

Advances in the Treatment of Stable Coronary Artery Disease and Peripheral Artery Disease

EMCREG-International Proceedings Monograph from the 2017 American Heart Association Symposium, November 12, 2017

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Dear Colleagues,

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, New Zealand, Japan, Singapore, Sweden, and the United Kingdom. Now in our 28th year, we remain committed to providing you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Cardiology, Internal Medicine, Family Medicine, Hospital Medicine, and Emergency Medicine with our EMCREG-International University of Cincinnati Office of CME accredited symposia and enduring materials.

In this EMCREG-International Monograph, *Advances in the Treatment of Stable Coronary Artery Disease and Peripheral Artery Disease*, you will find a detailed discussion regarding the treatment of these 2 critically important disease entities. This is a Proceedings Monograph based on the 2017 EMCREG-International Satellite Symposium which was held on November 12, 2017, in Anaheim during the American Heart Association Scientific Sessions. For cardiologists, internists, family physicians, hospitalists and emergency physicians, the current approach and evolution of treatment for stable coronary artery disease (CAD) and peripheral artery disease (PAD) are particularly relevant and represent a fertile area for improving care for these patients.

This Monograph is divided into 4 sections. The first section provides a description of the scientific basis for the current management of patients with stable coronary artery disease. For many patients, this approach uses antiplatelet monotherapy typically aspirin. The use of dual antiplatelet therapy and anticoagulant therapy has also been evaluated in these patients. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial which was published in late August 2017, is described in detail. This study was terminated prematurely because of the substantial superiority of the aspirin plus low dose rivaroxaban arm in patients with stable CAD and PAD. In the second section of this Monograph, the diagnosis and treatment of PAD is discussed in depth. Antiplatelet monotherapy serves as the predominant treatment for PAD though several other antiplatelet agents have been used as monotherapy or dual antiplatelet therapy. Balancing the positive benefits of these various therapeutic combinations versus the risk of bleeding has made monotherapy with aspirin or clopidogrel a Class Ia

recommendation by the American College of Cardiology/American Heart Association Guidelines for PAD. The recently published COMPASS trial demonstrated that dual therapy with aspirin and low dose rivaroxaban was superior to treatment with aspirin only for patients with PAD. In the third section of this Monograph, a detailed discussion of the clotting mechanism emphasizes the cell-based nature of the contemporary understanding of thrombosis. The intersection of the protein based clotting cascade with platelets, endothelial cells, and leukocytes represents a cohesive approach to understanding how antiplatelet and anticoagulant agents can prevent pathologic clot formation associated with disease processes such as chronic CAD and PAD. Finally, the clinical and economic value of appropriate anticoagulation with a Factor Xa inhibitor such as rivaroxaban help weave together a coherent approach to understanding the complex disease processes in stable CAD and PAD.

It is our sincere hope that you will find this EMCREG-International Proceedings Monograph from our 2017 EMCREG-International Satellite Symposium during the 2017 American Heart Association Scientific Sessions on the treatment of stable CAD and PAD useful to you in your daily practice as a cardiologist, internist, family physician, hospitalist, and emergency physician. Instructions for obtaining CME from the University of Cincinnati College of Medicine, Office of Continuing Medical Education are available at the conclusion of this January 2018, EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives and we hope you visit our website (www.emcreg.org) for future educational events and publications.



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DISCLOSURES

Dr. W. Brian Gibler has served on the Advisory Boards for AstraZeneca and Entegron and is a Shareholder for MyocardioCare and Entegron.

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Decreasing Major Adverse Clinical Events for Patients With Coronary Artery Disease or Peripheral Artery Disease: The COMPASS Trial

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Introduction: Chronic coronary artery disease (CAD) and peripheral artery disease (PAD) are common manifestations of atherosclerosis. Recent estimates suggest that 16.5 million adults in the United States have chronic CAD.¹ The prevalence of PAD is lower, affecting more than 5 million American adults.² Although CAD is the leading cause of death worldwide, both conditions contribute significantly to loss of disability-adjusted life-years.^{3,4} Atherosclerosis often manifests in several vascular beds, and the distinct clinical syndromes share many common major risk factors, including older age, smoking, hypertension, hypercholesterolemia, and diabetes mellitus.⁵ Platelets play pivotal roles in the inflammatory, thrombotic, and atherosclerotic processes. Therefore, targeting various pathways to inhibit platelet activation and aggregation is essential in preventing complications of progressive atherosclerotic disease.⁶

Single-Agent Antiplatelet Therapy: For more than 3 decades, platelet inhibition with the cyclooxygenase-1 inhibitor aspirin has been a cornerstone in the treatment and prevention of cardiovascular disease.^{7,8} In the secondary preventive setting, aspirin reduces the risk of myocardial infarction, stroke, or death from vascular causes by an absolute 1.5%.⁹ However, approximately 1 in 8 patients experiences a recurrent ischemic event while on aspirin.¹⁰

The randomized Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared clopidogrel, a P2Y₁₂ receptor antagonist, at a dose of 75 mg once daily with aspirin 325 mg once daily in 19,185 patients with a recent ischemic stroke, a recent myocardial infarction, or symptomatic PAD.¹¹ At a mean follow-up of 1.9 years, the primary composite endpoint of ischemic stroke, myocardial infarction, or vascular death was significantly lower in the clopidogrel group [relative risk reduction, 8.7%; 95% confidence interval (CI), 0.3–16.5; *P* = 0.04]. Subgroup analyses revealed a greater risk reduction in the PAD subgroup (Fig. 1).

Furthermore, the benefit of clopidogrel was more pronounced among subjects at high vascular risk, including those with diabetes or multiple prior ischemic events.^{12,13} Importantly, clopidogrel was as least as safe as aspirin.

Given the theoretical advantages of ticagrelor over clopidogrel, the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) investigators randomly assigned 13,885 patients with symptomatic PAD, defined as previous lower limb revascularization or an ankle-brachial index of 0.80 or less, to receive ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily.¹⁴ Poor clopidogrel metabolizers per cytochrome P-450 2C19 genotyping were excluded. At a median of 30 months, the primary efficacy endpoint, that is, a composite of cardiovascular death, myocardial infarction, or ischemic stroke, had occurred with similar rates in the 2 groups (ticagrelor vs. clopidogrel; hazard ratio, 1.02; 95% CI, 0.92–1.13; *P* = 0.65). Although the subset of patients with previous revascularization experienced more myocardial infarctions and acute limb ischemia events, there were no differences between patients treated with ticagrelor and clopidogrel.¹⁵ More patients in the ticagrelor group experienced dyspnea and any bleeding, but rates of major bleeding, fatal bleeding, and intracranial bleeding were similar for the 2 drugs.

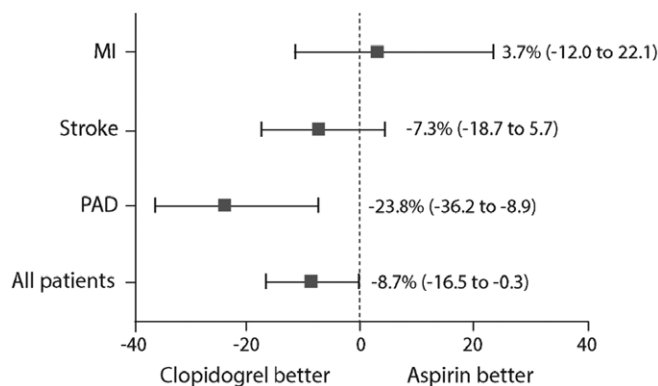


FIGURE 1. Relative risk reduction (95% confidence interval) for the primary endpoint (a composite of ischemic stroke, MI, or vascular death) in subgroups of the CAPRIE trial. MI indicates myocardial infarction. Based on data from *Lancet*. 1996;348:1329–1339.

Dual Antiplatelet Therapy: Dual antiplatelet therapy (DAPT) comprising aspirin and a P2Y₁₂ receptor antagonist is the best-established regimen for patients with an acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention and stent implantation.^{16,17} Accordingly, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial tested the use of DAPT with clopidogrel 75 mg daily plus aspirin 75–162 mg daily versus aspirin alone in 15,603 patients with either established vascular disease (documented CAD, cerebrovascular disease, or symptomatic PAD) or multiple atherothrombotic risk factors for a median of 28 months.¹⁸ Although the primary efficacy endpoint, a composite of myocardial infarction, stroke, or death from cardiovascular causes, was not significantly reduced with DAPT (relative risk, 0.93; 95% CI, 0.83–1.05; *P* = 0.22), there was a significant risk reduction in the subgroup of patients with established vascular disease (*P* = 0.045 for interaction). A post hoc analysis also showed greater efficacy of DAPT versus aspirin alone among patients with prior myocardial infarction, ischemic stroke, or symptomatic PAD.¹⁹ The relative risk reduction in the PAD subgroup was consistent with that observed for patients with myocardial infarction or stroke (Fig. 2). The primary safety endpoint of severe bleeding was not significantly increased with DAPT.

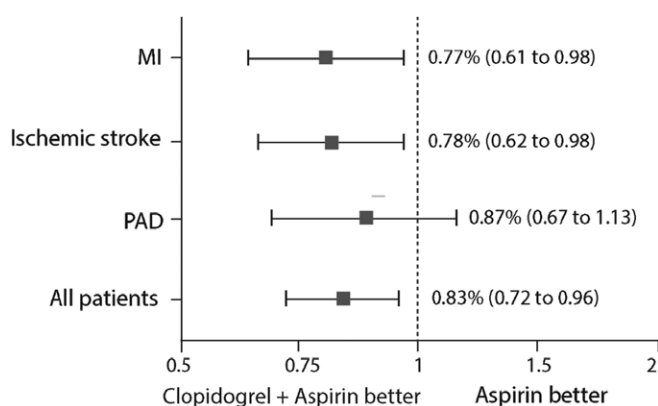


FIGURE 2. Hazard ratio (95% confidence interval) for the primary endpoint (a composite of cardiovascular death, MI, or stroke) in the subgroup of patients enrolled because of MI, ischemic stroke, or peripheral artery disease from the CHARISMA trial. MI indicates myocardial infarction. Based on data from *J Am Coll Cardiol*. 2007;49:1982–1988.

