Received: 10 December 2020 | Revised: 8 February 2021 | Accepted: 12 February 2021

DOI: 10.1002/rth2.12502

rpth research & practice in thrombosis & haemostasis

STATE OF THE ART ISTH 2020

Considerations for use of direct oral anticoagulants in arterial disease

Deborah M. Siegal MD, MSc[1,2] | Sonia S. Anand MD, PhD[3,4,5]

[1]Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[2]Ottawa Hospital Research Institute, Ottawa, ON, Canada

[3]Department of Medicine, McMaster University, Hamilton, ON, Canada

[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

[5]Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada

Correspondence
Sonia S. Anand, Population Health Research Institute, 237 Barton St East, Hamilton, ON L8L 2X2, Canada.
Email: anands@mcmaster.ca

Handling Editor: Dr Mary Cushman.

Abstract

Cardiovascular diseases including coronary heart disease, stroke, and peripheral arterial disease were responsible for an estimated 18 million deaths in 2017. Despite advances in management over the past several decades, these patients continue to have substantial risk of subsequent cardiovascular events. We provide a narrative review of randomized clinical trials evaluating direct oral anticoagulants (DOACs) for the treatment of acute coronary syndromes, noncardioembolic ischemic stroke, embolic stroke of undetermined source, and peripheral arterial disease. In these conditions, considerations for use of single antiplatelet therapy, dual antiplatelet therapy, or low-dose DOACs used together with antiplatelet therapy are presented.

KEYWORDS
acute coronary syndrome, anticoagulants, brain ischemia, direct oral anticoagulants, peripheral arterial disease, platelet aggregation inhibitors, stroke

Essentials

- Arterial cardiovascular diseases were responsible for 18 million deaths in 2017.
- Antiplatelet therapy is the mainstay of prevention and treatment.
- The risk of cardiovascular events remains high despite the use of antiplatelet drugs.
- Direct oral anticoagulants have an evolving role for prevention and treatment of arterial diseases.

1 | INTRODUCTION

Cardiovascular diseases including coronary heart disease, stroke, and peripheral arterial disease (PAD) were responsible for an estimated 18 million deaths in 2017.[1] These arterial vascular diseases arise from atherosclerosis, a pathologic process that results in the formation of plaques within the inner lining of coronary, cerebral, and peripheral arteries and the aorta.[2] Atherothrombosis arises from atherosclerotic plaque rupture, which (i) exposes tissue factor, thereby triggering coagulation; and (ii) activates platelets, upon which coagulation is amplified.[3] Because of the central role of platelets in the pathogenesis of atherothrombosis, antiplatelet therapy remains a cornerstone of prevention and treatment. However, the modest benefit of antiplatelet therapies and the role of coagulation in the pathophysiology of atherothrombosis have led to the evaluation of anticoagulant drugs for the prevention and treatment of arterial diseases. The purpose of this review is to summarize recent randomized clinical trials (RCTs) evaluating the use of direct oral anticoagulants (DOACs) for patients with atherosclerosis-based arterial diseases. In particular, we review acute coronary syndromes,

noncardioembolic ischemic stroke, embolic stroke of undetermined source (ESUS), and PAD. Table 1 provides a summary of phase III randomized trials of DOACs for arterial thrombosis.

2 | DOACs IN ACUTE CORONARY SYNDROME

Despite advances in reperfusion and antithrombotic strategies over the past several decades, patients with acute coronary syndrome (ACS) remain at high risk of cardiovascular events (9%-11% within 1 year of ACS) even since the widespread use of potent $P2Y_{12}$ inhibitors.[4-6] Increasing the intensity of antithrombotic effects with the addition of anticoagulants to antiplatelet therapies after ACS is predicated on the observation that elevation in thrombin levels and coagulation activity persist after ACS.[7,8] Enhanced risk reduction in cardiovascular events can indeed be achieved with anticoagulants, but this effect is counterbalanced by an increased risk of bleeding.

2.1 | Prior studies with vitamin K antagonists

Warfarin, when used alone or in combination with aspirin, may reduce the risk of ischemic events compared to aspirin alone, but this benefit is dependent on anticoagulation intensity and is counterbalanced by an increased risk of bleeding. In a meta-analysis of 14 RCTs including 25 307 patients, warfarin (irrespective of international normalized ratio [INR]) in combination with aspirin did not reduce the risk of all-cause death, nonfatal myocardial infarction (MI), or nonfatal thromboembolic stroke compared to aspirin alone (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.90-1.03) but increased the risk of major bleeding (OR, 1.77; 95% CI, 1.47-2.13).[9] When limited to studies with INR maintained between 2 and 3, combination therapy was associated with a reduced risk of all-cause death, nonfatal MI, or nonfatal thromboembolic stroke (OR, 0.73; 95% CI, 0.63-0.84) but also increased the risk of major bleeding (OR, 2.32; 95% CI, 1.63-3.29) compared to aspirin alone, suggesting that anticoagulant dose intensity influences cardiovascular morbidity and mortality.[9]

2.2 | Direct oral anticoagulants

DOACs are a potentially attractive option for increasing antithrombotic effect while minimizing bleeding in patients with ACS. They have been shown to reduce the risk of major, fatal, and intracranial bleeding compared to warfarin in patients with nonvalvular atrial fibrillation and are administered in fixed doses without routine monitoring.[10]

