Reducing Thrombotic Risk From Polyvascular Disease in Primary Care

Stephen Brunton, MD, FAAFP

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Describe the burden of disease and risk of atherothrombotic events in patients with polyvascular disease—peripheral arterial disease (PAD) and coronary artery disease (CAD).
- Implement screening and diagnostic procedures to improve detection of polyvascular disease and accurately assess overall atherothrombotic risk.
- Select evidence-based treatment to reduce cardiovascular and limb events in patients with polyvascular disease.

KEY TAKEAWAYS

- Polyvascular disease is classified as atherosclerosis in multiple arterial beds, and common presentations include a combination of CAD, PAD, and/or cerebrovascular disease (CVD).
- Patients with polyvascular disease are at a significantly increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) compared to patients with atherosclerosis in only 1 vascular bed.
- Routine screening for polyvascular disease after diagnosis of an initial atherosclerotic disease is controversial, but clinicians can detect disease in additional vascular beds with a careful history and physical examination.
- Antithrombotic agents such as clopidogrel, rivaroxaban, ticagrelor, vorapaxar, and aspirin can reduce thrombotic events in patients with polyvascular disease; the only antithrombotic agent approved for both CAD and PAD is rivaroxaban.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of cardiovascular disease.

FACULTY

Stephen Brunton, MD, FAAFP, Adjunct Associate Professor, Touro University California, College of Osteopathic Medicine, Vallejo, California.

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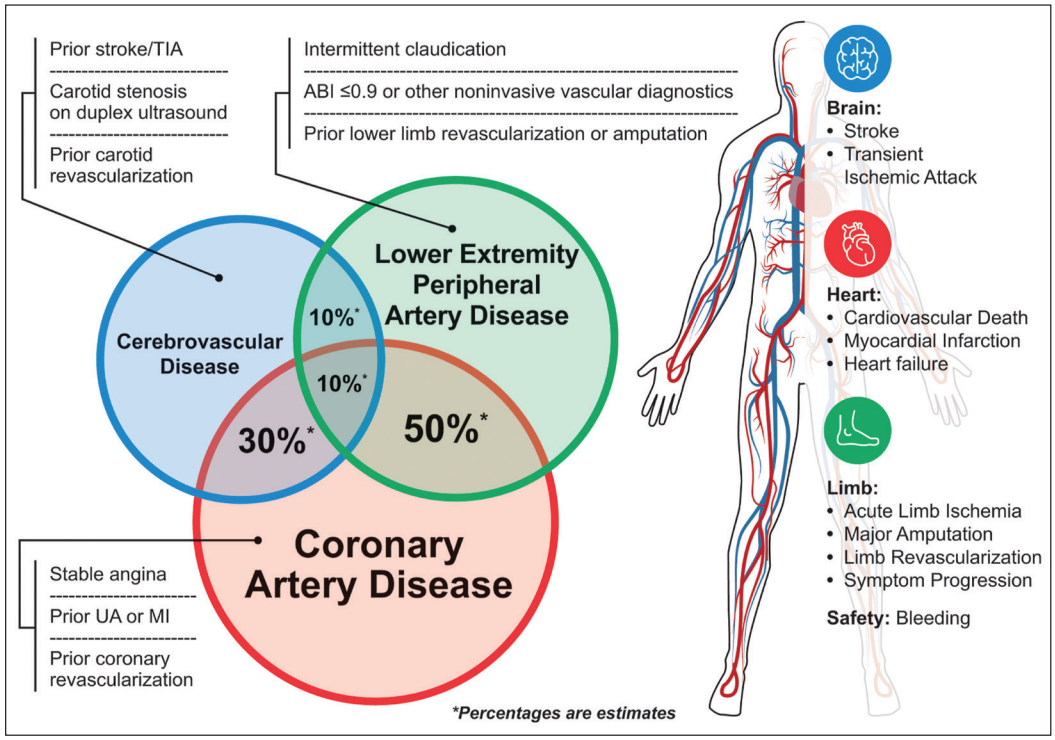
INTRODUCTION

Polyvascular disease is defined as the presence of atherosclerosis in 2 or more arterial beds, and is most commonly described as a combination of coronary artery disease (CAD) and peripheral arterial disease (PAD), though it can also include cerebrovascular disease (CVD) (**FIGURE**).[1-3] The atherosclerosis in these diseases comprises low-grade inflammation, plaque formation, and diseased endothelium in the

FIGURE. **Relative frequencies of polyvascular subtypes, broad diagnostic criteria for the vascular territories, and ischemic outcomes related to each territory[3]**



Approximate relative frequencies of each polyvascular disease subtype within the overall absolute polyvascular disease frequency of 15%–25% in patients with known atherosclerosis in 1 disease territory with related diagnostic criteria. Ischemic outcomes associated with atherosclerosis in each included arterial territory.