DAPT using ticagrelor instead of clopidogrel was tested in the Platelet Inhibition and Patient Outcomes (PLATO) trial, in which the P2Y₁₂ receptor antagonists were compared in patients with an ACS. Twelve months of ticagrelor was more effective than clopidogrel in preventing vascular events and provided a reduction in vascular death, without an increase in overall major bleeding.²⁰ Consequently, 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) trial examined the efficacy and safety of extended DAPT in 21,162 patients with a previous myocardial infarction and additional high-risk features for ischemic events.²¹ Patients received ticagrelor (90 mg twice daily or 60 mg twice daily) or placebo, on top of aspirin 75–150 mg daily. At 3 years, the primary efficacy endpoint of cardiovascular death, myocardial infarction, or stroke was significantly reduced with both ticagrelor regimens when compared with placebo: ticagrelor 90 mg (hazard ratio, 0.85; 95% CI, 0.75–0.96; *P* = 0.008) and ticagrelor 60 mg (hazard ratio, 0.84; 95% CI, 0.74–0.95; *P* = 0.004). Absolute risk reductions with extended DAPT were greater among subjects with diabetes and those with PAD, due to their higher baseline risk of ischemic events.²² Ticagrelor also reduced the risk of acute limb ischemia or peripheral artery revascularization. The rate of major bleeding was significantly greater with ticagrelor, but rates of intracranial hemorrhage or fatal bleeding were similar in the 3 groups.

An alternative antiplatelet strategy was tested in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50 (TRA 2°P-TIMI 50) trial, in which 26,449 patients with a history of myocardial infarction, ischemic stroke, or symptomatic PAD were randomly assigned to receive either vorapaxar, a protease-activated receptor-1 antagonist, at a dose of 2.5 mg daily or placebo, on a background of single or dual antiplatelet therapy.²³ Vorapaxar resulted in a significantly lower 3-year risk of the primary efficacy endpoint, a composite of death from cardiovascular causes, myocardial infarction, or stroke (hazard ratio, 0.87; 95% CI, 0.80–0.94; *P* < 0.001). However, this came at the expense of a significantly increased risk of moderate or severe bleeding, including intracranial hemorrhage. The risk of intracranial hemorrhage was particularly pronounced among patients with previous stroke and prompted the data and safety monitoring board to recommend discontinuation of study drug in this subgroup after a median of 2 years of follow-up. In patients with PAD, vorapaxar did not reduce the primary endpoint; however, the group of patients assigned to vorapaxar experienced significantly lower rates of hospitalization for acute limb ischemia and peripheral revascularization.²⁴

Very Low-Dose Anticoagulation: Patients with atherosclerotic disease remain at high risk for recurrent cardiovascular events despite antiplatelet therapy. Because these individuals also display an increased activation of the coagulation system, there has been an interest in examining the role of oral anticoagulation in this setting.²⁵

In stented patients, a vitamin K antagonist does not offer superior protection to DAPT and is associated with an increased risk of bleeding.²⁶ However, a phase 2 safety trial in patients who had been stabilized after ACS suggested that the direct factor Xa inhibitor, rivaroxaban, might decrease the risk of ischemic endpoints.²⁷ The subsequent Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS TIMI 51) trial tested the role of very low-dose rivaroxaban after ACS.²⁸ A total of 15,526 patients were randomized to rivaroxaban, at a dose of either 2.5 or 5 mg twice daily, or placebo, in addition to DAPT with low-dose aspirin and a thienopyridine (clopidogrel or ticlopidine). At a mean of 13 months, the primary composite efficacy endpoint of death from cardiovascular causes, myocardial infarction, or stroke was significantly reduced with both doses of rivaroxaban (hazard ratio, 0.84; 95% CI, 0.74–0.96; *P* = 0.008), albeit at the expense of more major bleeding and intracranial hemorrhage. The 2.5-mg rivaroxaban dose was associated with lower bleeding rates than 5 mg, and decreased rates of death from cardiovascular causes and all-cause mortality compared with the 5-mg dose.

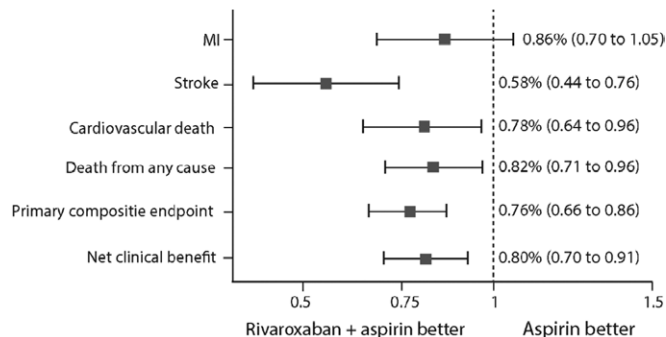


FIGURE 3. Primary and selected secondary efficacy endpoints in the COMPASS trial (all study patients). MI indicates myocardial infarction. Based on data from *N Engl J Med*. 2017;377:1319–1330.

These intriguing findings for very low-dose anticoagulation finally culminated in the Cardiovascular Outcomes for People Using Anti-coagulation Strategies (COMPASS) trial, in which 27,395 individuals with stable atherosclerotic vascular disease (CAD or PAD) without an indication for DAPT or anticoagulation were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg once daily.²⁹ The trial was stopped early, after a mean follow-up of 23 months, owing to a consistent benefit in favor of the combination therapy arm. Thus, the primary endpoint, a composite of cardiovascular death, stroke, or myocardial infarction, was significantly reduced with rivaroxaban plus aspirin versus aspirin alone (hazard ratio, 0.76; 95% CI, 0.66–0.86; *P* < 0.001), but not with rivaroxaban alone versus aspirin alone (hazard ratio, 0.90; 95% CI, 0.79–1.03; *P* = 0.12). Rivaroxaban–aspirin significantly lowered the individual endpoints of cardiovascular death, and stroke (Fig. 3). In 7470 participants included with PAD, major limb events were substantially lowered as well (Fig. 4). As expected, major bleeding was significantly increased with rivaroxaban–aspirin versus aspirin (hazard ratio, 1.70; 95% CI, 1.40–2.05; *P* < 0.001) and with rivaroxaban versus aspirin (hazard ratio, 1.51; 95% CI, 1.25–1.84; *P* < 0.001). However, the combination regimen did not significantly increase fatal or intracranial hemorrhage and was associated with significant net clinical benefit (hazard ratio, 0.80; 95% CI, 0.70–0.91; *P* < 0.001).

Summary and Conclusions: Patients with stable atherosclerotic disease derive benefit from secondary prevention with antiplatelet drugs. In this setting, clopidogrel is superior to aspirin. After an ACS event or percutaneous coronary intervention, DAPT with aspirin and a P2Y₁₂ receptor antagonist is

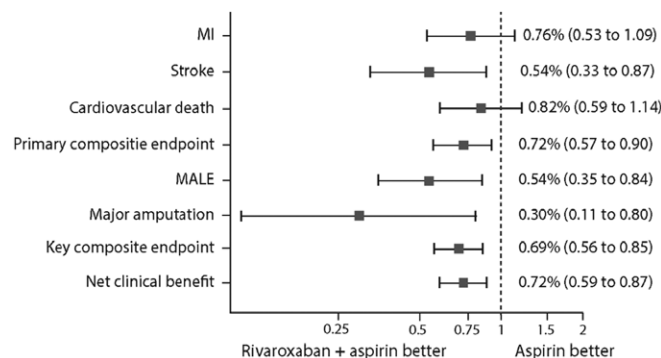


FIGURE 4. Primary and selected secondary efficacy endpoints in the COMPASS trial (subgroup with peripheral artery disease). MALE indicates major adverse limb event; MI, myocardial infarction. Based on data from *N Engl J Med*. 2017;377:1319–1330.

the preferred regimen. In many ACS patients at high risk for recurrent cardiovascular events and at low bleeding risk, extending DAPT beyond 12 months may be advantageous. The COMPASS trial has challenged the traditional antiplatelet-only paradigm by demonstrating a considerable ischemic benefit and, importantly, lower rates of cardiovascular mortality and all-cause mortality with very low-dose anticoagulation added to aspirin in patients with stable CAD or PAD. Still, as with any antithrombotic regimen, its use in clinical practice will require careful balancing of the risk of ischemia versus bleeding. Further analyses from the COMPASS trial are likely to identify individuals who will benefit the most from this new therapeutic approach.

DISCLOSURES

Dr. Manan Pareek discloses the following relationships. Advisory Board: AstraZeneca; Other Relationships: AstraZeneca and Medscape. Dr. Deepak L. Bhatt discloses the following relationships. Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; clinical trial steering committee), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (including for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda.

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Improving the Treatment of Peripheral Artery Disease: Providing Individualized, Innovative, and Efficient Care

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Introduction: Atherosclerotic peripheral artery disease (PAD) affects more than 200 million adults worldwide¹ and an estimated 8 million people in the United States. The prevalence of PAD in patients over 70 or 55 years of age with diabetes is estimated near 30% from the Partners study (Fig. 1).² Lower extremity PAD is considered a manifestation of systemic atherosclerosis that affects the arteries of the lower limbs. Despite recent advances in diagnosis and treatment, 5%–10% of patients with PAD have recurrent events and millions die from cardiovascular disease each year.³ Many medical strategies are considered important for patients with PAD. These include smoking cessation, diabetes control, blood pressure management, exercise therapy for claudication, and antithrombotic medications. Antithrombotic medications have been proven to reduce cardiovascular morbidity and mortality in a number of scenarios, including acute coronary syndrome, atrial fibrillation, and percutaneous coronary intervention.^{4–8} Statin therapy is considered a cornerstone

treatment to reduce the occurrence of major adverse cardiovascular events in patients with stable atherosclerotic disease.^{9,10} The evidence base for PAD therapies has evolved recently. The cardiovascular risk of patients with PAD, risk reduction strategies, recent antithrombotic trial data, and opportunities for care improvement moving forward will be reviewed here.

