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Review Article

Peripheral Arterial Disease and the Pharmacist's Role in Management

Zachary Stacy

Barnes Jewish West County Hospital, Creve Coeur, MO, USA

Correspondence should be addressed to Zachary Stacy; zachary.stacy@bjc.org

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Purpose. Atherosclerosis of arteries in the legs leads to peripheral arterial disease (PAD), increasing the risk of future cardiovascular events. Worldwide prevalence estimates indicate >200 million people have PAD, but this is likely underestimated given the variability in symptoms and lack of awareness by patients and clinicians. Antiplatelet therapy is recommended to reduce cardiovascular risk, but anticoagulation therapy may also be beneficial. This narrative review examined scientific literature for the burden and medical management of PAD, including use of anticoagulants in this population, and provides perspectives on the role of pharmacists to improve outcomes of PAD. *Summary*. A variety of antiplatelet therapies has been studied in patients with PAD, and treatment is recommended for those with symptomatic disease. The use of dual antiplatelet therapy is limited to patients with symptomatic PAD after revascularization. Anticoagulation with warfarin in combination with antiplatelet therapy did not improve efficacy over antiplatelet therapy alone and increased bleeding. In contrast, the direct factor Xa inhibitor rivaroxaban, when used in combination with low-dose aspirin, has been shown to significantly reduce the risk of cardiovascular death, myocardial infarction (MI), or stroke by 28% in patients with PAD compared with aspirin alone. Similarly, in patients with PAD who have undergone revascularization, rivaroxaban plus aspirin reduced the risk of acute limb ischemia, major amputation, MI, stroke, or cardiovascular death by 15% versus aspirin alone. Major bleeding was significantly increased with rivaroxaban plus aspirin, but with no differences in fatal bleeding, nonfatal intracranial hemorrhage, or symptomatic bleeding into a critical organ between groups. Pharmacist-led interventions for patients with PAD include identifying at-risk patients through medication reviews and clinical assessments, education and monitoring use of prescription and over-the-counter medications, and appropriate counseling on lifestyle modifications. *Conclusion*. Rivaroxaban plus aspirin reduces the risk of major cardiovascular events, including major adverse limb events and amputation, in patients with PAD. Pharmacists can play an integral role in identifying, screening, and managing patients with PAD to achieve favorable outcomes.

1. Introduction

Cardiovascular disease (CVD) is highly prevalent in adults and is the leading cause of mortality [1]. The risk of cardiovascular events is increased in people with peripheral arterial disease (PAD), a circulatory disease characterized by restricted blood flow to peripheral arteries caused by systemic atherosclerosis [2]. More than 200 million adults worldwide and 8.5 million Americans aged ≥40 years have PAD [3, 4], and the prevalence increases with age, affecting 25% of those aged >80 years [5]. Despite its prevalence, PAD tends to be underdiagnosed and undertreated because of a lack of awareness about adverse outcomes associated with PAD [6]. Furthermore, patients who experience adverse cardiovascular events associated with PAD have been shown to have substantial increases in their total healthcare costs [7].

Both PAD and coronary artery disease (CAD) are strong predictors for risk of future cardiovascular events, including major adverse cardiovascular events (MACE; i.e., cardiovascular death, myocardial infarction (MI), and stroke) and major adverse limb events (MALE; i.e., acute limb ischemia, thrombectomy or thrombolysis, major amputation, or repeat surgical revascularization of the target limb) [1, 8, 9]. However, patients with PAD often have more widespread vascular disease occurring in all vascular territories

compared with patients with CAD [10]. This systemic presence of atherosclerosis may explain the greater risk of complications associated with PAD. The international REduction of Atherothrombosis for Continued Health (REACH) registry identified higher rates of MACE among patients with PAD, and 40% of patients with PAD experienced cardiovascular death, MI, stroke, or rehospitalization over 3 years compared with 30% of patients with CAD and 28% of patients with cerebrovascular disease [11]. In addition, recent studies suggest involvement of microvascular disease in the progression of PAD, including a stronger association between retinopathy and PAD and critical limb ischemia than with CAD [6, 12]. A study of patients with PAD and critical limb ischemia who underwent amputations found acute or chronic thrombi in 73% of arteries with ≥70% luminal stenosis [13].

In this narrative review, the burden and medical management of PAD, focusing on the clinical trial results supporting the use of anticoagulants, are examined, with a perspective on the clinical implications of these data for pharmacists who can play an important role in managing PAD diagnosis, treatment, and outcomes.

1.1. Clinical Evaluation of Patients with PAD. PAD screening criteria are categorized by age group and risk factors in Table 1 [4]. PAD is suggested based on a patient's clinical history and review of symptoms, including claudication, other non–joint-related exertional lower-extremity symptoms, impaired walking, and ischemic pain at rest [4]. However, because symptoms of PAD are variable and few people with PAD (approximately 10%) exhibit the classic symptom of intermittent claudication [1, 8], clinical findings need to be confirmed with diagnostic testing. The initial, and usually only, diagnostic test required is the resting ankle brachial index (ABI), which is a simple, inexpensive, noninvasive test that measures the systolic blood pressure (SBP) at the arms (brachial arteries) and ankles (dorsalis pedis and posterior tibial arteries) in the supine position using a Doppler device [4]. Clinical pharmacists have been trained on the use of handheld Dopplers to implement PAD screening programs [14]. ABI is calculated for each leg by dividing the highest measured ankle SBP by the highest SBP measured in the right or left arm. A value of 1.00–1.40 is normal for ABI, 0.91–0.99 is considered borderline ABI, and an abnormal ABI is defined as ≤0.90, which indicates reduced blood flow to the limbs [4]. A value >1.40 indicates noncompressible arteries, usually resulting from calcification, and requires further evaluation.