However, despite their favorable characteristics and reduced risk of bleeding compared to warfarin in atrial fibrillation, the addition of DOACs to standard antiplatelet therapy following ACS is largely limited by an increased risk of major bleeding. A recent meta-analysis of 6 RCTs (29 667 patients) evaluated the efficacy and safety of DOACs in addition to antiplatelet therapy after ACS.[11] A range of DOAC dose intensities were studied, including apixaban (2.5 mg twice daily, 5 mg twice daily, 10 mg once daily), rivaroxaban (5, 10, 15, and 20 mg once daily), and dabigatran (50, 75, 110, and 150 mg twice daily). The study population included mostly young men (mean age, 62.5 years), of whom the majority received dual antiplatelet therapy (DAPT). When added to antiplatelet therapy, DOACs reduced the risk of cardiovascular death, MI, and stroke after ACS compared to antiplatelet therapy alone (OR, 0.85; 95% CI, 0.77-0.93) corresponding to a number needed to treat of 84 (95% CI, 55-176) or an absolute risk reduction of 1.2%.[11] However, this benefit was offset by a higher risk of major bleeding in patients receiving DOACs (OR, 3.17; 95% CI, 2.27-4.42) corresponding to a number needed to harm of 105 (95% CI, 84-139) or an absolute risk increase of 0.95% for major bleeding. An a priori subgroup analysis suggested that the benefit of DOACs may be enhanced in patients with ST-segment–elevation MI (STEMI; OR, 0.76; 95% CI, 0.66–0.88), but not those with non–ST-segment elevation ACS (NSTE-ACS; OR, 0.92; 95% CI, 0.78-1.09). The risk of major bleeding was increased in patients with STEMI (OR, 3.45; 95% CI, 1.95-6.09) and those with NSTE-ACS (OR, 2.19; 95% CI, 1.38-3.48). However, there were no statistically significant interactions found between treatment effects and ACS subtype with respect to efficacy or safety.

It is important to note, however, that the pooled estimates described above are derived from studies that evaluated a heterogeneous mix of dose intensities and do not specifically exclude the possibility that very-low-dose DOACs may provide benefit for some patients with an acceptable risk of bleeding, particularly those considered to be at high thrombotic risk and low bleeding risk. For example, in the anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome–thrombolysis in myocardial Infarction 51 study (ATLAS ACS-2-TIMI 51) , very-low-dose rivaroxaban (2.5 mg twice daily) but not rivaroxaban 5 mg twice daily added to DAPT (eg, aspirin and clopidogrel) reduced the rates of death from cardiovascular causes (2.7% vs 4.1%; hazard ratio [HR], 0.66; 95% CI, 0.51-0.86; $P = .002$) and death from any cause (2.9% vs 4.5%; HR, 0.68; 95% CI, 0.53-0.87; $P = .002$) compared to placebo in patients with recent ACS.[12] However, the rate of major bleeding not related to coronary artery bypass grafting (CABG) was higher with both rivaroxaban 2.5 mg (1.8% vs 0.6%; $P < .001$) and rivaroxaban 5 mg (2.4% vs 0.6%; $P < .001$) compared to placebo. The results of ATLAS ACS-2-TIMI-51 formed the rationale to investigate low-dose rivaroxaban and aspirin in patients with stable coronary and peripheral artery disease in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. Among 27 395 patients, lower-dose rivaroxaban (2.5 mg twice daily) in combination with aspirin (100 mg) significantly reduced the primary major adverse cardiovascular events (MACEs) composite of cardiovascular death, MI, and stroke by 24% (95% CI, 14%-34%; $P < .001$) compared to aspirin alone. Although major bleeding was significantly increased (HR, 1.70; 95% CI, 1.40-2.05; $P < .001$), there was no increase in fatal or critical organ bleeding such that an 18% mortality reduction was observed ($P = .01$), and a favorable net clinical benefit (HR, 0.80; 95% CI, 0.70-0.91; $P < .001$) was apparent.[13]

Moreover, in the recent 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-ACS-1) the rate of Thrombolysis in Myocardial Infarction (TIMI) non-CABG clinically significant bleeding (primary outcome) was similar in patients with recent ACS receiving rivaroxaban 2.5 mg twice daily compared to low-dose aspirin in addition to either clopidogrel or ticagrelor (5.3% vs 4.9%; HR, 1.09; 95% CI, 0.80-1.50).[14] Although the study was not powered to evaluate differences in efficacy, the rates of all-cause mortality (1.4% vs 1.5%) and a composite of cardiovascular death, MI, stroke, and definite stent thrombosis (5.0% vs 4.7%) were similar between the rivaroxaban and aspirin groups. This trial suggests that adding very-low-dose rivaroxaban to a $P2Y_{12}$ inhibitor instead of aspirin mitigates the increased bleeding risk seen in other DOAC studies in ACS. However, net clinical benefit must be established in a larger randomized trial powered to evaluate thrombotic outcomes. Rivaroxaban 2.5 mg is currently approved for use in combination with antiplatelet therapy after ACS in Europe but not in the United States.