PAD Patient Population and Treatment Opportunities: Most patients with PAD are asymptomatic, and those with symptoms can present with a variety of complaints including atypical leg pain, intermittent claudication (leg pain that occurs with exertion and improves with rest), ischemic rest pain, ulceration, or gangrene.¹¹ The symptom presentation often dictates how patients are identified and brought to clinical specialties. The ankle-brachial index is the guideline recommended and most frequently used diagnostic test to determine the presence of PAD; the degree of hemodynamic abnormality is often used along with symptoms to determine treatment strategies.

Medical treatment of patients with PAD has traditionally involved antiplatelet monotherapy (eg, aspirin or clopidogrel) and moderate- to high-intensity statin medication to reduce cardiovascular risk over time.¹¹ Although PAD is generally considered a coronary artery disease (CAD) risk equivalent, antiplatelet and statin medications are used significantly less frequently in patients with PAD than in patients with CAD. As such, there is significant opportunity to improve treatment rates and compliance with antiplatelet and statin medications in patients with PAD.^{12,13} In patients with persistent symptoms despite background medical therapy, cilostazol and supervised exercise training for intermittent claudication have been shown to improve walking distance and quality of life.^{14,15} Until recently, supervised exercise training has been seldom used by eligible patients due to lack of insurance reimbursement and sparse availability around the country. In May 2017, however, the Centers for Medicare and Medicaid Services announced a National Coverage Determination that will reimburse providers for supervised exercise training in patients with intermittent claudication.

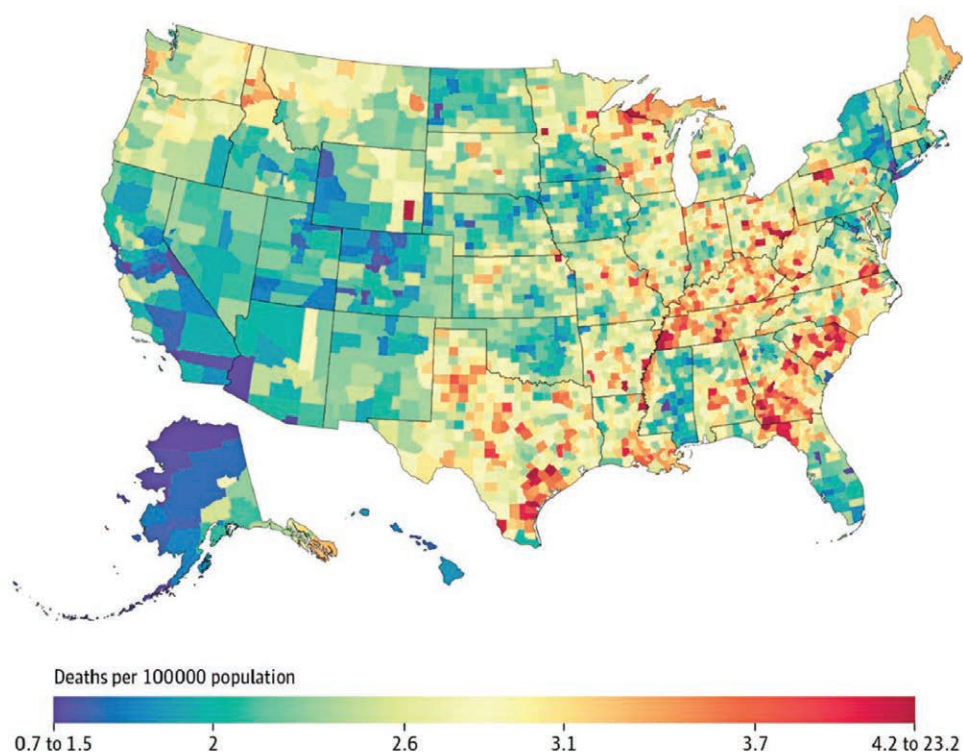


FIGURE 1. Age-standardized mortality rate for patients with peripheral artery disease, 2014. Reprinted with permission from *JAMA*. 2010;317:1976–1992.

There are few proven medical therapies for patients with critical limb ischemia, the most severe form of PAD. In patients with limb-threatening ischemia, noninvasive and invasive imaging is recommended to define the burden and severity of obstructive disease and revascularization is frequently recommended to preserve limb function and mobility. Typically, only 30% of patients who undergone a limb amputation have an arterial diagnostic study of any kind performed before the amputation. The heterogeneity that exists in the application of these diagnostic and interventional strategies is also geographically variable across the country.^{16,17} Finally, in Medicare patients, the mortality rate of patients with critical limb ischemia at 1 year is nearly 50%, signaling the need for therapies aimed at this population.¹⁸

Dual Antiplatelet Therapy: When compared with patients with other forms of atherosclerotic disease, including CAD, patients with PAD have a higher risk of cardiovascular death, myocardial infarction (MI), and stroke. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, PAD patients had a 21.1% annual risk of cardiovascular death, MI, stroke, or hospitalization for an atherothrombotic cause.¹⁹ Also, the risk of major adverse limb events, typically defined as major amputation or surgical intervention, varies from 2% to 10% annually depending on age, symptom classification, concomitant medical therapy, and prior revascularization procedures.

Importantly, major amputation of the lower extremities due to PAD has decreased significantly in the United States, but it remains an important public health concern because mortality rates are nearly 50% at 1 year and 70% at 3 years after major amputation in Medicare patients.²⁰ Lower extremity peripheral vascular interventions have increased significantly over the last 2 decades (Fig. 2).

Risk Reduction From Antithrombotic Agents: Antiplatelet therapies have been the center of treatment for patients with atherosclerotic vascular disease; the American College of Cardiology/American Heart Association (ACC/AHA) guidelines place a Class Ia recommendation for antiplatelet monotherapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) to reduce the incidence of MI, stroke, and vascular death in patients with symptomatic PAD.¹¹ Because the data for antiplatelet therapy in asymptomatic patients with PAD are derived from small studies and are more heterogeneous, the ACC/AHA guidelines place a Class IIa recommendation for antiplatelet therapy in these patients. There remains uncertainty about the long-term safety and efficacy of dual antiplatelet therapy in patients with PAD based on a single subgroup analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study, thus prolonged dual antiplatelet therapy for all patients with PAD remains a Class IIb recommendation.

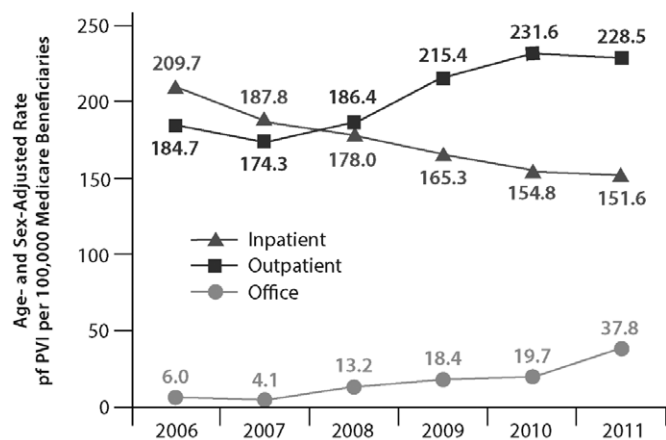


FIGURE 2. Trends in PVI in US Medicare beneficiaries. PVI indicates peripheral vascular intervention. Reprinted with permission from *J Am Coll Cardiol.* 2015;65:920–927.

There are multiple antithrombotic targets to reduce the risk of atherothrombosis in stable patients with PAD (Fig. 3). Therapies have targeted platelet activity and receptors and include aspirin, clopidogrel, ticagrelor, and vorapaxar (targeting thromboxane, P2Y₁₂, and protease-activated receptor-1, respectively). Aspirin has been the dominant therapy used by vascular physicians because of its low cost, availability, and safety; however, patients remain at high risk for life-threatening events such as MI and stroke despite aspirin therapy.²¹ With the introduction of ticlopidine²² and clopidogrel, multiple studies were performed in high-risk patients, including those with PAD. The use of ticlopidine was truncated due to an excess risk of thrombotic thrombocytopenic purpura, and although clopidogrel was found to reduce the risk of vascular death, MI, or stroke by 23.8% in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,²³ the substitution of clopidogrel for aspirin did not routinely occur in clinical practice due to cost. More recently, the use of oral anticoagulants has been studied in patients with atherosclerotic disease including PAD.

Recent Antithrombotic Clinical Trial Data: Vorapaxar is a protease-activated receptor-1 inhibitor that binds to platelets and has been studied in the setting of acute coronary syndrome and stable atherosclerotic disease (prior MI or PAD) as an addition to baseline antiplatelet therapy. In the pivotal Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50 (TRA 2°P-TIMI 50) study, 26,449 patients (3787 with PAD) were randomized to vorapaxar or placebo.²⁴ Eighty-eight percent of these patients were receiving aspirin therapy, 37% were taking a thienopyridine, and 28% were receiving dual antiplatelet therapy on study entry. In the overall cohort, vorapaxar reduced the incidence of the composite endpoint (cardiovascular death, MI, or stroke) by 1.2%. In the PAD cohort, the risk reduction for the primary composite endpoint was not statistically significant [11.3% vs. 11.9%; hazard ratio, 0.94; 95% confidence interval (CI), 0.78–1.14; $P = 0.53$]. Vorapaxar did reduce the risk of hospitalization for acute limb ischemia and peripheral revascularization, but the hazard of Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) moderate and severe bleeding and intracranial hemorrhage was statistically significantly higher with vorapaxar. In 2014, the US Food and Drug Administration approved the use of vorapaxar in patients with prior MI or PAD albeit with a warning for bleeding on the label.