1.2. Medication Management for Patients with PAD. Pharmacists frequently provide patient education, review medication management, and monitor treatment goals for patients with CVD, which can be extended specifically to patients with PAD [15, 16]. Pharmacotherapy for patients with PAD includes antiplatelet therapy along with individualized therapy based on patients' risk factors and their need for treatment of hypertension, diabetes, and hyperlipidemia [4]. Antiplatelet agents have been studied in patients with PAD with variable results (Table 2) and are strongly recommended for patients with symptomatic PAD based on high-quality evidence. For patients with asymptomatic PAD and ABI ≤0.90, antiplatelet therapy is reasonable based on expert opinion [4]. Aspirin therapy for secondary prevention of vascular disease reduced the risk of MACE by 20% and cardiovascular death by 9% compared with placebo [17]. In a post hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, clopidogrel plus aspirin did not demonstrate superiority to aspirin alone for the primary endpoint of first occurrence of MACE (i.e., MI, stroke, or cardiovascular death) in patients with PAD [20]. However, clopidogrel plus aspirin showed a significantly lower rate of MI (2.3% vs. 3.7%) and hospitalization for ischemic events (16.5% vs. 20.1%) compared with aspirin alone [20]. Similarly, the clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial found no significant benefit of clopidogrel and aspirin for patients requiring below-knee vascular grafting for PAD [25].

Ticagrelor, an inhibitor of the platelet $P2Y_{12}$ receptor, was evaluated in the prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infarction 54 (PEGASUS-TIMI 54) and the examining use of ticagrelor in peripheral arterial disease (EUCLID) trials [22, 23]. In the PEGASUS-TIMI 54 versus aspirin alone in patients with symptomatic PAD who had undergon trial of patients with prior MI and PAD ($n = 1{,}143$), PAD was associated with a >2-fold increase in the rate of MACE and ticagrelor reduced the rate of events versus placebo (15.2% vs. 19.3%; (HR), 0.75; 95% confidence interval(CI), 0.55–1.01) [23]. Among 13,885 patients with symptomatic PAD in the EUCLID trial, rates of MACE were similar with ticagrelor and clopidogrel (10.8% vs. 10.6%; HR, 1.02; 95% CI, 0.92–1.13) [22].

Table 1: PAD screening criteria by age group and risk factors [4].

Age group	Risk factors
<50 years	Diabetes and 1 additional atherosclerotic risk factor: (i) Smoking (ii) Hyperlipidemia (iii) Hypertension (iv) Family history of PAD
50–64 years	Atherosclerotic risk factors: (i) Diabetes (ii) Smoking (iii) Hyperlipidemia (iv) Hypertension (v) Family history of PAD
≥65 years	None required
No age restrictions	Individuals with known atherosclerotic disease in another vascular bed: (i) Coronary (ii) Carotid (iii) Subclavian (iv) Renal (v) Mesenteric artery stenosis (vi) Abdominal aortic aneurysm

PAD: peripheral arterial disease.

Table 2: Summary of medication trials in patients with PAD.

Study/reference	No. of patients	Treatment	Key efficacy outcomes
Meta-analysis; antithrombotic trialists' collaboration, 2009 and 2002 [17, 18]	Primary prevention trials ($n = 6$) included 95,000 individuals Secondary prevention trials ($n = 16$) included 17,000 individuals	Aspirin vs. no aspirin (with no other antiplatelet regimen) Primary: aspirin 75–500 mg QD Secondary: aspirin 100–1,500 mg QD	Risk of MACE (MI, coronary death, or sudden death) reduced by 18% and 20% in primary and secondary trials, respectively Risk of vascular death reduced by 9% in secondary trials
CAPRIE study; CAPRIE Steering Committee, 1996 [19]	19,185 with stroke, MI, or symptomatic PAD	Clopidogrel 75 mg QD vs. aspirin 325 mg QD	Stroke, MI, or CV death occurred in 5.3% vs. 5.8%, favoring clopidogrel vs. aspirin with relative risk reduction of 8.7% ($P = 0.043$)
CHARISMA trial; Cacoub et al. 2009 [20]	3,096 with PAD (92% symptomatic)	Clopidogrel 75 mg QD plus low-dose aspirin 75–162 mg QD vs. low-dose aspirin	Stroke, MI, or CV death occurred in 7.6% in the clopidogrel group and 8.9% in the placebo group, a nonsignificant difference (HR, 0.85; 95% CI, 0.66–1.08; $P = 0.18$)
TRA2°P-TIMI 50 trial; Bonaca et al. 2016 [21]	3,787 with symptomatic PAD	Vorapaxar 2.5 mg QD vs. placebo (patients could be on antiplatelet therapy)	ALI events occurred in 108 patients (1.3%/year) Vorapaxar reduced total ALI events by 41% (RR, 0.59; 95% CI, 0.38–0.93; $P = 0.022$)
EUCLID trial; Hiatt et al. 2017 [22]	13,885 with symptomatic PAD	Ticagrelor 90 mg BID vs. clopidogrel 75 mg QD	Stroke, MI, or CV death occurred in 10.8% receiving ticagrelor vs. 10.6% receiving clopidogrel (HR, 1.02; 95% CI, 0.92–1.13; $P = 0.65$)
PEGASUS-TIMI 54 trial; Bonaca et al. 2016 [23]	1,143 with prior MI and PAD	Ticagrelor 90 mg BID, ticagrelor 60 mg BID, or placebo, all on background low-dose aspirin	Stroke, MI, or CV death occurred in 15.2% receiving ticagrelor (pooled) vs. 19.3% receiving placebo (HR, 0.75; 95% CI, 0.55–1.01)
WAVE trial; Anand et al. 2007 [24]	2,161 with PAD	Warfarin plus antiplatelet therapy vs. antiplatelet therapy (aspirin 81–325 mg QD, ticlopidine, and clopidogrel)	Stroke, MI, or CV death occurred in 12.2% of the combination therapy group and 13.3% of the antiplatelet group, a nonsignificant difference (RR, 0.92; 95% CI, 0.73–1.16; $P = 0.48$) Increased bleeding with combination therapy