Abbreviations: ABI, ankle-brachial index; MI, myocardial infarction; TIA, transient ischemic attack; UA, unstable angina.

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vasculature, which leads to vessel occlusion.[4,5] Progression of atherosclerosis increases the risk of occlusion and subsequent cardiovascular, limb, and neurologic events including stroke, myocardial infarction (MI), heart failure, limb ischemia, and amputation.[3,5,6] Historically, polyvascular disease has been underrecognized, but clinical and research efforts to address noncoronary atherosclerosis has increased awareness of this condition.[1] The relevance for polyvascular disease centers on an increased risk of adverse cardiovascular and limb events in patients with this condition.[1]

Worldwide, prevalence of CAD is estimated at 5%-8% and prevalence of PAD is estimated at 10%-20% of the general population.[5] To better characterize atherothrombotic diseases, an international prospective cohort was established in 2003-2004.[7] The Reduction of Atherothrombosis for Continued Health (REACH) registry evaluated patients in 44 countries with CAD, PAD, and CVD, as well as those with at least 3 risk factors for atherothrombosis.[7] In the REACH cohort, approximately 18%-35% of patients with CAD and 46%-68% of patients with PAD had disease in more than 1 vascular bed.[5,8]

Despite the significant risks of polyvascular disease, patients with PAD are often underdiagnosed, leading to underdiagnosis of polyvascular disease overall.[9,10] Since patients with PAD usually first present to their primary care practitioner (PCP), clinicians in the primary care setting can improve detection of PAD and polyvascular disease and assist with early intervention to reduce atherothrombotic risk.[11,12]

THROMBOTIC RISK IN POLYVASCULAR DISEASE

Observational studies of patients with polyvascular disease have demonstrated that patients with both PAD and CAD experienced up to 60% higher rates of atherothrombotic risk compared to patients with either disease alone.[7,13] Additionally, as the number of symptomatic arterial disease locations increased in a 1-year analysis of the REACH registry, so too did the event rates significantly increase.[7] The REACH registry also identified that polyvascular disease was the strongest predictor of future ischemic events, with a 99% increase in major adverse cardiovascular events (MACE) after 4 years of follow-up.[14]

In patients with polyvascular disease, the risk of major adverse limb events (MALE) is also increased, primarily driven by the presence of PAD.[15] MALE represents a significant burden for patients with PAD, and it includes acute limb ischemia, critical limb ischemia, lower-extremity revascularization, and major amputation.[16] Patients at the highest risk for limb ischemia include those with prior peripheral revascularization, current smokers, and those with an ankle-brachial index (ABI) of ≤0.5 or ≥1.3.[16] In the primary care setting,

presentation with acute or limb-threatening ischemia represents a medical emergency that necessitates urgent referral to a vascular surgeon.[12]

Since patients with polyvascular disease, especially those with CAD and PAD, experience significant increases in the risk of thrombotic events, they can benefit from proper implementation of antithrombotic and cholesterol-lowering therapies.[1] Several studies indicate that patients with polyvascular disease have reductions in MACE and MALE with intensive antithrombotic and/or cholesterol-lowering treatment.[17-21]

CASE SCENARIO

A 59-year-old woman presents to her PCP with complaints of leg pain she's been having on and off for about a year. She notices the pain mostly when she's walking, and it is not alleviated by over-the-counter pain medication. She has a history of CAD, medically managed by her cardiologist for the past 7 years. Her ABI today is 0.4, she is a former smoker (quit 20 years ago), and she has not had any prior revascularization.

DETECTION OF POLYVASCULAR DISEASE AND RISK STRATIFICATION

In the case scenario above, the patient's complaints of leg pain should be addressed with medical therapy; upon further discussion, this pain might be identified as intermittent claudication, a hallmark symptom of PAD.[12] Additionally, the increased risk of thrombosis due to potential for polyvascular disease should also be realized, based on a likely new diagnosis of PAD, in addition to her history of CAD.