Another antiplatelet agent, ticagrelor, has been tested extensively in patients with PAD. 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) trial enrolled 21,162 patients with a history of MI, of which 1143 had PAD.²⁵ Patients were randomized in a 1:1:1 fashion to ticagrelor 90 mg twice daily versus ticagrelor 60 mg twice daily versus placebo on a background of aspirin. PAD patients in the ticagrelor 60 mg arm had a statistically significant reduction in cardiovascular death, MI, or stroke, but the reduction with the ticagrelor 90 mg dose was not statistically significant. Hospitalization for acute limb ischemia or peripheral revascularization was significantly reduced in the ticagrelor 90 mg arm, but the reduction in the 60 mg arm was not statistically significant.²⁵ The Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial randomized 13,885 symptomatic patients with PAD in a 1:1 fashion to ticagrelor or clopidogrel monotherapy.²⁶ Patients were followed for approximately 30 months, and there was no difference between the 2 groups in terms of the primary composite endpoint of cardiovascular death, MI, or stroke (10.8% vs. 10.6%; hazard ratio, 1.02; 95% CI, 0.84–1.43; $P = 0.49$) and hospitalization for acute limb ischemia (1.7% vs. 1.7%; hazard ratio, 1.03; 95% CI, 0.79–1.33; $P = 0.85$) were also similar between treatment groups.

In the recently published Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, a total of 27,395 patients with stable atherosclerotic vascular disease (CAD, PAD, or both) were

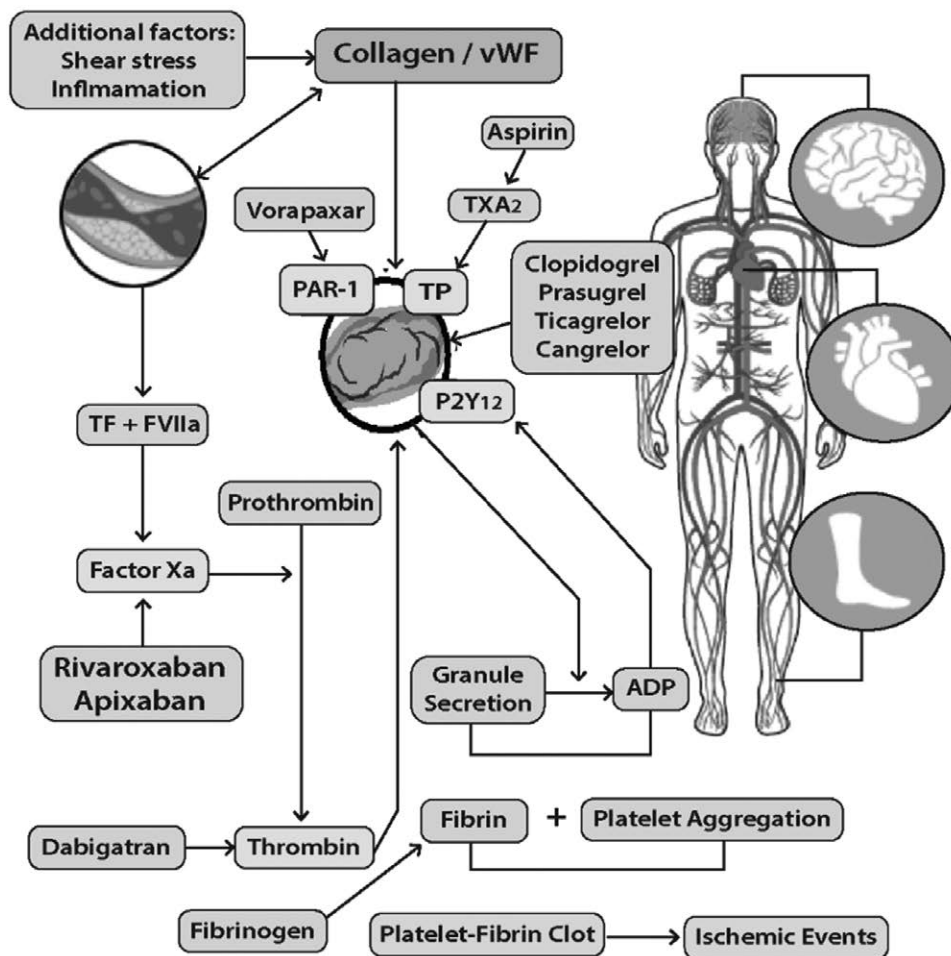


FIGURE 3. Mechanisms of antithrombotic medications and clinical endpoints important to patients with PAD. ADP indicates adenosine diphosphate; TF, tissue factor; TP, thromboxane receptor; TxA₂, thromboxane A₂; vWF, von Willebrand factor. Reprinted with permission.

randomized to 3 arms (aspirin 100 mg daily vs. rivaroxaban 5 mg twice daily vs. aspirin 100 mg daily plus rivaroxaban 2.5 mg twice daily) at 602 centers worldwide.²⁷ The study was terminated earlier than expected due to overwhelming efficacy in the aspirin and low-dose rivaroxaban arm. Over approximately 2 years of follow-up, patients randomized to aspirin plus rivaroxaban 2.5 mg twice daily had a significantly lower rate of the primary composite endpoint (MI, ischemic stroke, cardiovascular death) when compared with aspirin alone (4.1% vs. 5.4%; hazard ratio, 0.76; 95% CI, 0.66–0.86; $P < 0.001$). There was a significantly higher rate of major bleeding in the aspirin plus rivaroxaban group when compared with aspirin alone (3.1% vs. 1.9%; hazard ratio, 1.70; 95% CI, 1.40–2.15; $P < 0.001$). Nevertheless, there was an 18% risk reduction in all-cause mortality in favor of aspirin and low-dose rivaroxaban (3.4% vs. 4.1%; hazard ratio, 0.82; 95% CI, 0.71–0.96; $P < 0.001$).

In a simultaneous report, rivaroxaban was shown to have similar efficacy in the PAD cohort from the COMPASS trial. In 7470 patients who met inclusion criteria based on a history of PAD, 55.2% had symptomatic limbs, 25.7% had carotid disease, and 19.1% had a low ankle-brachial index. The rate of the primary composite endpoint was reduced with aspirin plus rivaroxaban 2.5 mg twice daily when compared with aspirin alone (5.1% vs. 6.9%; hazard ratio, 0.72; 95% CI, 0.57–0.90; $P < 0.001$). The risk of major bleeding was also very similar to the main trial results, with aspirin plus rivaroxaban 2.5 mg twice daily being associated with a significantly higher rate of major

bleeding when compared with aspirin alone (3.1% vs. 1.9%; hazard ratio, 1.61; 95% CI, 1.12–2.31; $P < 0.001$). However, this finding is also significant in that PAD patients did not have an elevated risk of major bleeding when compared with patients without PAD.

In aggregate, these recent trial results provide some insight into the potential pathobiology of cardiovascular and limb events in patients with PAD. These recent data demonstrated no improvement in cardiovascular outcomes with more potent mono antiplatelet therapy (EUCLID). Subgroups of studies with dual therapy versus mono antiplatelet therapy show some benefit (PEGASUS and CHARISMA). Finally, there is now evidence that dual pathway therapy with antiplatelet and antithrombotic therapy (COMPASS PAD) may provide the most significant cardiovascular and limb protection for PAD patients. Table 1 summarizes clinical trials of antithrombotic agents in patients with stable peripheral arterial disease and patients undergoing peripheral revascularization.

Ongoing Clinical Trial: The Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects with Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremity (VOYAGER PAD) study is a 1:1 randomized, placebo-controlled trial of rivaroxaban 2.5 mg twice daily or placebo on a background of aspirin 100 mg daily after peripheral surgical and/or endovascular revascularization. VOYAGER will enroll over 6500 patients and should be reported in early 2019.

TABLE 1. Clinical Trials of Antithrombotic Agents in Patients With Stable Peripheral Arterial Disease and Patients Undergoing Peripheral Revascularization