ALI: acute limb ischemia; BID: twice daily; CAPRIE: clopidogrel versus aspirin in patients at risk of ischemic events; CHARISMA: clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance; EUCLID: examining use of ticagrelor in peripheral artery disease; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MI: myocardial infarction; PAD: peripheral arterial disease; PEGASUS-TIMI 54: prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infraction 54; QD: once daily; RR: risk ratio; TRA2°P-TIMI 50: trial to assess the effects of vorapaxar in preventing heart attack and stroke in patients with atherosclerosis-thrombolysis in myocardial infarction 50; WAVE: warfarin antiplatelet vascular evaluation.

Vorapaxar is a protease-activated receptor-1 (PAR-1) antagonist approved for the reduction of thrombotic cardiovascular events in patients with a history of MI or PAD based on the results of the trial to assess the effects of vorapaxar in preventing heart attack and stroke in patients with atherosclerosis-thrombolysis in myocardial infarction 50 (TRA2°P-TIMI 50) [21]. Among patients with PAD, vorapaxar reduced the risk of acute limb ischemia by 41% versus placebo (56 events vs. 94 events; HR, 0.59; 95% CI, 0.38–0.93; $P = 0.022$); however, vorapaxar was associated with a significant increase in moderate or severe bleeding events versus placebo (6.6% vs. 4.5%; HR, 1.50; 95% CI, 1.14–1.98; $P = 0.003$) and a similar rate of intracranial hemorrhage (0.6% in both groups; HR, 1.14; 95% CI, 0.50–2.58) [21]. Current guidelines indicate that the overall clinical benefit of vorapaxar plus antiplatelet therapy is uncertain. Dual antiplatelet therapy is recommended only for those with symptomatic PAD after lower-extremity revascularization [4]. In the warfarin antiplatelet vascular evaluation (WAVE) trial, combining warfarin with antiplatelet therapy was not more effective than antiplatelet therapy alone for preventing MACE (15.9% vs. 17.4%; relative risk, 0.91; 95% CI, 0.74–1.12; $P = 0.37$) and was associated with a significantly increased risk of life-threatening bleeding (4.0% vs. 1.2%; relative risk, 3.41; 95% CI, 1.84–6.35; $P < 0.001$) and intracranial bleeding [24, 26]. Pharmacist-driven antithrombotic evaluations of patients receiving dual antithrombotic therapy or triple antithrombotic therapy, consisting of warfarin, aspirin, oral $P2Y_{12}$ inhibitor, and/or dipyridamole, found one-quarter to more than one-half of patients with no clear indication for the combination therapy and increased bleeding risk [27, 28].

Generally, direct oral anticoagulants (DOACs) are recommended over warfarin for the prevention and treatment of venous thromboembolism and to reduce the risk of stroke in patients with nonvalvular atrial fibrillation due to their improved safety, comparable efficacy, and reduced laboratory monitoring requirements [29]. In a retrospective review of 189 patients who received warfarin, 108 (57.1%) were switched to a DOAC, most commonly for less monitoring and patient preference [29]. Clinical trials have demonstrated benefits of the DOAC rivaroxaban, leading to its approval for the treatment of patients with PAD. Results from 2 clinical trials of rivaroxaban in patients with PAD are presented in detail: the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS; ClinicalTrials.gov identifier, NCT01776424) and the vascular outcomes study of acetylsalicylic acid along with rivaroxaban in endovascular or surgical limb revascularization for PAD (VOYAGER-PAD; NCT02504216) trials.

2. Methods

Available clinical trial data for antiplatelet agents and rivaroxaban in patients with PAD were identified through a review of the published scientific literature identified using PubMed searches through October 2021.

2.1. Rivaroxaban Mechanism and Dosing. Rivaroxaban is an oral, direct factor Xa inhibitor acting on free and prothrombin complex-bound factor Xa, with a low inhibition constant of 0.4 nM (Figure 1) [30–35]. By inhibiting factor Xa, rivaroxaban inhibits thrombin generation in a concentration-dependent manner, with a 10 mg dose achieving free plasma concentrations that are approximately 3-fold higher than the inhibition constant [34]. Thus, at therapeutically relevant concentrations, thrombin generation is almost completely inhibited. The anti-factor Xa activity of rivaroxaban can be reversed by andexanet alfa [36].