ESTABLISHING THE PRESENCE OF POLYVASCULAR DISEASE

While screening and diagnostic techniques for PAD and CAD have been thoroughly explored and described in published literature, routine screening for polyvascular disease after initial detection of atherosclerosis in a single arterial bed is controversial.[1,22,23] Possible reasons for the lack of guidance on follow-up screening for polyvascular disease include a lack of cost-effectiveness analyses; no difference in recommended treatment (in some guidelines); and difference in risk perception between CAD, PAD, and CVD.[1]

PAD. Screening for and diagnosing PAD involves a comprehensive medical history, physical exam, and ABI testing. The US Preventive Services Task Force (USPSTF) has stated that there is insufficient evidence to recommend for or against the use of the ABI to screen for PAD in asymptomatic adults, primarily due to the lack of studies evaluating benefits and harms of screening with ABI.[24] However, in patients with suspected PAD based on risk factors or symptoms, the ABI is considered a core diagnostic test, and the only one required to establish a diagnosis of PAD.[22] The 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of lower-extremity PAD suggest an algorithm to aid clinicians in using a systematic approach to diagnostic testing for PAD.[22]

CAD. Despite substantial research and countless publications, the optimal approach to diagnosis of CAD remains unclear and poses a major challenge to healthcare systems in the United States.[23] Identifying stable CAD via functional or stress testing to detect ischemia is the most common noninvasive diagnostic test.[23,25] However, newer diagnostic tests such as coronary computed tomography angiography (CCTA) and simple, low-cost tests such as electrocardiogram (ECG) stress testing are also considered options for diagnosing CAD.[23,25-28] For patients with unacceptable ischemic symptoms or whose clinical characteristics indicate a high likelihood of severe ischemic cardiovascular disease, invasive testing via coronary angiography may be indicated.[29]

To enhance detection of polyvascular disease, PCPs should be attentive to signs and symptoms of atherosclerosis in other vascular beds for patients with established atherosclerotic disease.[1] A careful history and physical examination can often reveal noncardiac symptoms including amaurosis fugax and claudication.[1] The presence of polyvascular disease designates higher risk for MACE and MALE due to atherothrombotic events, and may indicate a need for aggressive antithrombotic therapy or even revascularization.[1]

MANAGING THROMBOTIC RISK FROM POLYVASCULAR DISEASE IN PRIMARY CARE

Pharmacologic treatment for polyvascular disease involves antithrombotic agents, comprising a variety of antiplatelet and anticoagulant drugs. Several guidelines can aid PCPs in selecting antithrombotic treatment, but not all guidelines have incorporated the most recent data.[12,22,30] US Food and Drug Administration (FDA)-approved agents for reducing thrombotic risk in PAD include clopidogrel, rivaroxaban, ticagrelor, and vorapaxar; aspirin has also been used.[31-34] Of note, rivaroxaban is the only agent indicated for reducing events in both PAD and CAD, including patients who have undergone lower-extremity revascularization.[32]

CURRENT RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPY IN PAD/CAD

PAD. Current recommendations for antithrombotic therapy in PAD are informed by several clinical guidelines.[12,22,30,35,36] Overall, the guidelines recommend the following principles to reduce atherothrombotic risk in PAD:

- In patients with symptomatic PAD, antiplatelet agents are recommended to reduce MI, vascular death, and stroke.[22]

- Combination treatment with aspirin and low-dose rivaroxaban for prevention of cardiovascular events and MALE should be considered for patients with PAD and/or stable coronary artery disease.[30,36]
- Following revascularization, statins and antiplatelet drugs are recommended to decrease cardiovascular complications.[35]
- Rivaroxaban plus aspirin may also be an option for decreasing amputations and mortality after revascularization.[20,35]

CAD. For patients with established atherosclerotic CAD, antiplatelet agents are commonly used to prevent secondary events.[37,38] Historically, aspirin has been a cornerstone for secondary prevention, though studies of other antiplatelet agents as well as anticoagulants have demonstrated improvement in ischemic outcomes, usually at the expense of increased bleeding.[30,38] Clinicians are encouraged to balance the risk of recurrent ischemic and bleeding events when considering antithrombotic therapy in patients with CAD.[38] In regard to lipid therapy, high-intensity statin treatment is indicated for patients with atherosclerotic CAD, with a low-density lipoprotein (LDL) target of <70 mg/dL.[39]