Stable PAD	1 vs. 0 (Antiplatelet agent)			1 vs. 1 (Antiplatelet agent)	
TRIAL Description	POPADAD ASA 100 mg daily vs. Control 1,276 patients	Aspirin for Asymptomatic Atherosclerosis Trialists ASA 100 mg daily vs. Control 3,350 patients	STIMS Ticlopidine vs. Placebo 687 patients	CAPRIE ASA 100 mg daily vs. Clopidogrel 6,452 patients	EUCLID Ticagrelor vs. Clopidogrel 13,885 patients
Major adverse cardiac events	Vascular death, MI, stroke: 18.2% vs. 18.3% HR 0.98, 95% CI .76-1.26	Fatal or non-fatal MI/stroke or revascularization: HR 1.03, 95% CI 0.84-1.27	*All-cause mortality: 18.5% vs. 26.1%	Vascular death, MI, or ischemic stroke: HR 0.76, 95% CI 0.64-0.91	CV death, MI, or stroke: 10.8% vs. 10.6% HR 1.02, 95% CI .92-1.13
Major adverse limb events	Major amputation: 2% vs. 2%	Not reported	Not reported	Not reported	Not reported
Acute limb ischemia	Not reported	Not reported	Not reported	Not reported	1.7% vs. 1.7% HR 1.03, 95% CI .79-1.33
Major bleeding	Not reported	HR 1.71, 95% CI 0.99-2.97	*Ticlopidine group had 5% rate of hemorrhagic event	Not reported for PAD subgroup	TIMI Major Bleeding: 1.6% vs. 1.6%
	2 vs. 1 (Antiplatelet Intensity)			2 vs. 2 (Antiplatelet and Anticoagulant)	
TRIAL Description	CHARISMA ASA vs. ASA/Clopidogrel 3,096 patients	TRA2°P Vorapaxar vs. placebo on background of antiplatelet (88% aspirin, 28% on ASA & thienopyridine) 3787 patients	PEGASUS Ticagrelor 90mg BID vs. Ticagrelor 60 BID vs. placebo on background of ASA 1,143 patients	WAVE Antiplatelet (ASA, clopidogrel or ticlopidine) + warfarin vs. Antiplatelet 2,161 patients	COMPASS Rivaroxaban 2.5 mg BID + ASA 100 mg daily vs. Rivaroxaban 5 mg BID vs. ASA 100 mg daily 7,470 patients
Major adverse cardiac events	CV death, MI, or stroke: 7.6% vs. 8.9% HR 0.85, 95% CI .66-1.08	CV death, MI, or stroke: 11.3% vs. 11.9% HR 0.94, 95% CI .78-1.14	CV death, MI, or stroke: Ticagrelor 60mg HR 0.69, 95% CI .47-.99 Ticagrelor 90mg HR 0.81 95% CI 0.57-0.15	CV death, MI, or stroke: HR 0.92, 95% CI 0.73-1.16	CV death, MI, or stroke: HR 0.72, 95% CI .57-.90
Major adverse limb events	Not reported	Not reported	Not reported	Not reported	1.2% vs. 2.2% HR 0.54, 95% CI .35-.84
Acute limb ischemia	Not reported	2.3% vs. 3.9% HR 0.58, 95% CI 0.39-0.86	Ticagrelor 60mg HR 0.67, 95% CI .24-.87 Ticagrelor 90mg HR 0.45, 95% CI .14-1.45	Not reported	Not reported
Major bleeding	GUSTO Severe bleeding: 1.7% vs. 1.5% HR 0.97, 95% CI .56-1.66	GUSTO Mod/Sev bleeding: 7.4% vs. 4.5% HR 1.62, 95% CI 1.21-2.18	TIMI Major bleeding: Ticagrelor 60mg: HR 1.18, 95% CI .29-4.70 Ticagrelor 90 mg: HR 1.46, 95% CI .39-5.43	Life threatening bleeding: 4.0% vs. 1.2% RR 3.41, 95% CI 1.84- 6.35	ISTH Major bleeding: 3.1% vs. 1.9% HR 1.61, 95% CI 1.12-2.31
Post-Revasc	2 vs. 1 (Antiplatelet Intensity)			2 vs. 2 (Antiplatelet and Anticoagulant)	
TRIAL Description	CASPAR Clopidogrel vs. placebo on background of ASA 851 patients	VOYAGER Rivaroxaban vs. placebo on background of ASA 6,500 patients	ePAD ASA/Edoxaban vs. ASA/Clopidogrel 203 patients		
Major adverse cardiac events	*Death 24 patients vs. 17 HR 1.44, 95% CI .77-2.68	Not available – trial ongoing	Not reported		
Major adverse limb events	*Primary endpoint (graft occlusion, major amputation or death) HR 0.98, 95% CI .78-1.23	Not available – trial ongoing	Not reported		
Acute limb ischemia	Not reported	Not available – trial ongoing	Not reported		
Major bleeding	GUSTO Severe bleeding: 2.1% vs. 1.2%	Not available – trial ongoing	TIMI Major bleeding: 0 patients (E) vs. 2 patients (C)		

ASA indicates aspirin; BID, twice daily; CASPAR, Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral Arterial Disease; CV, cardiovascular; ePAD, Edoxaban in Peripheral Arterial Disease; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; RR, relative risk; STIMS, Swedish Ticlopidine Multicentre Study; WAVE, Warfarin Antiplatelet Vascular Evaluation.

Conclusions: In conclusion, PAD is a systemic manifestation of atherosclerosis that affects over 200 million people worldwide. Proven therapies such as blood pressure reduction, statin therapy, and smoking cessation are variable and used less in patients with PAD compared to patients with CAD. Antithrombotic therapy for patients with PAD has recently evolved, and monotherapy with clopidogrel has been shown to be similar to ticagrelor. Rivaroxaban 2.5 mg twice daily in addition to aspirin was shown to reduce cardiovascular events and limb events when compared with aspirin alone. Clinicians and patients will need to have personalized discussions on how to reduce their cardiovascular and limb risk for clinical events.

DISCLOSURES

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Factor Xa Mechanism of Action: Impact on Clotting Cascade, Inflammation, and Platelet Activation

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Richard C. Becker

Introduction: A contemporary view of thrombosis emphasizes the importance of cellular surface biochemistry and the integrated contribution of platelets, leukocytes, nucleic acids, histones, and perturbed endothelial cells. Initiation of coagulation occurs on tissue factor (TF)-bearing cells, whereas amplification (or priming) requires activation of platelets and coagulation proteases. The final phase, propagation, is determined by thrombin generation on platelet surfaces (Fig. 1).¹

The cell-based model of thrombosis highlights specific phases or biochemical stages rather than a traditional view of independent coagulation pathways or cascades. Accordingly, TF is considered the key element for initiation of thrombosis, wherein its ability to complex with factor VIIa (fVIIa) and activate factor X (fXa) ultimately causes thrombin generation. Although thrombin is a pivotal enzyme in thrombosis, the importance of fXa and its diverse effects on thrombin generation, inflammatory processes, smooth muscle cell proliferation, and endothelial cell activation represents a point of convergence for each component part.

Factor X: Factor X (fX) is a vitamin K–dependent glycoprotein synthesized in the liver and subsequently secreted into the plasma as a precursor to an active serine protease fXa. The human protein is composed of a light chain and a heavy chain linked by a single disulfide bond. The catalytic domain of fXa is contained within the heavy chain.

Factor X is activated by excision of a small peptide from its heavy chain. The cleavage of an alanine–isoleucine peptide bond by either TF-fVIIa

or fVIIIa-fIXa complex liberates the 52 amino acid peptide, providing a potentially measurable marker of fX activation. Under optimal conditions (high concentrations of TF), the TF-fVIIa complex can activate fX and, in essence, bypass the contribution of fVIII–fIX.

Prothrombinase Assembly on Platelet Surfaces: Platelets play a critical role in localizing and controlling the burst of thrombin generation leading to fibrin formation. Procoagulant phospholipids (microparticles), particularly phosphatidylserine, stimulate prothrombinase assembly by several orders of magnitude. Factor X activation requires a phospholipid surface; however, recent work suggests that thrombin-stimulated platelets also expose nonlipid-binding sites for fVIIIa, fIXa, and fXa. The platelet receptor for fXa may include membrane bound fVa, effector protease receptor-1, and an anion-exposed binding site in complex with glycoprotein Ib.²⁻⁴

Emerging Paradigms in Thrombosis: A traditional perspective of thrombosis begins with vessel wall injury and exposure of subendothelial proteins, including collagen and TF, to circulating cellular and noncellular components. Adhesion and activation of platelets, mediated by their interaction with von Willebrand protein and collagen, respectively, coupled with TF-mediated activation of coagulation proteins results in thrombin generation and fibrin formation. The events as they take place on cell surfaces are summarized above. Although this time-honored paradigm remains firm and soundly based, emerging evidence suggests that thrombosis is much more complex and dynamic than originally believed. Several novel triggers, templates, and facilitators, such as cell-free nucleic acids (cfNAs), histones, DNA-histone complexes, polyphosphates, and microvesicles, have recently been identified and require inclusion in the expanding universe of thrombosis as a dominant phenotype of human conditions, disorders, and diseases.

Neutrophil extracellular traps (NETs) are platforms of intact chromatin fibers with antimicrobial proteins that are produced by neutrophils to “trap and disarm” microbes in the extracellular milieu. These NETs have been shown to interact with the vascular endothelium, platelets, red blood cells, and coagulation factors, each of which is known to participate actively in thrombus formation. Specifically, NETs have been shown to induce endothelial cell death via interactions with NET-associated proteases or cationic proteins, including histones. Histones, in turn, can induce pore formation and influx of ions into cells by binding to their cellular membranes. These interactions promote increased intracellular calcium levels, endothelial activation, and Weibel-Palade content release of von Willebrand factor and other prothrombotic constituent proteins.⁵⁻⁷

Beyond their ability to bind endothelial cells and cause activation, NETs directly activate platelets. NETs have been shown in flow systems to bind platelets and facilitate aggregation. These properties are believed to be the result of both direct and indirect effects, as platelets are known to bind with

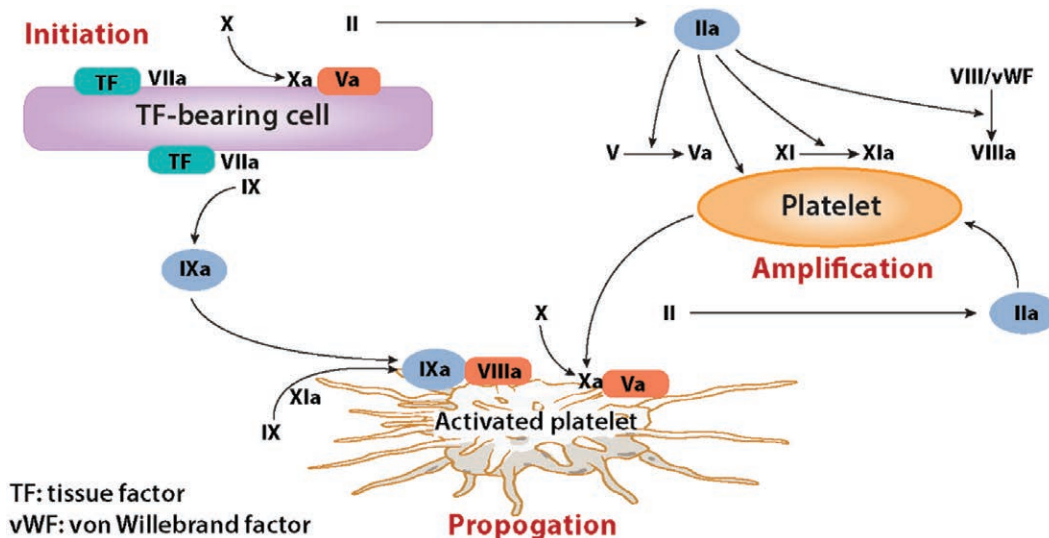


FIGURE 1. A contemporary understanding of thrombosis emphasizes the importance of cellular surface biochemistry. TF, tissue factor; vWF, von Willebrand factor. Reprinted with permission from *Thromb Hemost.* 2001;85:958–965.