Platelet aggregation is induced by signaling of the glycoprotein IIb/IIIa receptor on the platelet membrane [33]. Thrombin generation contributes to atherothrombosis by converting soluble fibrinogen to fibrin monomers that form the fibrin network for platelet aggregation [31]. By inhibiting thrombin, rivaroxaban indirectly inhibits platelet aggregation induced by thrombin [37]. In addition, factor Xa and thrombin have been shown to modulate signaling of proteinase-activated receptors and inflammatory pathways, which may provide additional mechanisms of action against atherosclerosis for agents that inhibit factor Xa [33, 38, 39].

Rivaroxaban is rapidly absorbed and the absolute oral bioavailability is dose dependent [30, 35]. Based on clinical pharmacology studies, oral bioavailability is high at 80%–100% and unaffected by food at doses of ≤10 mg daily. Thus, in patients with PAD, the recommended dose of 2.5 mg twice daily (BID) can be taken with or without food. Rivaroxaban demonstrates maximum factor Xa inhibition within 4 hours of administration and has a mean terminal half-life of 7–11 hours [34].

Rivaroxaban has been approved by the US Food and Drug Administration for several conditions, including reducing MACE in patients with chronic PAD or CAD, preventing and treating venous thromboembolism [40–42], and preventing stroke or systemic embolism in patients with atrial fibrillation [43]. Recommended doses of rivaroxaban for each indication are shown in Table 3. Rivaroxaban is available as 2.5 mg, 10 mg, 15 mg, and 20 mg tablets. If a patient is unable to swallow whole tablets, rivaroxaban tablets (all strengths) can be crushed and combined with a small amount of applesauce for administration followed by food. For patients with a nasogastric tube or a gastric feeding tube, the tablets can be crushed to a fine powder and mixed with 50 mL of water and administered through the tube [45, 46].

2.2. COMPASS

2.2.1. Overview. In the COMPASS trial, 27,395 patients with stable PAD or CAD were randomized to receive rivaroxaban 2.5 mg BID with aspirin 100 mg once daily (QD), rivaroxaban 5 mg BID, or aspirin 100 mg QD to assess secondary cardiovascular protection [47]. The study was stopped early due to overwhelming benefit of rivaroxaban plus aspirin after a mean follow-up of 23 months [48]. The primary efficacy outcome of the composite of MI, stroke, or cardiovascular death occurred in 4.1% of patients receiving rivaroxaban plus aspirin compared with 5.4% of patients receiving aspirin alone