CLINICAL TRIALS WITH DATA IN PATIENTS WHO HAVE POLYVASCULAR DISEASE

As noted previously, the risk of ischemic outcomes increases with the number of vascular beds with atherosclerosis, but so also does the potential benefit of antithrombotic agents. Since recent clinical trials have included data on atherosclerosis in noncardiac vascular beds, there are many trials that have at least 1 subgroup of patients that can be classified as having polyvascular disease and give insight for clinical management (**TABLE**).

CAPRIE. The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was one of the first to incorporate patients with atherosclerotic disease in noncoronary vascular territories.[40] This trial randomized patients with symptomatic PAD, recent ischemic stroke, or recent MI to clopidogrel or aspirin and found high rates of MACE (20%) in patients with polyvascular disease randomized to aspirin. The clopidogrel group demonstrated a relative risk reduction of 8.7% in MACE (95% confidence interval [CI], 0.3-16.5; *P*=0.043).[40]

TRA2°P-TIMI 50. 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) included patients with PAD, ischemic stroke, or stable prior MI and randomized them to vorapaxar or placebo.[41] After 3 years of follow-up, the vorapaxar group experienced a lower rate of MACE than the placebo group (9.3% vs 10.5%; hazard ratio [HR] 0.87; *P*<0.001). Additionally, the rates of MACE increased across groups with the number of atherosclerotic vascular beds (1 bed, 7.8%; 2 beds, 14.7%; and 3 beds, 21.7%).[42]

PEGASUS-TIMI 54. In the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial, patients with prior MI were treated with low-dose aspirin and were randomized to ticagrelor or placebo.[18] At 3 years of follow-up, ticagrelor reduced MACE compared to placebo for patients with PAD (absolute risk reduction 4.1% [95% CI, -1.07% - 9.29%]) and without PAD (absolute risk reduction 1.0% [95% CI, 0.14%-1.9%]). Patients with CAD and PAD combined had higher rates of MACE than those with CAD only (19.3% vs 8.4%).[18]

EUCLID. The Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease (EUCLID) trial included patients with PAD who were randomized to ticagrelor or clopidogrel.[43] There was no difference between the 2 treatment groups in rates of MACE (10.8% for ticagrelor vs 10.6% for clopidogrel; *P*=0.65).[44] Patients with PAD and CAD had higher rates of MACE than those with PAD only (15.3% vs 8.9%; HR 1.28 [95% CI, 1.13-1.99]). Additionally, in this cohort, polyvascular disease was independently associated with a higher risk of lower-extremity revascularization.[15]

SAVOR-TIMI 53, LEADER, and IMPROVE-IT. These 3 trials included patients with type 2 diabetes (T2D) and polyvascular disease since these conditions are closely related. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus (SAVOR-TIMI 53) trial, patients with T2D at risk for cardiovascular disease randomized to saxagliptin or placebo experienced similar rates of MACE, but those rates increased with additional vascular bed involvement.[45] In Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER), patients with T2D and high cardiovascular disease risk took liraglutide or placebo with no significant difference in MACE between groups; however, those with polyvascular disease were at higher risk of MACE than those with single-bed disease (22.2% vs 15.3%; HR 1.52 [95% CI, 1.33-1.72]).[46] The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) included patients with and without T2D and polyvascular disease, and found an increased rate of MACE in those with polyvascular disease compared to those without polyvascular disease (37.8% vs 19.5%; HR 1.55 [95% CI, 1.41-1.70]).[47] In the IMPROVE-IT trial, the simvastatin-ezetimibe group demonstrated lower rates of MACE than the simvastatin monotherapy group (32.7% vs 34.7%; HR 0.936; *P*=0.016).[48]

FOURIER. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial included participants with high-risk cardiovascular

TABLE. **Clinical trials evaluating risks of polyvascular disease and benefits of antithrombotic therapy**[1]