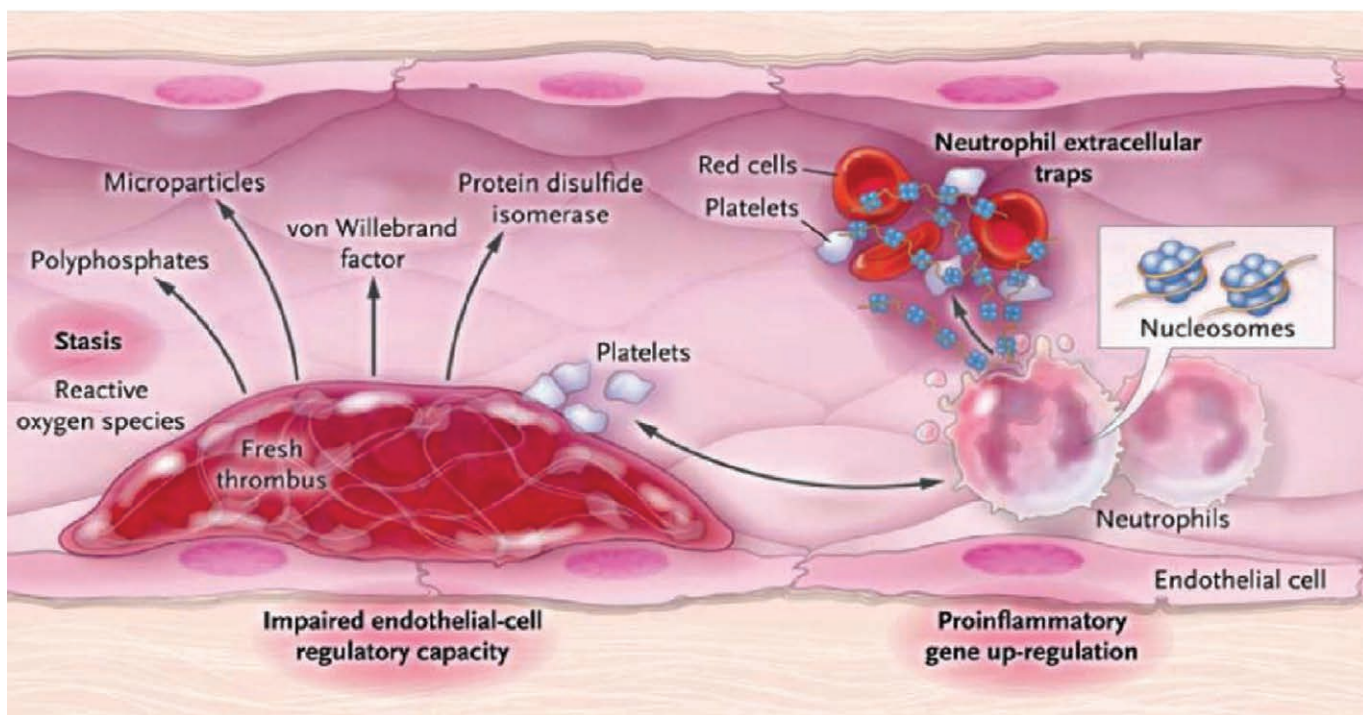


FIGURE 2. Neutrophil extracellular traps (nets) may provoke thrombus formation through direct stimulation of both the contact and tissue factor–mediated coagulation pathways. RBC indicates red blood cell; ROS, reactive oxygen species. Reprinted with permission from *N Engl J Med.* 2012;366:21.

histones through phospholipids, carbohydrates, and toll-like receptors (TLRs). In addition, platelets can bind double- and single-stranded DNA in vitro, representing an alternative mechanism for NET-induced platelet activation.

Also, NETs may provoke thrombus formation through direct stimulation of both the contact and TF-mediated coagulation pathways (Fig. 2).⁸ In vitro, NETs have been shown to stimulate fibrin formation and deposition and to colocalize with fibrin in blood clots. The NETs contain neutrophil elastase, which can effectively cleave TF pathway inhibitor and augment fXa activation. By binding to TF pathway inhibitor, NETs also attenuate the endothelium's primary means to regulate TF. Last, NETs can stimulate thrombin generation and fibrin formation through fXII-mediated contact activation. Similar to cfNAs, DNA-histone complexes have prothrombotic properties. The responsible mechanisms, however, are likely the product of inflammatory states and cellular damage rather than functional pathways.

DNA-Histone Complexes: Histones are cationic proteins that are normally found bound to DNA within the nucleus of a cell, specifically within nucleosomes. Similar to cfNAs, histones and DNA-histone complexes can be released into the circulation from dying or damaged cells. Although release of both DNA-histone complexes and NETs is hypothesized to serve primarily anti-inflammatory and pathogen restricting or constraining roles, recent studies have identified functions for these complexes in thrombosis.

Circulating histones and DNA-histone complexes have been observed in several acute and chronic inflammatory conditions. In addition, extracellular histones function as late mediators of cell damage and organ dysfunction in sepsis. Histones may provoke thrombin generation by activating platelets through stimulation of TLR2 and TLR4. In addition, histone-DNA complexes augment thrombin generation more than histones alone. Considered collectively, these data support the existence of an integrated and complex interface of inflammation, host defenses, and coagulation.⁹

Factor Xa: Inflammatory and Proliferative Effects: Factor Xa binds to human umbilical vein endothelial cells via a single class of binding sites with a dissociation constant value of $6.6 \pm 0.8 \text{ nM}$ and density of $57,460 \pm 5200$ sites per cell. The binding kinetics are considered “pseudo” first order with association and

dissociation constants of $0.15 \times 10^{-6} \text{ s}^{-1} \text{ m}^{-1} \cdot \text{s}^{-1}$ and $4.0 \times 10^{-4} \text{ s}^{-1}$, respectively. FXa binding to vascular endothelial cells is not influenced by thrombin, fVa, antithrombin, or TF pathway inhibitor but is blocked by antibodies specific for effector protease receptor-1, supporting its role in fXa–endothelial cell interactions. The binding of fXa is associated with the following events: (1) increased intracellular calcium; (2) increased phosphoinositide turnover; (3) TF expression; (4) tissue plasminogen activator release; (5) plasminogen activator inhibitor release; (6) interleukin-6 and interleukin-8 release; (7) cellular proliferation; (8) expression of E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1; and (9) nitric oxide release. The ability of indirect and direct antagonists to inhibit fXa-mediated cellular effects, without impacting its surface-binding capacity, suggests strongly that catalytic activity is the determining feature (Fig. 3).⁷ Macrophages localized within atherosclerotic plaques can synthesize fX. An ability of fXa to promote smooth muscle cell proliferation suggests that local prothrombotic responses may also influence arterial remodeling after injury. The mitogenic response to fXa probably involves proteinase-activated receptor-2. Functional proteinase-activated receptor-2, an auto-activating–tethered ligand, is widely distributed in human vascular endothelial cells and smooth muscle cells. FXa also exerts mitogenic effects through platelet-derived growth factor. Leukocyte proliferation has been observed after fX activation. In turn, proinflammatory cytokines that activate fX (fXa) are released. FXa also promotes recruitment of mast cells and their secretion of vasoactive mediators including histamine and serotonin.

Translating the Anticoagulant and Anti-Inflammatory Effects of Factor Xa Inhibition to Patient Care: Systemic inflammation has been implicated in coronary artery disease and common phenotypes including acute coronary syndrome. Investigation of plaques points to inflammatory mechanisms as key regulators of fibrous cap fragility and the overall thrombotic capacity of necrotic lipid core constituents. Activated macrophages, neutrophils, and monocytes elaborate enzymes that degrade extracellular matrix proteins that, in turn, pave the way for plaque instability and rupture.¹⁰⁻¹²

Clinical trials performed over the past decade suggest strongly that attenuating inflammation exerts a beneficial effect among patients at risk for coronary artery disease-related events. In addition, the recently completed, presented, and