Some notable uncertainty remains. The meta-analysis by Chiarito and colleagues[11] suggests that the balance of benefit and harm may be more favorable in patients with STEMI compared to those with NSTE-ACS, a hypothesis that requires confirmation in randomized trials. Further, the findings above including the reduction in mortality seen with very-low-dose rivaroxaban may not be generalizable to women and patients of older age who were underrepresented in these trials. Finally, these studies did not include patients receiving the more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor. In the GEMINI-ACS-1 trial, patients with ACS randomized to rivaroxaban 2.5 mg twice daily had a similar risk of TIMI non-CABG major bleeding compared to those receiving aspirin 100 mg daily (1% vs 1%; HR, 1.25; 95% CI, 0.49-3.17) in addition to clopidogrel or ticagrelor, but a higher risk of ISTH major bleeding (2% vs 1%; HR, 1.83; 95% CI, 1.01–3.31; $P = .042$).[14]

3 | DOACs IN ISCHEMIC STROKE

Based on their enhanced safety and efficacy for preventing ischemic stroke and systemic embolism compared to warfarin in atrial fibrillation, DOACs are attractive options for enhancing antithrombotic benefit compared to aspirin in acute noncardioembolic ischemic stroke and ESUS.

3.1 | Dual versus single antiplatelet therapy

Antiplatelet therapies are the mainstay of antithrombotic strategy for the acute treatment of noncardioembolic ischemic stroke or transient ischemic attack (TIA). However, high rates of recurrent ischemic stroke (up to 8% within 90 days) are seen even with early administration of DAPT.[15-17] The clopidogrel in high-risk patients with acute nondisabling cerebrovascular events (CHANCE) and platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trials demonstrated enhanced efficacy and safety of early DAPT initiation (within 12 hours and 24 hours, respectively) compared to aspirin alone in patients with acute minor stroke or high-risk TIA. A meta-analysis of these trials (n = 10 051 patients) showed that DAPT was associated with a lower risk of ischemic stroke, MI, or death from ischemic vascular causes at 90 days (6.5% vs 9.1%; HR, 0.70; 95% CI, 0.61-0.81) compared to aspirin.[18] Major bleeding was not statistically different between the treatments (0.6% vs 0.4%; HR, 1.59; 95% CI, 0.88-2.86).

3.2 | Prior studies of anticoagulants for noncardioembolic ischemic stroke

Heparin, low-molecular-weight heparin, and warfarin have been evaluated as potential antithrombotic strategies. Evidence from numerous studies shows that anticoagulation with these agents reduces the risk of recurrent ischemic stroke compared to aspirin after acute noncardioembolic stroke, but this benefit is offset by an increase in symptomatic hemorrhagic transformation.[19,20] More recently, in the thrombin receptor antagonist in secondary prevention of atherothrombotic ischemic events (TRA 2P)–TIMI-50 (TRA 2P-TIMI-50) trial, which evaluated a novel protease-activated receptor 1 (PAR-1) antagonist, vorapaxar (2.5 mg daily), or placebo in patients with a history of MI, ischemic stroke, or PAD, study treatment was discontinued in patients with a history of stroke due to an increased risk of intracranial hemorrhage.[21]

3.3 | DOACs for acute noncardioembolic stroke

Dabigatran is the only DOAC to have been evaluated in RCTs for the treatment of acute noncardioembolic ischemic stroke.[22] The dabigatran treatment following transient ischemic attack and minor stroke II (DATAS II) study suggested that dabigatran may be safe for treatment of acute ischemic stroke/TIA; there were no hemorrhagic transformation events in 154 patients randomized to dabigatran (n = 154; 150 mg twice daily, or 110 for individuals ≥80 years of age or creatinine clearance 30-50 mL/min) or aspirin (n = 151) within 90 days of acute minor noncardioembolic ischemic stroke or TIA.[23] However, the study was not powered to detect differences in the rates of clinically overt recurrent ischemic events in the dabigatran and aspirin groups (3.9% vs 2.7%; relative risk [RR], 1.49; 95% CI, 0.41-5.39). Therefore, larger definitive RCTs are needed to established the net clinical benefit of this strategy in patients with acute noncardioembolic ischemic stroke.

3.4 | DOACs for embolic stroke of undetermined source

Embolic stroke of undetermined source denotes nonlacunar cryptogenic ischemic strokes that occur without evidence of a cardioembolic source, stenosis (≥50%) of cervical or intracranial arteries proximal to the infarct and other causes of stroke identified.[24] In the randomized, double-blind, evaluation in secondary stroke prevention

TABLE 1 Summary of phase III randomized clinical trials evaluating direct oral anticoagulants (DOACs) for arterial thrombosis