Study	Risks of polyvascular disease	Benefits of therapy
CAPRIE[40]	Increased CV death, MI, or stroke	Clopidogrel vs aspirin; lower CV death, MI, or stroke overall; no separate polyvascular analysis
TRA2°P-TIMI 50[41,42]	Increased CV death, MI, or stroke	Vorapaxar vs placebo; lower CV death, MI, or stroke; lower peripheral revascularization
PEGASUS-TIMI 54[18]	Increased CV death, MI, or stroke; composite and individual	Ticagrelor + aspirin vs aspirin alone; lower CV death, MI, or stroke; lower MALE
EUCLID[15,43]	Increased CV death, MI, or stroke; increased LE revascularization	Ticagrelor vs clopidogrel; no difference in CV death, MI, or stroke
SAVOR-TIMI 53[45]	Increased CV death, MI, or stroke	Saxagliptin vs placebo; lower CV death, MI, or stroke overall; no additional benefit in polyvascular subgroups
LEADER[46]	Increased CV death, MI, or stroke	Liraglutide vs placebo; no difference in CV death, MI, or stroke
IMPROVE-IT[47]	Increased CV death, MI, or stroke	Ezetimibe vs placebo; lower CV death, MI, or stroke overall; no additional benefit in polyvascular subgroups
FOURIER[17,49]	Increased CV death, MI, or stroke	Evolocumab vs placebo; lower CV death, MI, or stroke; lower MALE
COMPASS[20,50]	Increased CV death, MI, or stroke	Low-dose rivaroxaban + aspirin vs aspirin + placebo; lower CV death, MI, or stroke; lower MALE
VOYAGER-PAD[21]	Higher CV death, MI, stroke, acute limb ischemia, or major amputation for vascular causes	Low-dose rivaroxaban + aspirin vs aspirin + placebo; lower CV death, MI, stroke, acute limb ischemia, or major amputation for vascular causes

Source: Adapted from: Gutierrez JA, Aday AW, Patel MR, Jones WS. Polyvascular disease: reappraisal of the current clinical landscape. *Circ Cardiovasc Interv*. 2019;12(12):e007385.

disease or symptomatic PAD receiving appropriate statin therapy and randomized them to evolocumab or placebo.[49] There was a significant reduction in MACE with evolocumab (5.9% vs 7.4%; HR 0.80 [95% CI, 0.73-0.88]) in the overall study population, but not in the subgroup with polyvascular disease.[17]

COMPASS. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, patients with stable atherosclerotic disease were randomized to rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg daily, or aspirin 100 mg daily.[20] In patients with polyvascular disease, rivaroxaban 2.5 mg twice daily plus aspirin demonstrated fewer net clinical benefit adverse outcomes (incorporating adverse efficacy events as well as safety bleeding events) vs aspirin (HR 0.80 [95% CI, 0.70-0.91]), primarily through reduction of adverse efficacy events.[50]

VOYAGER PAD. The Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) study enrolled patients with PAD (about one-third of whom had symptomatic CAD) who had undergone revascularization to rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.[21] The rivaroxaban group experienced a lower rate of the composite efficacy outcome (acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes) at 3 years (17.3% vs 19.9%; HR 0.85 [95% CI, 0.76-0.96]; *P*=0.009).[21]

Although data are now emerging about the benefits of antithrombotic therapy in polyvascular disease, clinical evidence does not support specific antithrombotic therapy based on polyvascular disease phenotype.[1] Once polyvascular disease is identified, clinicians must decide whether to intensify therapy based on balance between reduction in the risk of ischemic events and the risk of bleeding.[1] Additionally, high-intensity statin therapy targeting an LDL of <70 mg/dL for patients with polyvascular disease is consistent with current guideline recommendations.[39]

CASE SCENARIO (CONT'D)

The 59-year-old woman is given a diagnosis of PAD, in addition to CAD, and thus has polyvascular disease. Due to the increased risk of MACE and MALE, she should be prescribed a high-intensity statin (if she's not taking one already). She should also be prescribed antithrombotic therapy, either with one of the antiplatelet agents with proven reduction in MACE (clopidogrel, ticagrelor, or vorapaxar), or with rivaroxaban 2.5 mg twice daily plus aspirin.

SUMMARY

Polyvascular disease is an underrecognized condition with significant clinical consequences. Patients with atherosclerosis in multiple vascular beds were consistently at higher risk for thrombotic events compared to those without polyvascu-

lar disease. PCPs can help initiate and monitor adequate antithrombotic and statin therapy in these patients and refer to specialists when necessary.

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