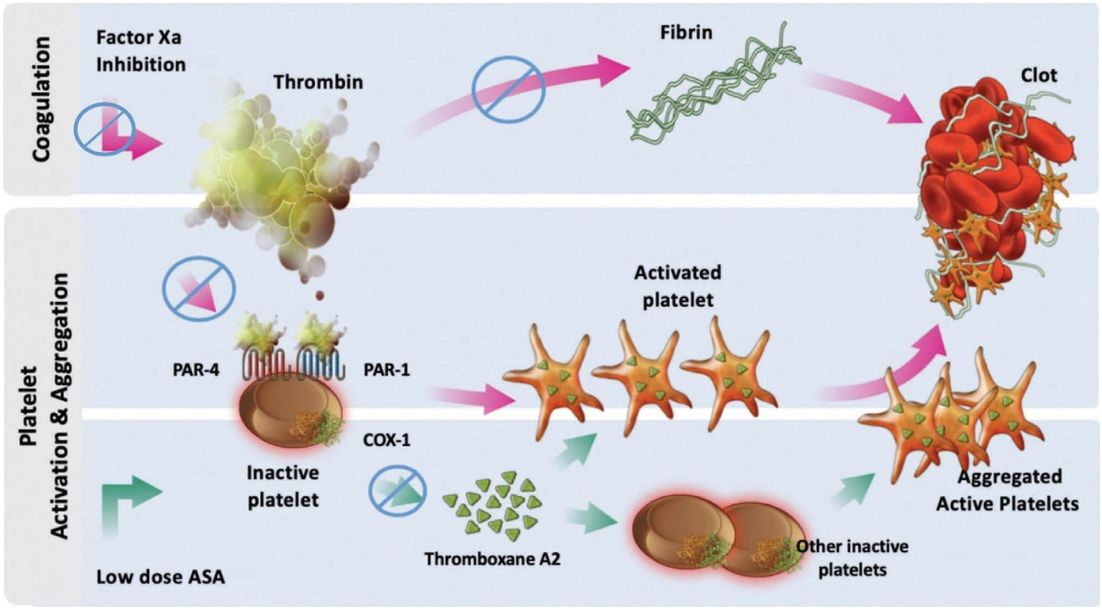

Figure 1: Synergy of dual pathway inhibition on platelet activation. Combining direct inhibitors of factor Xa (such as apixaban, edoxaban, and rivaroxaban) or direct thrombin inhibitors (such as dabigatran) with antiplatelet agents (such as acetylsalicylic acid; P2Y12 antagonists, such as ticagrelor; or PAR-1 antagonists, such as vorapaxar) synergistically targets 2 essential components of atherothrombosis: coagulation and platelet activation [33]. Inhibition of factor Xa modulates thrombin generation, a critical step in the coagulation cascade. Factor Xa is the main component of the prothrombinase complex (comprising factors Xa, Va, Ca^{2+}, and phospholipids) on the platelet membrane, which is the principal generator of thrombin. Thrombin, in turn, is the most potent inducer of platelet activation, mainly via PAR-1 and PAR-4, and is critical for fibrin generation. Therefore, dual pathway inhibition with a direct factor Xa inhibitor or direct thrombin inhibitor and an antiplatelet agent works synergistically to reduce platelet activation, leading to the delayed and/or reduced formation of prothrombinase coagulation complexes and reduced platelet aggregation, thereby increasing the antithrombotic potency of the regimen [33]. *Notes*: reprinted from *Thrombosis Research*, volume 184, Ramacciotti E., Weitz J. I., rivaroxaban plus aspirin for cardiovascular protection: rationale for the vascular dose and dual pathway inhibition, pages 44–49, copyright (2019), with permission from Elsevier [31]. PAR-1: protease-activated receptor-1; PAR-4: protease-activated receptor-4.

(HR, 0.76; 95% CI, 0.66–0.86; $P < 0.001$) [48]. The effects of rivaroxaban plus aspirin versus aspirin on the individual components of this composite were significant for stroke (0.9% vs. 1.6%; HR, 0.58; 95% CI, 0.44–0.76; $P < 0.001$) and cardiovascular death (1.7% vs. 2.2%; HR, 0.78; 95% CI, 0.64–0.96; $P = 0.02$) but not MI (1.9% vs. 2.2%; HR, 0.86; 95% CI, 0.70–1.05; $P = 0.14$) [48]. Rivaroxaban alone was not significantly different for the primary efficacy endpoint compared with aspirin alone. Major bleeding, defined as fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, or bleeding that led to hospitalization or presentation to an acute care facility (modified from the International Society on Thrombosis and Haemostasis [ISTH] criteria), occurred in more patients receiving rivaroxaban plus aspirin compared with those receiving aspirin alone (3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40–2.05; $P < 0.001$). Importantly, there were no significant between-group differences in fatal bleeding (0.2% vs. 0.1%), intracranial bleeding (0.2% vs. 0.2%), or symptomatic bleeding into a critical organ (0.5% vs. 0.3%) [48]. Patients who received rivaroxaban 5 mg BID alone without aspirin did not achieve a significant benefit compared with aspirin alone (HR, 0.90; 95% CI, 0.79–1.03) and they experienced more major bleeding events (2.8% vs. 1.9%; HR, 1.51; 95% CI, 1.25–1.84; $P < 0.001$); thus, this comparison will not be discussed further [48].

2.2.2. COMPASS Patients with PAD. A subgroup analysis of the 7,470 patients with PAD enrolled in COMPASS was conducted and their conditions leading to inclusion in the study are provided in Table 4 [49]. Patients were excluded from COMPASS if they had a need for dual antiplatelet therapy, other nonaspirin antiplatelet therapy, or oral anticoagulant therapy; a high risk of bleeding; stroke within 1 month; a history of hemorrhagic or lacunar stroke; severe heart failure with a known ejection fraction <30%; or estimated glomerular filtration rate (eGFR) <15 mL/min. Patient characteristics at baseline were balanced across randomized treatment groups (mean age, 68 years; 72% men) [49]. The majority of patients with PAD were receiving guideline-recommended medication for secondary prevention of cardiovascular events, including antiplatelet agents (86.9%), lipid-lowering agents (83.5%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (70.1%), and beta-blockers (59.5%).

The combination of rivaroxaban plus aspirin significantly reduced the risk of developing the primary outcome of stroke, cardiovascular death, or MI by 28% compared with aspirin alone (5.1% vs. 6.9%; HR, 0.72; 95% CI, 0.57–0.90; $P = 0.0047$) [49]. The magnitudes of benefit for rivaroxaban plus aspirin compared with aspirin alone for the individual components in patients with PAD were similar to those observed in the overall COMPASS trial population: stroke

Table 3: Rivaroxaban indications and dosing recommendations [44].

Indication	Renal considerations[a,b]	Recommended rivaroxaban dosage
Reduction of major cardiovascular/thrombotic vascular events in patients with chronic CAD or PAD	No dose adjustment needed based on CrCl	2.5 mg BID + aspirin (75–100 mg) QD
Reduction in risk of stroke in patients with NVAF	CrCl >50 mL/min	20 mg QD
	CrCl ≤50 mL/min	15 mg QD
Treatment of DVT/PE	CrCl ≥15 mL/min	15 mg BID for 21 days, followed by 20 mg QD
	CrCl <15 mL/min	Avoid use
Prophylaxis of DVT/PE following hip replacement or knee replacement surgery	CrCl ≥15 mL/min	10 mg QD[c]
	CrCl <15 mL/min	Avoid use

[a]CrCl was calculated based on actual body weight. [b]Patients with CrCl <30 mL/min were not studied, but administration of rivaroxaban is expected to result in serum concentrations similar to those in patients with moderate renal impairment (i.e., CrCl 30 to < 50 mL/min). [c]Dosing recommended to begin 6–12 hours following surgery once hemostasis is established. Following hip replacement, dosing is recommended to continue for 35 days; following knee replacement, dosing is recommended to continue for 12 days. BID: twice daily; CAD: coronary artery disease; CrCl: creatinine clearance; DVT: deep vein thrombosis; NVAF: nonvalvular atrial fibrillation; PAD: peripheral arterial disease; PE: pulmonary embolism; QD: once daily.