Study	Population	Primary outcomes	Follow-up (months)
Acute coronary syndrome			
APPRAISE–2[53]	ACS within 7 d[a,b] N = 7392	*Primary efficacy outcome:* CV death, MI, ischemic stroke *Primary safety outcome:* major bleeding (TIMI-major)	8
ATLAS ACS-2-TIMI 51[12]	ACS within 7 d[a,b] N = 15526	*Primary efficacy outcome:* CV death, MI, or stroke *Primary safety outcome:* major bleeding not related to CABG (TIMI-major)	13
Noncardioembolic ischemic stroke/embolic stroke of undetermined source			
RE-SPECT ESUS[25]	ESUS within 3 mo, or if ≥1 vascular risk factor within 6 mo N = 5390	*Primary efficacy outcome:* recurrent (ischemic, hemorrhagic, undefined) *Primary safety outcome:* major bleeding (ISTH)	42
NAVIGATE ESUS[26]	ESUS between 7 d and 6 mo before screening N = 7213	*Primary efficacy outcome:* recurrent stroke (ischemic, hemorrhagic, undefined) *Primary safety outcome:* major bleeding (ISTH)	11
Coronary or peripheral arterial disease			
COMPASS[13]	Stable atherosclerotic vascular disease (coronary artery disease, peripheral arterial disease, or both) N = 27,395 (7470 with PAD)	*Primary efficacy outcome:* CV death, stroke, or MI *Primary safety outcome:* modified ISTH major bleeding	23
VOYAGER[35]	Infrainguinal Peripheral arterial revascularization N = 6,564	*Primary efficacy outcome:* CV death, ischemic stroke, MI, ALI, major vascular amputation *Primary safety outcome:* Major bleeding (TIMI)	36

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CV, cardiovascular; DSMB, Data Safety Monitoring Board; ESUS, embolic stroke of undetermined source; HR, hazard ratio; MI, myocardial infarction; NA, not available; RCT, randomized controlled trial; TIMI, Thrombolysis in Myocardial Infarction.

[a] DOACs or placebo were given in addition to standard antiplatelet therapies.

[b] Study treatments were given in addition to clopidogrel or ticagrelor (at investigator discretion before randomization).

[c] Clopidogrel could be added up to 6 mo.

comparing the efficacy and safety of the oral thrombin inhibitor dabigatran etexilate versus acetylsalicylic acid in patients with embolic stroke of undetermined source (RE-SPECT ESUS) study, dabigatran 150 mg or 110 mg twice daily was associated with a similar risk of ischemic, hemorrhagic, or unspecified stroke compared to aspirin 100 mg daily (4.8% vs 4.1%; HR, 0.84; 95% CI, 0.69-1.03) in patients with ESUS.[25] Safety analyses showed a similar risk of major bleeding (1.7% vs 1.4%; HR, 1.19; 95% CI, 0.85-1.66) but higher risk of major or clinically relevant nonmajor bleeding (3.3% vs 2.3%; 95% CI, 1.12-1.85) in dabigatran- versus aspirin-treated patients. Similar results were shown in the new approach rivaroxaban inhibition of factor Xa in a global trial versus ASA to prevent embolism in embolic stroke of undetermined source (NAVIGATE-ESUS) trial, which was stopped early after an interim analysis revealed that patients with ESUS treated with rivaroxaban (15 mg daily) had higher rates of major bleeding (1.8% vs 0.7%; HR, 2.72; 95% CI, 1.68-4.39) but similar risk of recurrent stroke or systemic embolism compared to those treated with aspirin (100 mg daily).[26]

Intervention	Control	Primary efficacy outcome Absolute events, n (%) HR (95% CI)	Primary Safety outcome Absolute events, n (%) HR (95% CI)	Notes
Apixaban 5 mg twice daily	Placebo	A: 279/3705 (7.5) P: 293/3687 (7.9) 0.95 (0.80- 1.11)	A: 46/3705 (1.3) P: 18/3687 (0.5) 2.59 (1.50 -4.46)	Terminated early after 7392 patients recruited due to excess bleeding in apixaban arm
Rivaroxaban 2.5 mg twice daily	Placebo	R: 313/5114 (9.1) P: 376/5113 (10.7) 0.84 (0.74 -0.97)	R: 65/5114 (1.8) P: 19/5113 (0.6) 3.46 (2.08-5.77)	*Rivaroxaban groups combined versus placebo:* Primary efficacy outcome HR 0.84 (95% CI, 0.74-0.96) Primary safety outcome HR 3.96 (95% CI 2.46-6.38)
Rivaroxaban 5 mg twice daily		R: 313/5115 (8.8) P: 376/5113 (10.7) 0.85 (0.73-0.98)	R: 28/5115 (2.4) P: 19/5113 (0.6) 4.47 (2.71-7.36)	
Dabigatran 150 mg twice daily (or 100 mg twice daily if >75 y and/or CrCl 30-50 mL/min) for 30 d	Aspirin 100 mg once daily	D: 177/2695 (4.1) A: 207/2695 (4.8) 0.85 (0.69-1.03)	D: 77/2695 (1.7) A: 64/2695 (1.4) 1.19 (0.85-1.66)	
Rivaroxaban 15 mg once daily	Aspirin 100 mg once daily	R: 175/3609 (5.1) A: 160/3604 (4.8) 1.07 (0.87-1.33)	R: 62/3609 (1.8) A: 23/3604 (0.7) 2.72 (1.68-4.39)	Terminated early at the recommendation of the DSMB due to excess risk of bleeding in patients assigned to rivaroxaban
Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily	Aspirin 100 mg QD	R + A: 379/9152 (4.1) A: 496/9126 (5.4) 0.76 (0.66-0.86)	R + A: 288/9152 (3.1) A: 170/9126 (1.9) 1.70 (1.40-2.05)	Terminated early for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 mo
Rivaroxaban 5 mg twice daily		R: 448/9117 (4.9) A: 496/9126 (5.4) 0.90 (0.79-1.03)	R: 255/9117 (2.8) A: 170/9126 (1.9) 1.51 (1.25-1.84)	
Rivaroxaban 2.5 mg twice daily on background aspirin 100 mg once daily[c]	Placebo (background Aspirin 100 mg once daily) [c]	R: 508/3286 (17.3) P: 584/3278 (19.9) 0.85 (0.76-0.96)	R: 62/3256 (1.90) P: 44/3248 (1.35) 1.43 (0.97-2.10)	Met primary end point