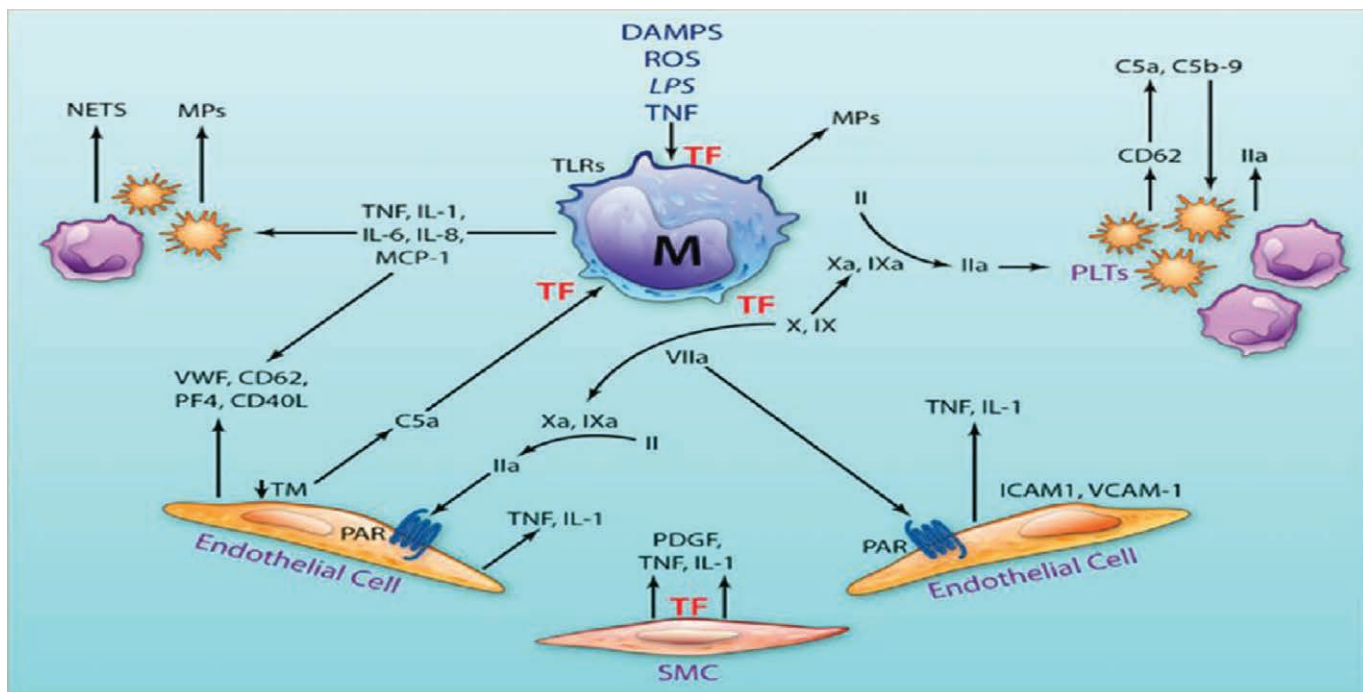


FIGURE 3. Integrated cellular and protein clotting pathways demonstrate the importance of cellular involvement in this complex process. DAMPs indicates danger-associated molecular patterns; ICAM, intercellular adhesion molecule; IL, interleukin; LPS, lipopolysaccharide; M, monocyte; MCP, monocyte chemoattractant protein; MPs, mononuclear phagocytes; PAR, proteinase-activated receptors; PDGF, platelet-derived growth factor; PF, platelet factor; PLTs, platelets; ROS, reactive oxygen species; SMC, smooth muscle cell; TLRs, toll-like receptors; TM, thrombomodulin; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; vWF, von Willebrand factor. Reprinted with permission from *Circ Res.* 2016;118:1392–1408.

published Canakinumab Antiinflammatory Thrombosis Outcomes Study trial, in which over 10,000 patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein level received a monoclonal antibody targeting interleukin-1 β or placebo in addition to evidence-based therapy, supports the inflammatory hypothesis of coronary artery disease and its natural history.¹³

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a randomized, double-blind study of 27,395 patients with stable atherosclerotic vascular disease who received either rivaroxaban, a direct inhibitor of the pluripotent coagulation protease fXa, at a dose of 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg daily. The primary outcome measure was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban plus aspirin group after a mean follow-up of 23 months.¹⁴

Summary: Factor Xa is a coagulation protease that has procoagulant, pro-inflammatory, and proliferative effects. Its importance in atherosclerotic vascular disease is based on these properties that are known to underlie the pathobiology of atherosclerotic plaque development, rupture, and thrombosis as the causal underpinnings for the transition from stable to unstable disease and resulting clinical events. The findings from COMPASS support the importance of factor Xa and its inhibition as a viable, readily available, and safe therapeutic strategy for patients with atherosclerotic vascular disease at risk for cardiovascular death, stroke, and myocardial infarction.

DISCLOSURES

Dr. Richard C. Becker discloses the following relationships: Advisor or Review Panel Member: Ionis and Portola.

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Clinical and Economic Value of Rivaroxaban in Coronary Artery Disease

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Christopher B. Granger

Introduction: Coronary heart disease is the number one cause of death and disability in the world and is projected to continue to be so for the foreseeable future.¹ An estimated 16.5 million Americans have coronary heart disease based on current data from the National Health and Nutrition Examination Survey (NHANES).²

The combination of control of risk factors and use of effective medical treatments cut the death rate from coronary heart disease in half over 20 years from 1980 to 2000.³ Patients with peripheral artery disease have fewer available options that improve outcomes. Thus, there remains a major need for more effective treatments for patients with peripheral vascular disease.

Oral Anticoagulation Prevents Vascular Events and Causes Bleeding: Although antiplatelet therapy has been the mainstay of antithrombotic therapy for patients with stable vascular disease, there is strong evidence that oral anticoagulation with warfarin provides protection against myocardial infarction (MI). This benefit is counterbalanced by increased bleeding, and the net effect, including the effect on mortality, is neutral (Fig. 1).⁴ A similar pattern has been seen in chronic heart failure without atrial fibrillation where warfarin reduces stroke but causes bleeding, resulting in a net neutral effect on mortality.⁵ Therefore, oral anticoagulation has been shown to reduce arterial vascular events, but at a cost in bleeding that counterbalances the benefits. Because of this reduction in net clinical benefit, warfarin is not used for these patients.

In recent years, non-vitamin K antagonist oral anticoagulants (NOACs), which have the advantage of less life-threatening bleeding than warfarin, have been tested for treatment of vascular disease. The Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial found reduced rates of MI and stent thrombosis with apixaban in addition to dual antiplatelet therapy after acute coronary syndromes (ACSs). This reduction in events was accompanied by more bleeding, including intracranial hemorrhage.⁶ The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome (ATLAS-2) investigators used a different strategy, testing low-dose rivaroxaban in addition to dual antiplatelet therapy in 93% of patients without a history of stroke. They showed benefit that exceeded risk, with a reduction in mortality using the lower dose of rivaroxaban (2.5 mg twice daily) added to antiplatelet therapy.⁷ There was also a reduction in stent thrombosis with rivaroxaban added to antiplatelet therapy. This trial showed that oral Xa inhibitor therapy can provide overall benefit in patients with ACS. Benefit from oral factor IIa (thrombin) inhibition for patients with ACS is less clear. There is a modestly higher rate of MI with dabigatran than with warfarin across the randomized trials of atrial fibrillation and venous thromboembolic disease.⁸ Phase II trials have suggested that targeting thrombin may provide some benefit after ACS, although these trials have not progressed to phase III.

Rivaroxaban or Dabigatran With Clopidogrel—Safer Than Warfarin Triple Therapy: Two completed trials have tested oral anticoagulation with warfarin versus NOACs, rivaroxaban in the Open-Label, Randomized,

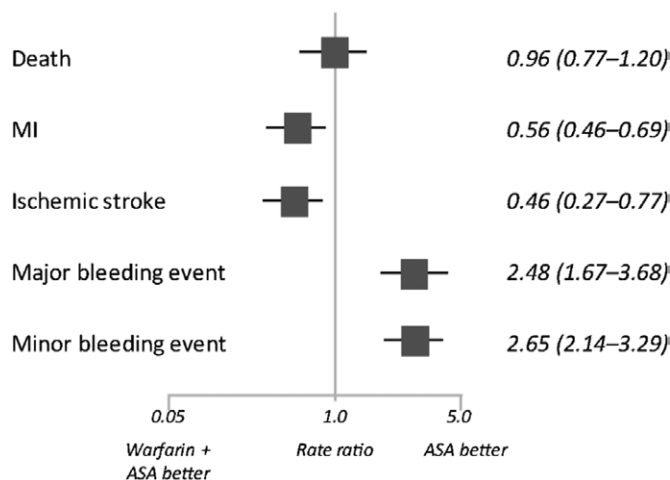


FIGURE 1. Secondary prevention with warfarin and aspirin versus aspirin alone after acute coronary syndrome. ASA indicates aspirin; CI, confidence interval. Reprinted with permission from *Ann Intern Med.* 2005;143:241–225.

Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER) trial⁹ (Fig. 2 and Table 1) and dabigatran in the Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL) trial,¹⁰ for stroke prevention in patients with atrial fibrillation who underwent stent placement and were also treated with P2Y12 inhibitor therapy. These trials found that NOACs with P2Y12 inhibitors (without aspirin) are safer than the combination of warfarin, aspirin, and P2Y12 inhibitors.

Rivaroxaban 15 mg daily without aspirin or 2.5 twice daily with aspirin and dabigatran 110 mg or 150 mg twice daily appeared to be nearly equally effective at preventing thrombotic events, although the number of thrombotic events was too small to have high confidence in those findings. The 110 mg twice daily dose of dabigatran without aspirin had numerically more MIs and stent thromboses than warfarin with aspirin, although the differences were not statistically significant. The use of rivaroxaban 15 mg daily or dabigatran 150 mg twice daily with a P2Y12 inhibitor, but without aspirin beyond the first few days after coronary stenting, appears to result in comparable rates of stent thrombosis compared to “triple therapy” with warfarin, clopidogrel, and aspirin. The observation that aspirin may not be required to prevent stent thrombosis in the presence of a NOAC, and P2Y12 inhibitor was also seen in the Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome (GEMINI) trial¹¹ in which low-dose rivaroxaban and clopidogrel had comparable rates of stent thrombosis as aspirin and clopidogrel. An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial will test, in a full factorial design, the impact of aspirin versus placebo combined with either warfarin or apixaban¹² in patients with atrial fibrillation and coronary stenting and/or ACS.