Table 4: Characteristics of patients with PAD enrolled in COMPASS [49].

Characteristic/inclusion criteria met	Patients with PAD ($n = 7,470$)
Symptomatic PAD	6,048 (81.0%)
Symptomatic PAD of the lower extremities (intermittent claudication with ABI <0.90 or stenosis ≥50%; previous aorta-femoral or lower-extremity bypass surgery, percutaneous transluminal angioplasty of iliac, or infrainguinal arteries; or limb or foot amputation for arterial vascular disease)	4,129 (55.2%)
Intermittent claudication with ABI <0.90 or stenosis ≥50%	3,402 (45.5%)
Previous aorta-femoral or lower-extremity bypass surgery, percutaneous transluminal angioplasty of iliac, or infrainguinal arteries	2,045 (27.4%)
Previous limb or foot amputation	335 (4.5%)
Previous carotid artery revascularization or carotid stenosis ≥50%	1,919 (25.7%)
Asymptomatic PAD (CAD with ABI <0.90)	1,422 (19.0%)

ABI: ankle brachial index; CAD: coronary artery disease; PAD: peripheral arterial disease.

(1.0% vs. 1.9%; HR, 0.54; 95% CI, 0.33–0.87), MI (2.0% vs. 2.7%; HR, 0.76; 95% CI, 0.53–1.09), and cardiovascular death (2.6% vs. 3.1%; HR, 0.82; 95% CI, 0.59–1.14) [49]. A significant benefit was observed with rivaroxaban plus aspirin versus aspirin alone for the composite endpoints that included acute limb ischemia [49]. There was no significant reduction in all-cause mortality with rivaroxaban plus aspirin versus aspirin alone. Overall, the benefits of low-dose rivaroxaban plus aspirin suggest that the drugs have an additive effect for patients with arterial vascular disease.

In secondary analyses, patients with a history of ≥2 vascular beds affected, heart failure, and/or lower eGFR were at the highest risk of a vascular event [50]. The benefits of rivaroxaban plus aspirin on the primary composite endpoint (6.4% vs. 8.4%; HR, 0.75; 95% CI, 0.60–0.94), without an excess hazard of bleeding, were preserved in patients with moderate renal dysfunction, defined as eGFR <60 and ≥15 mL/min/1.73 m^2 ($n = 6,276$) [51].

2.2.3. MALE and Amputations. MALE, defined as the development of acute or chronic limb ischemia, including major amputations (above the forefoot or front part of the foot from the ball to end of toes) due to a vascular event that was not included in acute or chronic limb ischemia, and the composite of MALE or MACE were reduced with rivaroxaban plus aspirin by 46% (1.2% vs. 2.2%; HR, 0.54; 95% CI, 0.35–0.84) and 31% (6.2% vs. 8.9%; HR, 0.69; 95% CI, 0.56–0.85), respectively, compared with aspirin alone [49]. Major amputations were reduced by 70% in patients with PAD receiving rivaroxaban plus aspirin versus aspirin alone (0.2% vs. 0.7%; HR, 0.30; 95% CI, 0.11–0.80) [49].

For those with lower-extremity PAD ($n = 6,391$), 128 (2.0%) developed MALE [52]. Independent predictors of MALE included severe ischemic symptoms at baseline (defined as pain at rest mostly in the feet or necrosis/gangrene of the limb based on Fontaine classification III or IV), previous limb or foot amputation at baseline, history of peripheral revascularization surgery or angioplasty, and randomization to the aspirin arm of the trial. The risk of developing MALE was reduced by 43% (1.5% vs. 2.6%; HR, 0.57; 95% CI, 0.37–0.88; $P = 0.01$) in patients receiving rivaroxaban plus aspirin versus aspirin alone, while total amputations and major amputations were reduced by 58% (0.5% vs. 1.2%; HR, 0.42; 95% CI, 0.21–0.85; $P = 0.01$) and 67% (0.2% vs. 0.7%; HR, 0.33; 95% CI, 0.12–0.92; $P = 0.03$), respectively. MALE was associated with a poor prognosis; the cumulative incidence 1-year risk of subsequent outcomes after MALE was 61.5% for hospitalization, 20.5% for total vascular amputation, 8.3% for death, and 3.7% for MACE [52]. In patients with symptomatic lower-extremity PAD ($n = 4,129$), rivaroxaban plus aspirin reduced MACE by 26% (HR, 0.74; 95% CI, 0.58–0.92) and MALE by 45% (HR, 0.55; 95% CI, 0.35–0.85) as well as the composite of MACE or MALE, including major amputation, by 29% (HR, 0.71; 95% CI, 0.57–0.87) compared with aspirin alone [53]. Similar risk reductions were observed for patients with high-risk limb presentations (49%) or high-risk comorbidities (84%) treated with rivaroxaban plus aspirin compared with aspirin alone.

In the subgroup analysis of PAD patients, major bleeding occurred in 77 (3.1%) patients receiving rivaroxaban plus aspirin, 79 (3.2%) patients receiving rivaroxaban, and 48 (1.9%) patients receiving aspirin, with a significant increase in both rivaroxaban groups versus aspirin alone [49]. Similar to the overall COMPASS trial results, there were no differences in fatal bleeding (<1% in each treatment group), nonfatal intracranial hemorrhage (<1% in each group), or symptomatic bleeding into a critical organ (1% in each group) between treatment groups in patients with PAD.