These large trials found no benefit and greater harm with DOACs compared to aspirin for secondary prevention of stroke in patients with ESUS. This may be explained, at least in part, by heterogeneous stroke mechanisms included within the ESUS construct (ie, embolism vs atherosclerosis).[27] Research directed at enhancing the characterization of stroke mechanisms in ESUS may help optimize antithrombotic treatment by identifying subgroups of patients that may benefit from different antithrombotic strategies (eg, anticoagulation for occult embolic causes and antiplatelet therapies for atherosclerosis).

Dual pathway inhibition strategies with low-dose DOACs in combination with antiplatelet therapy may offer enhanced efficacy in patients with ESUS. For example, in the COMPASS trial, rivaroxaban (2.5 mg twice daily) in combination with aspirin (100 mg daily) compared to aspirin alone, the relative risk reduction of all stroke was 42%, and ischemic stroke was 31% in patients with stable coronary artery disease, PAD, or both.[13] The rate of disabling or fatal stroke (modified Rankin Scale scores, 3–6) was lower in patients receiving rivaroxaban and aspirin compared to those receiving aspirin alone (0.2% vs 0.3%;

HR, 0.58; 95% CI, 0.37-0.89), and similar in patients receiving rivaroxaban (0.3%) or aspirin (0.3%) alone.[28] Thus, given the results of the ESUS and COMPASS trials, possible options for stroke prevention after noncardioembolic stroke include (i) antiplatelet agents, either single or dual; or (ii) low-dose rivaroxaban and aspirin.

4 | DOACs IN PAD

Patients with PAD have widespread atherosclerosis and are at high risk for the development of MACEs and major adverse limb events (MALEs), including acute limb ischemia and major vascular amputation.[29,30] The pathophysiological basis for this is atherothrombosis, and thus therapies that prevent thrombin generation and platelet activation have been evaluated in patients with PAD over the past 5 decades.[31,32]

4.1 | Prior trials of antithrombotic agents in patients with PAD

There have been numerous RCTs that have evaluated a range of antiplatelet agents and anticoagulants in patients with PAD across the spectrum of symptom severity, from mildly symptomatic to those undergoing elective revascularization, to more acute patients including those with severe symptoms of limb ischemia and or nonhealing ulcers. However, large RCTs conducted in PAD patients are few in number, although in the past 15 years there have been at least four large trials that have helped to clarify the role of oral anticoagulants and antiplatelet agents, and most recently have demonstrated the benefit of low-dose (one-quarter of a full dose) DOACs used together with antiplatelet agents in patients with PAD.[33-36]

4.2 | Single antiplatelet therapy

The antiplatelet trialist collaboration meta-analysis forms the basis for the 2017 European Society of Cardiology PAD guidelines[37] and 2016 American Heart Association/American College of Cardiology PAD Guidelines,[29] both of which endorse single-agent antiplatelet therapy (SAPT) (ie, aspirin 75-325 mg once daily or clopidogrel 75 mg once daily) as a Class 1A recommendation in patients with symptomatic PAD. While the clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) trial demonstrated a modest benefit of clopidogrel over aspirin in vascular patients including those with PAD,[38] worldwide a single daily aspirin is the most common antiplatelet agent used in patients with PAD.

4.3 | More potent single antiplatelet therapy versus aspirin

As noted above in the TRA 2P trial, vorapaxar was compared to placebo in patients with a history of MI, ischemic stroke, or symptomatic PAD, with a substantial proportion of patients taking DAPT. This therapy was effective in reducing MACEs and MALEs, including urgent hospitalization for a peripheral artery cause.[39] However, there was an excess of major bleeding with this therapy, and although approved by regulatory bodies, vorapaxar has not been widely used by clinicians.

More recently, the examining use of ticagrelor in peripheral artery disease (EUCLID) trial evaluated a more potent $P2Y_{12}$ antagonist, ticagrelor (90 mg twice daily), as compared to clopidogrel in 13 885 patients with PAD.[33] However, no differences in MACE or MALE outcomes were observed.

4.4 | Dual antiplatelet therapy

A number of RCTS in which patients with PAD were enrolled as part of larger randomized trials in a broad range of vascular patients, patients following MI, or patients with coronary artery disease with diabetes, including Charisma (clopidogrel and aspirin vs aspirin),[40] 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; ticagrelor and aspirin vs aspirin)[39]; and the effect of ticagrelor on health outcomes in diabetes mellitus patients intervention study (THEMIS)[41] (ticagrelor and aspirin vs aspirin). Each demonstrated reduced ischemic events with DAPT compared to aspirin. However, these trials also demonstrated increased risks of major bleeding with DAPT versus SAPT. Thus, a careful risk-benefit assessment is required before using one of these DAPT regimens when more potent therapies than SAPT are desired.

