basic pathophysiology of atherosclerotic disease is often not included within their literature. Cardiology and hematology specialties are following these studies, as are physicians dealing with MI, stroke, and venous thrombotic disease. Furthermore, recent data from Kolte and Albright identify appropriate members of a multidisciplinary team and illustrate the effectiveness of employing such a team, respectively. Patients with diabetes treated by a multidisciplinary team tended to have fewer major amputations than those treated without a multidisciplinary team.[46,47] With these new advances in the treatment of PAD, it is of crucial importance for podiatrists, as well as all physicians dealing with limb preservation, to become aware of newer pharmacologic therapies that reduce the development of atherosclerotic disease, and to become familiar with the options for the treatment of this disease once it reaches a symptomatic or critical level.

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