2.3. VOYAGER-PAD. Patients with PAD who undergo peripheral revascularization have an increased risk of subsequent vascular complications compared with those who have never had revascularization [54], possibly due to endothelial damage and activation of inflammatory and coagulation pathways following the revascularization procedure [8]. One of the most serious complications, acute limb ischemia, is associated with prolonged hospitalization, limb loss, disability, and death. The VOYAGER-PAD trial evaluated rivaroxaban 2.5 mg BID plus aspirin 100 mg QD versus aspirin alone in patients with symptomatic PAD who had undergone lower-extremity revascularization, including 20.2% of patients with an eGFR <60 mL/min/1.73 m^2 [54].

The primary composite efficacy endpoint of acute limb ischemia, major amputation, MI, ischemic stroke, or cardiovascular death occurred in 508/3,286 (15.5%) patients receiving rivaroxaban plus aspirin and 584/3,278 (17.8%) patients receiving aspirin. Kaplan–Meier estimates at 3 years were 17.3% and 19.9%, respectively, representing a 15% relative reduction with combination therapy (HR, 0.85; 95% CI, 0.76–0.96; $P = 0.009$). The benefits of adding rivaroxaban to aspirin therapy occurred after approximately 3 months and were consistent among subgroups of patients by age, sex, and CVD risk factors. Major bleeding according to the Thrombolysis in Myocardial Infarction classification (principal safety outcome) occurred in more patients receiving rivaroxaban and aspirin ($n = 62$) compared with aspirin ($n = 44$), but the difference was not statistically significant (HR, 1.43; 95% CI, 0.97–2.10; $P = 0.07$). Major bleeding based on the ISTH definition was significantly more frequent with rivaroxaban based on Kaplan–Meier 3-year estimates (5.9% vs. 4.1%; HR, 1.42; 95% CI, 1.10–1.84; $P = 0.007$), but there was no excess of intracranial hemorrhage or fatal bleeding. These results support the use of low-dose rivaroxaban with aspirin in patients with PAD to reduce adverse limb and cardiovascular outcomes that occur after revascularization procedures.

An additional analysis showed the total burden of vascular events (acute limb ischemia, major amputation for vascular causes, nonfatal MI, nonfatal ischemic stroke, and cardiovascular death) and the effect of rivaroxaban on total events, including subsequent revascularizations or thromboembolic events, were evaluated in patients with PAD undergoing lower-extremity revascularization [55]. A total of 4,714 vascular events (1,614 primary and 3,100 other vascular events) were reported in the 6,564 randomized patients. Treatment with rivaroxaban plus aspirin reduced total vascular events by 14% versus aspirin alone (88.4 vs. 75.9 events per 100 patients; HR, 0.86; 95% CI, 0.79–0.95; $P = 0.003$) [55]. Combination therapy with rivaroxaban and aspirin was also shown to reduce venous thromboembolism risk in these patients with PAD undergoing lower-extremity revascularization with 3-year event rates of 0.8 versus 1.7 events per 100 patients for aspirin alone (HR, 0.61; 95% CI, 0.37–0.998; $P = 0.047$) [56].

Clopidogrel is commonly used in combination with aspirin after revascularization. In VOYAGER-PAD, 50.6% of patients received clopidogrel for a median of 29 days after revascularization [57]. There was no difference in HRs for the primary endpoint of rivaroxaban versus placebo for patients who received clopidogrel (16.0% vs. 18.3%; HR, 0.85; 95% CI, 0.71–1.01) and for those who did not (18.7% vs. 21.5%; HR, 0.86; 95% CI, 0.73–1.01) [57]. More major bleeding was observed with rivaroxaban among patients who received clopidogrel for >30 days. Thus, a short course of clopidogrel did not impact the benefit of rivaroxaban in patients with symptomatic PAD undergoing revascularization.

3. Discussion

3.1. Assessment of Patients and Risk Factor Modification. Pharmacists can have a role in PAD prevention, screening, and treatment management. PAD results from poor circulation in the legs and is often an indicator of other CVDs; thus, promoting healthy living through diet, exercise, and smoking cessation is useful to prevent and manage PAD. Implementation of risk factor modification is a crucial component of treatment guidelines for PAD, but it is routinely underperformed in patients with the disease [58]. Key targets for risk modification include improving control of blood pressure, diabetes, and cholesterol levels. Another challenging factor of PAD is that the symptoms are variable among patients and often overlooked [58]. Patients may complain of leg cramps or pain associated with walking or other physical activities as well as shiny skin on the legs, lower-extremity hair loss, decreased temperature of the leg or foot, or poor nail growth on the toes. Personal and family histories, along with thorough review of typical/atypical symptoms, are important for evaluating PAD.

Pharmacists may be able to identify at-risk patients based on their medication history, including treatment of hypertension, diabetes, and hyperlipidemia. They can discuss PAD and its diagnosis with these individuals and encourage them to see a healthcare professional for evaluation. In addition, medication reviews by pharmacists have been shown to improve control of hypertension, type 2 diabetes, and high cholesterol, which may lead to a reduced risk for CVD [59]. Clinical pharmacists in patient care centers can be involved in screening of individuals for PAD by administering questionnaires to measure PAD symptoms [14]. Pharmacy schools now include instruction on the use of a handheld Doppler device to obtain ankle blood pressure measurements providing data to calculate and interpret ABI. Patients with an ABI outside the normal range or symptoms indicative of PAD should be referred to their primary healthcare provider.