4.5 | Vitamin K antagonists (INR 2-3) with or without antiplatelet agents

Oral anticoagulants have been used to treat patients with PAD for the past 50 years. Contemporary trials have been evaluated vitamin K antagonists with or without antiplatelet agents in RCTs in outpatients with stable PAD,[36] a Veterans Affairs patient population,[42] and after lower extremity revascularization.[43] Overall, in patients with PAD, vitamin K antagonists when tested at moderate to high intensity with or without antiplatelet agents, show no clear reduction in ischemic events and a significant excess in life-threatening bleeding, such that vitamin K antagonists are not recommended for long-term use in patients with PAD.

4.6 | Direct oral anticoagulants

The use of full-dose DOACs in PAD is increasing, yet there are limited data directing their widespread use. However, the outcomes of patients with PAD with atrial fibrillation treated with full-dose DOACs in large databases have been reported.[44] An adjusted indirect comparison meta-analysis between DOACs for prevention of

acute limb ischemia in patients with atrial fibrillation was conducted. A total of 44 563 patients from three RCTs met the criteria for inclusion. Patients randomly assigned to DOACs had a nonsignificant decreased risk for acute limb ischemia (RR, 0.57; 95% CI, 0.26-1.2). In the analysis between agents, rivaroxaban significantly lowered the risk of acute limb ischemia compared to warfarin (RR, 0.23; 95% CI, 0.064–0.82), and other DOACs. In a peripheral vascular registry of 9682 patients following limb revascularization, the use of DOACs (n = 619 patients) were reported to be associated with a shorter length of stay, and a trend toward lower transfusion compared to patients receiving vitamin K antagonists (n = 1379).[45] However, these data are observational in nature and subject to confounding and thus cannot be considered conclusive. Future observational studies and/or RCTs of full-dose DOACs in patients in whom full-dose anticoagulation are required to fully characterize their efficacy and safety profiles.

4.7 | Dual pathway inhibition with low-dose DOACs and antiplatelet therapy

Among the large subgroup of 7470 patients with PAD enrolled in the COMPASS trial, the combination of rivaroxaban 2.5 mg twice daily with aspirin 100 mg significantly reduced the primary MACE outcome of cardiovascular death, stroke, and MI by 28% (HR, 0.72; 95% CI, 0.57-0.90; $P = .005$), as well as the MALE composite of severe limb ischemia including major vascular amputation by 46% (HR, 0.54; 95% CI, 0.35-0.84; $P = .005$).[46] As expected, the combination of rivaroxaban and aspirin was associated with a 61% increase in major bleeding defined using the modified ISTH criteria (HR, 1.61; 95% CI, 1.12-2.31; $P = 0.009$). However, no significant increase in fatal or critical organ bleeding (ie, intracranial bleeding) was observed.[21] Furthermore, the net clinical benefit (considering MACEs, MALEs, and fatal/critical organ bleeding) favored low-dose rivaroxaban and aspirin (HR, 0.72; 95% CI, 0.59-0.87; $P = .008$), acknowledging that individuals with high bleeding risk were excluded from the trial at the outset.[21] The combination of aspirin and rivaroxaban 2.5 mg twice daily represents the most robust antithrombotic option shown to definitively reduce both cardiovascular and limb outcomes in patients with PAD.[34] In addition, the COMPASS data showed that when a MALE does occur, the combination of low-dose rivaroxaban and aspirin decreased the severity of the MALE, thereby improving prognosis after the MALE, as compared to patients who received aspirin alone.[34]

The vascular outcomes study of ASA (acetylsalicylic acid) along with tivaroxaban in endovascular or surgical limb revascularization for PAD (VOYAGER PAD) trial was a large international multicenter RCT that enrolled patients undergoing primarily elective peripheral revascularization. Patients were randomly assigned 1:1 to either low-dose rivaroxaban (2.5 mg twice daily) and aspirin (100 mg daily) in combination or to aspirin (100 mg daily) alone, with or without short-term clopidogrel at the discretion of the participating physician. Compared with aspirin, the combination of low-dose rivaroxaban and aspirin reduced rates of the primary outcome composite of acute limb ischemia, major vascular amputation, MI, ischemic stroke, or death from cardiovascular causes (HR, 0.85; 95% CI, 0.76-0.96). Unplanned index limb revascularization for recurrent ischemia was similarly reduced (HR, 0.88; 95% CI, 0.79-0.99). While a numeric increase in TIMI major bleeding was observed (HR, 1.43; 95% CI, 0.97-2.10), this was not statistically significant, although ISTH major bleeding was increased. Subgroup analysis performed to assess the effect of adding clopidogrel showed it did not add to the benefit of low-dose rivaroxaban and aspirin alone.[47]

The e-PAD trial tested full-dose edoxaban (60 mg) plus aspirin compared with clopidogrel plus aspirin in a small trial of 203 patients undergoing femoropopliteal endovascular intervention. A numerically lower incidence of restenosis and/or rate of reocclusion with edoxaban compared with clopidogrel was observed; however, the difference was not statistically significant. Numerically, more major/life-threatening bleeding occurred with clopidogrel and aspirin as compared to edoxaban and aspirin. A larger trial is needed to compare these strategies for efficacy and safety after endovascular intervention, however, in light of the VOYAGER trial results, it is uncertain if such a trial will be conducted.[48]

Taken together, two recent large RCTs have demonstrated that the use of low-dose DOACs used together with aspirin daily compared to aspirin alone is effective in reducing MACEs and MALEs in stable and postrevascularized patients with PAD who are deemed not to be at high risk for bleeding and who do not have an indication for full-dose oral anticoagulation long term. This represents high-quality evidence derived from large RCTs.[48] Further trials evaluating full-dose DOACs in the setting of acute limb ischemia are needed.