Oral Anticoagulation and Coronary Disease Events in Patients With Atrial Fibrillation: A substantial portion of the populations in the clinical trials of NOACs versus warfarin for atrial fibrillation also had coronary artery disease. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, 17% of the population had prior MI.¹² Not surprisingly, these patients were at higher

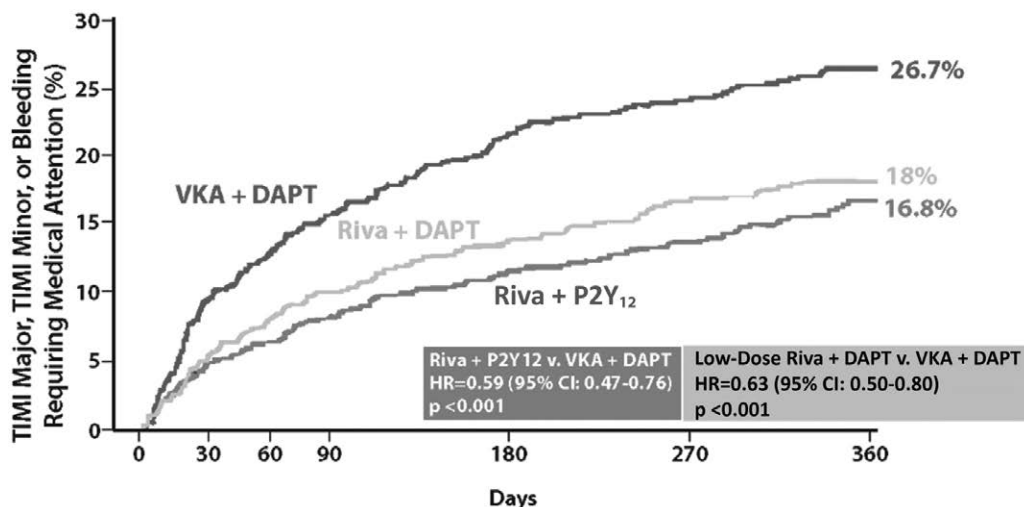


FIGURE 2. Clinically significant bleeding events in the PIONEER trial. CI indicates confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; Riva, rivaroxaban; VKA, vitamin K antagonist. Reprinted with permission from *N Engl J Med.* 2016;375:2423–2434.

TABLE 1. Major Adverse Cardiac Events in the PIONEER Trial

	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
	Riva + P2Y ₁₂ (N=694)	Riva + DAPT (N=704)	VKA + DAPT (N=695)	Low-Dose Riva + P2Y ₁₂ vs. VKA + DAPT	Riva + DAPT vs. VKA + DAPT
Overall					
Adverse CV Event	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	1.29 (0.59-2.80) p=0.523	1.19 (0.54-2.62) p=0.664
MI	19 (3.0%)	17 (2.7%)	21 (3.5%)	0.86 (0.46-1.59) p=0.625	0.75 (0.40-1.42) p=0.374
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	1.07 (0.39-2.96) p=0.891	1.36 (0.52-3.58) p=0.530
Stent Thrombosis	5 (0.8%)	6 (0.9%)	4 (0.7%)	1.20 (0.32-4.45) p=0.790	1.44 (0.40-5.09) p=0.574
Adverse CV Events + Stent Thrombosis	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765

CI indicates confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; Riva, rivaroxaban; VKA, vitamin K antagonist. Reprinted with permission from *N Engl J Med.* 2016;375:2423–2434.

risk for ischemic events and for bleeding, and they were more likely to be on concomitant aspirin. Overall, the rates of ischemic events tended to be lower with rivaroxaban than with warfarin, with a 14% reduction in hazard with rivaroxaban, $P = 0.05$. The hazard ratio of MI with rivaroxaban versus warfarin was 0.81 (95% confidence interval, 0.63–1.06). These findings, and similar findings with apixaban and edoxaban, suggest that factor Xa inhibitors are at least as effective as warfarin at preventing coronary events with lower risk of life-threatening bleeding.

Rivaroxaban in Patients With Stable Coronary Disease: Whether patients with coronary disease without atrial fibrillation may benefit from low-dose rivaroxaban with or without aspirin, compared to aspirin alone, was tested in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. Overall, 91% of the trial population had coronary artery disease; 20% of these were women. Half of those with prior MI had their infarction within 5 years of enrollment, and only 5% within 1 year. Importantly, the patients were on good background medical therapy to reduce vascular events, with 92% on lipid lowering drugs and

72% on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

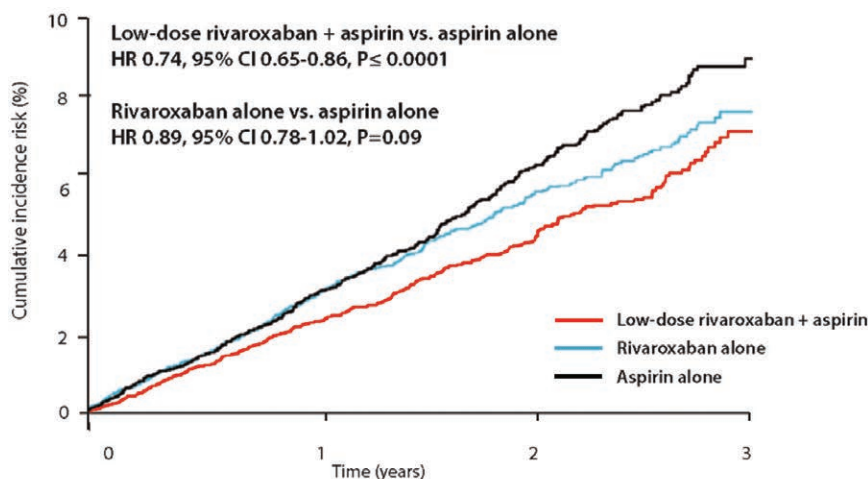
The 26% relative risk reduction in the primary outcome of cardiovascular death, MI, or stroke with low-dose rivaroxaban plus aspirin versus aspirin alone in the coronary disease subgroup ($P < 0.0001$) was similar to the effect in the overall trial (Fig. 3). The hazard ratio for major bleeding was 1.66 ($P < 0.0001$) with rivaroxaban plus aspirin versus aspirin. In the coronary disease population, the 1.3% absolute reduction in cardiovascular death, MI, and stroke was counterbalanced by a 1.2% absolute increase in major bleeding. The overall impact on mortality becomes key to understanding the net effect. There was a 23% relative risk reduction in all-cause mortality in the coronary disease population ($P = 0.001$),¹⁴ providing strong evidence of an overall benefit.

With respect to ischemic heart disease outcomes in the coronary disease population, MI was not significantly reduced (hazard ratio, 0.86; 95% confidence interval, 0.70–1.05) perhaps related to small numbers, but the hazard of a broader ischemic heart disease composite (MI, coronary heart disease death, sudden death, resuscitated cardiac arrest, or unstable angina) was reduced by 17% ($P = 0.03$) (Table 2).¹⁴ The 46% relative risk reduction ($P < 0.0001$) in stroke in this population, similar to in the overall trial, was the most striking effect on major clinical outcomes.

Cost Implications of Rivaroxaban for Patients With Stable Coronary Disease: The overall effects of rivaroxaban plus aspirin versus aspirin alone compare favorably to other commonly used treatments to improve outcome for patients with vascular disease, such as antiplatelet therapy, lipid lowering agents, and blood pressure lowering agents. Preliminary data regarding the cost impact of rivaroxaban in the COMPASS trial have been presented.¹⁶ Examining direct costs of care, not including costs of the drug, rivaroxaban plus aspirin resulted in substantially lower health care costs than aspirin alone, driven largely by lower costs related to the reduction in stroke. There were larger differences favoring rivaroxaban in patients with peripheral artery or polyvascular arterial disease. Formal cost-effectiveness analyses are ongoing.

Summary: Coronary heart disease continues to be the most important cause of death and disability in the United States and around the world. There is now another treatment proven to prevent vascular events in patients with stable coronary disease—low-dose rivaroxaban added to aspirin—with an even larger absolute benefit for patients who have both coronary disease and concomitant peripheral or cerebrovascular disease. The net benefit of low-dose rivaroxaban with aspirin, compared to aspirin alone, is underscored by the 23% relative risk reduction in all-cause mortality.

Primary outcome: cardiovascular death, MI, stroke



Major Bleeding

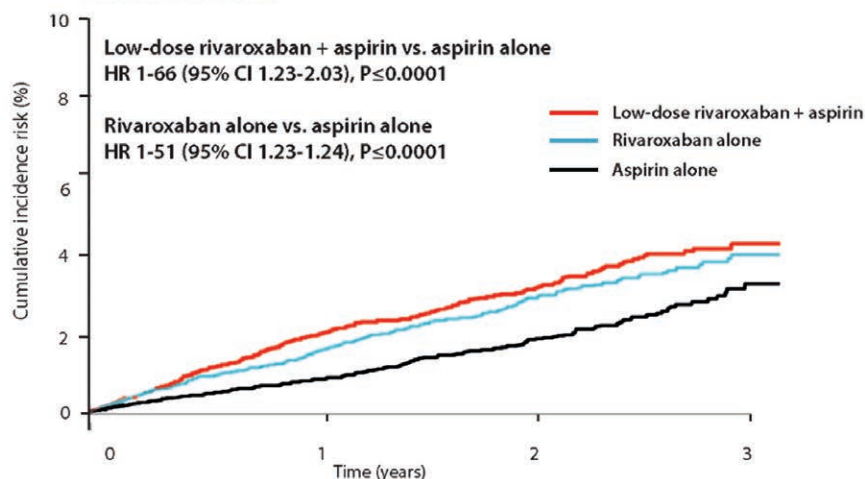


FIGURE 3. Primary efficacy and safety outcome in the coronary artery disease subgroup of the COMPASS trial. CI indicates confidence interval; HR, hazard ratio. Reprinted with permission from *N Engl J Med.* 2017;377:1319–1330.

TABLE 2. Coronary Disease Outcomes in the Coronary Disease Subgroup in the COMPASS Trial

Event	Rivaroxaban and aspirin N=8,313	Aspirin N=8,261	Rivaroxaban and aspirin vs. aspirin	
	N (%)	N (%)	HR (95% CI)	p
Myocardial infarction (MI)	169 (2%)	195 (2%)	0.86 (0.70-1.05)	0.15
MI or sudden cardiac death	234 (3%)	273 (3%)	0.85 (0.71-1.01)	0.065
MI, coronary heart disease death, SCD, resuscitated cardiac arrest, or unstable angina	264 (3%)	314 (4%)	0.83 (0.71-0.98)	0.028

CI indicates confidence interval; HR, hazard ratio.

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