3.2. Identifying Treatment Options. Identification of patients with PAD allows a pharmacist the opportunity to review potential therapies that may need to be initiated and/or optimized. The 2016 American Heart Association and American College of Cardiology guidelines recommend pharmacotherapy for patients with PAD, including antiplatelet and statin agents [4]. It is also valuable for pharmacists to be aware of new data that support the use of different therapeutic options for patients with PAD. Results of the COMPASS and VOYAGER-PAD trials in patients with PAD indicated significant reductions in cardiovascular outcomes, including MALE and amputations, for the combination of rivaroxaban plus aspirin versus aspirin alone. In addition, a substantial benefit was shown with rivaroxaban plus aspirin in reducing MACE or MALE in patients with symptomatic lower-extremity PAD with high-risk limb presentations or high-risk comorbidities. These

high-risk groups were defined by previous amputation or lower-extremity revascularization, substantial symptoms (pain at rest, necrosis, or gangrene), and comorbid conditions of polyvascular disease, diabetes, heart failure, and renal insufficiency [53]. In this setting, rivaroxaban is used at a low dose of 2.5 mg BID with 100 mg of aspirin. Community pharmacists are an easily accessible and helpful resource for patients selecting an aspirin product. As an over-the-counter medication, patients are not given a prescription and often need assistance selecting the correct product and dose.

3.3. Treatment Monitoring and Counseling. Following a diagnosis of PAD, pharmacists can provide appropriate counseling on treatments and lifestyle modifications. In addition to their traditional educational roles, pharmacists can offer collaborative services aimed at CVD prevention and management as part of multidisciplinary teams, including assessing vital signs, reviewing laboratory parameters, screening for medication-related problems, monitoring adherence to therapy, identifying barriers to adherence, reviewing medication doses for adjustment/titration, and providing routine follow-up [16, 60–62]. These types of interventions in the management of CVD have resulted in improved adherence to therapy and reduced mortality risk, hospitalization, and healthcare costs. Additional benefits of pharmacist-led goal setting and medication management programs for patients with CVD include improved common behavioral goals around diet and physical activity [15].

Avoiding drug-drug interactions with both prescription and over-the-counter medications (i.e., additional aspirin-containing products) may help reduce the potential for bleeding and other adverse drug reactions. Pharmacists can inform patients about these potential risks, particularly when combination therapy is used, and work with patients to improve safety outcomes. In contrast to warfarin, currently recommended agents do not require routine laboratory monitoring. The need for laboratory monitoring has historically driven provider-patient interactions, and as the need for monitoring has reduced with DOAC therapy, there is a reduced frequency of these interactions. Community pharmacists may be the one provider patients see on a regular basis (i.e., monthly) to pick up their prescriptions. Pharmacists can assist in ensuring that the appropriate dose is chosen based on the medical condition and the patient's renal function. In a recent study using clinical decision support in an outpatient setting, pharmacists found inappropriate DOAC prescriptions in 15/105 (14.3%) patients, of whom 40% had an inappropriate dose [63]. In the case of rivaroxaban, dose adjustments are required for renal function but not when using the 2.5 mg dose in combination with aspirin for patients with PAD [51, 54]. No dose adjustments are required for rivaroxaban in obese patients or those who have undergone bariatric surgery [64, 65]. In addition, pharmacists can help to ensure proper medication administration and adherence by suggesting techniques to help patients remember to take their medicine and verifying appropriate refills of medication. In these roles, pharmacists offer another touchpoint in the healthcare system to manage PAD and prevent serious cardiovascular events.

4. Conclusions

In summary, patients with PAD are at an increased risk of adverse cardiovascular events, and there is an important need for additional support to prevent and diagnose PAD as well as manage medications to ensure optimal outcomes. Results from clinical trials support the use of rivaroxaban in combination with aspirin to reduce the risk of major cardiovascular events, including major adverse limb events and amputation, in patients with PAD, while considering an increased risk of major bleeding. As additional data become available, pharmacists may play a critical role in educating and managing patients with PAD about their diagnosis and serving as a resource for understanding treatment options. Pharmacists should consult the latest guidelines for specific recommendations as guideline updates are expected to come later in 2023.

Abbreviations

ABI: Ankle brachial index
BID: Twice daily
CAD: Coronary artery disease
CI: Confidence interval
CVD: Cardiovascular disease
DOAC: Direct oral anticoagulant
eGFR: Estimated glomerular filtration rate
HR: Hazard ratio
MACE: Major adverse cardiovascular events
MALE: Major adverse limb events
MI: Myocardial infarction
PAD: Peripheral arterial disease
PAR-1: Protease-activated receptor-1
QD: Once daily
SBP: Systolic blood pressure.

Data Availability

This article is based on previously conducted studies and no new data were generated for inclusion in this article.

Ethical Approval

This article is based on previously conducted studies and does not contain any studies with human participants or animals carried out by the author.

Disclosure

The sponsor was involved in the decision to publish the article.

Conflicts of Interest

The author declares that there are no conflicts of interest.

Authors' Contributions

Z. Stacy contributed to development of the manuscript concept, drafted and revised the article, and approved the article for submission.

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