5 | ISTH CONGRESS REPORT

Several abstracts related to the use of DOACs for the prevention and treatment of arterial thrombosis were presented at the ISTH 2020 Congress.

Petzold and colleagues[49,50] demonstrated that rivaroxaban reduced arterial thrombosis through inhibition of platelet activation mediated by factor Xa through the PAR-1 receptor and its downstream signaling pathways in a series of experiments. In a mouse model of arterial thrombosis, they showed that rivaroxaban attenuated thrombus stability evaluated using intraviral microscopy in vivo following carotid artery injury. Rivaroxaban reduced platelet aggregation in vitro as measured using whole-blood multiple-electrode aggregometry and light transmission aggregometry. In rivaroxaban-treated patients, platelet adhesion and thrombus formation under flow were also reduced. Finally, they demonstrated that factor Xa directly activates platelet activation and thrombus formation on atherosclerotic plaque material, an effect that was dependent on PAR-1 and attenuated by rivaroxaban treatment. The results of these studies suggest an antiplatelet effect of rivaroxaban exerted through inhibition of factor Xa.

Wang and colleagues[51] characterized the antithrombotic treatment patterns among 499 757 total adult patients with acute

ischemic stroke (and without atrial fibrillation) from four administrative claims databases in the United States. Medications obtained without a prescription, such as aspirin, and medications received during hospitalizations were not captured in these databases. The proportion of patients treated with DOACs in these data sets ranged from 0.6% to 1.2%. Although the rationale for DOAC treatment in these patients is unknown, future studies may evaluate their clinical characteristics and outcomes.

Biaginoni and colleagues presented the rationale and design for the Apixaban Versus Clopidogrel on a Background of Aspirin in Patients Undergoing Infrapopliteal Angioplasty for Critical Limb Ischemia (AGRIPPA) trial.[52] This is an ongoing prospective, randomized, open-label, blinded end point exploratory trial evaluating the efficacy of apixaban 2.5 mg orally twice daily (for 12 months) compared to clopidogrel 75 mg daily (for 3 months) in addition to aspirin 100 mg daily (for 12 months) in patients with critical limb ischemia undergoing endovascular infrapopliteal revascularization. The primary end point is a composite of target lesion revascularization, major amputation, or restenosis/occlusion plus MACE at 12 months. The study is currently enrolling patients in Brazil with a target enrollment of 200. The results of this trial will be used to inform a future large RCT.

6 | CONCLUSION

Single or dual antiplatelet therapy is used as first line among patients with coronary artery disease, cerebrovascular disease, and PAD. However, there is increasing evidence of the efficacy and safety of low-dose DOACs used together with aspirin in preventing atherothrombosis, demonstrating a new management option through dual pathway inhibition.

ACKNOWLEDGMENTS

We thank Natalie Williams for her assistance in formatting and submitting the article.

RELATIONSHIP DISCLOSURE

SSA receives speaking honoraria and consultant fees from Bayer and Janssen, and served on the COMPASS trial steering committee and VOYAGER trial executive committee. DMS has received honoraria from BMS-Pfizer, Leo Pharma, Novartis, Portola, and Servier.

AUTHOR CONTRIBUTIONS

DS and SA jointly conceived and wrote this article.

ORCID

Deborah M. Siegal https://orcid.org/0000-0003-3806-3245
Sonia S. Anand https://orcid.org/0000-0003-3692-7441

TWITTER

Deborah M. Siegal @DebSiegal
Sonia S. Anand @DrSoniaAnand1

REFERENCES

1. Group WCRCW. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health*. 2019;7(10):e1332-e1345.
2. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473(7347):317-325.
3. Borissoff JI, Spronk HM, ten Cate H. The hemostatic system as a modulator of atherosclerosis. *N Engl J Med*. 2011;364(18):1746-1760.
4. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502.
5. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
6. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
7. Carreras ET, Mega JL. Role of oral anticoagulants in patients after an acute coronary syndrome. *Arterioscler Thromb Vasc Biol*. 2015;35(3):520-524.
8. Christersson C, Oldgren J, Bylock A, Wallentin L, Siegbahn A. Long-term treatment with ximelagatran, an oral direct thrombin inhibitor, persistently reduces the coagulation activity after a myocardial infarction. *J Thromb Haemost*. 2005;3(10):2245-2253.
9. Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J*. 2006;27(5):519-526.
10. Ruff CT, Giugliano RP, Braunwald E et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.
11. Chiarito M, Cao D, Cannata F et al. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. *JAMA Cardiol*. 2018;3(3):234-241.
12. Mega JL, Braunwald E, Wiviott SD et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366(1):9-19.
13. Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-1330.
14. Ohman EM, Roe MT, Steg PG et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet*. 2017;389(10081):1799-1808.
15. Chen ZM, Sandercock P, Pan HC et al. Indications for early aspirin use in acute ischemic stroke : a combined analysis of 40 000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. On behalf of the CAST and IST collaborative groups. *Stroke*. 2000;31(6):1240-1249.
16. Wang Y, Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369(1):11-19.
17. Johnston SC, Easton JD, Farrant M et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379(3):215-225.
18. Pan Y, Elm JJ, Li H et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials. *JAMA Neurol*. 2019;76(12):1466.
19. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2015(3):CD000024.
20. Whiteley WN, Adams HP Jr, Bath PM et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve

outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol*. 2013;12(6):539-545.
21. Morrow DA, Braunwald E, Bonaca MP et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366(15):1404-1413.
22. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
23. Butcher KS, Ng K, Sheridan P et al. Dabigatran treatment of acute noncardioembolic ischemic stroke. *Stroke*. 2020;51(4):1190-1198.
24. Hart RG, Diener HC, Coutts SB et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13(4):429-438.
25. Diener HC, Sacco RL, Easton JD et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med*. 2019;380(20):1906-1917.
26. Hart RG, Sharma M, Mundl H et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*. 2018;378(23):2191-2201.
27. Paciaroni M, Kamel H. Do the results of RE-SPECT ESUS call for a revision of the embolic stroke of undetermined source definition? *Stroke*. 2019;50(4):1032-1033.
28. Sharma M, Hart RG, Connolly SJ et al. Stroke outcomes in the COMPASS trial. *Circulation*. 2019;139(9):1134-1145.
29. Gerhard-Herman MD, Gornik HL, Barrett C et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(12):e686-e725.
30. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156-170.
31. Narula N, Dannenberg AJ, Olin JW et al. Pathology of peripheral artery disease in patients with critical limb ischemia. *J Am Coll Cardiol*. 2018;72(18):2152-2163.
32. Hackam DG, Goodman SG, Anand SS. Management of risk in peripheral artery disease: recent therapeutic advances. *Am Heart J*. 2005;150(1):35-40.
33. Hiatt WR, Fowkes FG, Heizer G et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376(1):32-40.
34. Anand SS, Eikelboom JW, Dyal L et al. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. *J Am Coll Cardiol*. 2019;73(25):3271-3280.
35. Bonaca MP, Bauersachs RM, Anand SS et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382(21):1994-2004.
36. Anand S, Yusuf S, Xie C et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357(3):217-227.
37. Aboyans V, Ricco JB, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2017;39:763–821.
38. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339.
39. Bonaca MP, Scirica BM, Creager MA et al. Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50. *Circulation*. 2013;127(14):1522-1529, 1529e1521-1526.
40. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA, Investigators C. Patients with peripheral arterial disease in the CHARISMA trial. *Eur Heart J*. 2009;30(2):192-201.
41. Steg PG, Bhatt DL, Simon T et al. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med*. 2019;381(14):1309-1320.
42. Johnson WC, Williford WO. Department of Veterans Affairs Cooperative Study 362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg*. 2002;35(3):413-421.
43. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet*. 2000;355(9201):346-351.
44. De Haro J, Bleda S, Varela C, Canibano C, Acin F. Meta-analysis and adjusted indirect comparison of direct oral anticoagulants in prevention of acute limb ischemia in patients with atrial fibrillation. *Curr Med Res Opin*. 2016;32(6):1167-1173.
45. Obi AT, Barnes GD, Wakefield TW et al. Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. *J Vasc Surg Venous Lymphat Disord*. 2020;8(4):526-534.
46. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):219-229.
47. Hiatt WR, Bonaca MP, Patel MR et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: impact of concomitant clopidogrel on efficacy and safety. *Circulation*. 2020;142(23):2219-2230.
48. Moll F, Baumgartner I, Jaff M et al. Edoxaban plus aspirin vs dual antiplatelet therapy in endovascular treatment of patients with peripheral artery disease: results of the ePAD trial. *J Endovasc Ther*. 2018;25(2):158-168.
49. Petzold T, Thienel M, Dannenberg L et al. Rivaroxaban reduces arterial thrombosis by inhibition of FXa-driven platelet activation via protease activated receptor-1. *Circ Res*. 2020;126(4):486-500.
50. Petzold T, Thienel M, Dannenberg L et al. Rivaroxaban reduces arterial thrombosis by inhibition of FXa driven platelet activation via protease activated receptor-1 [abstract]. *Res Pract Thromb Haemost*. 2020;126(4):486-500.
51. Wang L, Weaver J, Hardin J et al. Characterization and antithrombotic treatment of patients with acute ischemic stroke and no atrial fibrillation: a real-world study [abstract]. *Res Pract Thromb Haemost*. 2020;4(Suppl. 1):43.
52. Biagioni R, Lopes R, Agati L, Ramacciotti E. Rationale and design for the study apixaban versus clopidogrel on a background of aspirin in patients undergoing InfraPoPliteal angioplasty for critical limb ischemia – AGRIPPA Trial [abstract]. *Res Pract Thromb Haemost*. 2020;4(Suppl 1):52.
53. Alexander JH, Lopes RD, James S et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365(8):699-708.

How to cite this article: Siegal DM, Anand SS. Considerations for use of direct oral anticoagulants in arterial disease. *Res Pract Thromb Haemost*. 2021;5:e12502. https://doi.org/10.1002/rth2.12502