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Review Article

Rivaroxaban plus aspirin for cardiovascular protection: Rationale for the vascular dose and dual pathway inhibition

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A B S T R A C T

This review provides the rationale for dual pathway inhibition with the combination of low-dose rivaroxaban (2.5 mg twice daily) to attenuate thrombin generation and aspirin (100 mg once daily) to reduce platelet activation. Such therapy has been licensed for secondary prevention in patients with coronary or peripheral artery disease.

1. Introduction

Cardiovascular disease (CVD) is a prevalent disease and the leading cause of global mortality, accounting for 17.9 million deaths per year, and increasing to projected more than > 23.6 million by 2030 [1]. Atherosclerosis is the leading underlying CVD cause. A complex pathological process, atherosclerosis starts early in life with plaque formation and remains asymptomatic until inflammation leads to plaque disruption and superimposed thrombosis, so-called atherothrombosis.

Atherosclerosis affects the coronary, cerebral and peripheral arteries, leading to coronary artery disease (CAD), ischemic stroke, and peripheral artery disease (PAD). Affecting endothelial dysfunction, atherogenic lipoproteins transmigrate across the leaky endothelial barrier and become cytotoxic, pro-inflammatory, and chemotactic. Expression of adhesion molecules on the dysfunctional endothelium leads to focal recruitment of monocytes, which migrate into the intima in response to chemotactic stimuli. These monocytes differentiate into macrophages, which engulf atherogenic lipoproteins and are transformed into foam cells. With the progression of the immune and inflammatory response, there is smooth muscle proliferation and plaque growth. Macrophages and smooth muscle cells within the plaque undergo apoptosis and their disintegration leads to the formation of a destabilizing lipid-rich core covered by a rupture-prone fibrous cap. Plaque disruption triggers platelet activation, while exposure of tissue factor initiates coagulation. Activated platelets provide a surface onto which clotting factors assemble to produce the burst of thrombin generation that prompts further platelet activation and formation of a platelet-rich thrombus [2].

Until recently, treatment of atherothrombosis focused on platelets with the use of single or dual antiplatelet therapy. For secondary prevention, current guidelines recommend low dose aspirin or clopidogrel if aspirin cannot be tolerated. Dual antiplatelet therapy (DAPT), consisting of aspirin plus a P2Y12 antagonist, is recommended for patients with acute coronary syndrome (ACS) [3]. Despite the use of single or dual antiplatelet therapy, however, there remains a risk of serious atherothrombotic events. The limitations of antiplatelet treatment raised the possibility that combining antiplatelet therapy with an anticoagulant might improve atherothrombotic outcomes.

The first anticoagulants to be tested in this setting were the vitamin K antagonists (VKAs). A meta-analysis that included data on over 20,000 patients with myocardial infarction (MI) revealed that compared with aspirin, VKAs alone or VKAs in combination with aspirin reduced the risk of recurrent MI and ischemic stroke, but any benefit was offset by at least a 2.5-fold increase in major bleeding, including intracranial bleeding [4]. Furthermore, when warfarin plus aspirin was compared with aspirin alone for secondary prevention in PAD patients, warfarin was of no benefit for reduction in the risk of recurrent ischemic events and it increased the risk of life-threatening bleeds by 3.4-fold [5]. Therefore, because of the lack of a net clinical benefit, VKAs are rarely used for secondary prevention in CAD or PAD patients.

Rivaroxaban is an oral direct factor Xa (FXa) inhibitor that inhibits free FXa and FXa incorporated into the prothrombinase complex [6–10]. The drug is licensed for several indications and for most of these, rivaroxaban is given once daily (Table 1).

An innovative reduced dose rivaroxaban regimen (2.5 mg twice daily) on top of aspirin (100 mg once daily) was compared with

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Table 1
Rivaroxaban doses names and regimens according to its indications.

Rivaroxaban dose	Indication	Name
Rivaroxaban 15 mg twice daily	VTE treatment acute phase	Highest full dose anticoagulation
Rivaroxaban 20 mg once daily	Stroke prevention in atrial fibrillation VTE secondary prevention long-term phase	Full dose anticoagulation
Rivaroxaban 10 mg once daily	VTE prophylaxis Secondary VTE prevention	Prophylactic dose
Rivaroxaban 2.5 mg twice daily + DAPT	Secondary prevention after ACS	Vascular dose
Rivaroxaban 2.5 mg twice-daily plus aspirin 100 mg once-daily	Reduce the risk of CV events, secondary prevention, in CAD and or PAD patients	Dual pathway inhibition (DPI)

rivaroxaban alone (5 mg twice daily) or aspirin alone for secondary prevention in 27,400 patients with stable CAD or PAD [11–14]. The 2.5 mg twice-daily rivaroxaban dose is known as the vascular dose, and its combination with aspirin provides dual pathway inhibition (DPI). This white paper reviews the rationale for the vascular dose of rivaroxaban and for DPI.

2. Dual pathway inhibition

Platelets predominate in arterial thrombi, which form under high shear conditions, whereas fibrin is the major component of venous thrombi because they form where blood flow is reduced. Because of the predominance of platelets in arterial thrombi, antiplatelet therapy is the current cornerstone for prevention and treatment of arterial thrombosis [15].

Despite antiplatelet regimens including dual antiplatelet therapy (DAPT), recurrent ischemic events are common with up to 11% of patients with ACS and 5% of patients with stable CAD or PAD having recurrent ischemic events each year [16]. Compared with aspirin alone, DAPT reduces cardiovascular mortality by about 30% in ACS patients, but at the price of a 1.8-fold increase in bleeding [17]. In the PEGASUS trial, differences in relative risk of major bleeding (RR = 1.66 in COMPASS versus RR = 2.32 in PEGASUS), in addition to the more pronounced relative reduction of the primary endpoint and the significant reduction in mortality in COMPASS when comparing both regimens, makes the COMPASS results very compelling. Indeed, physicians are now faced with the decision for which more intensive antithrombotic regimen to choose in their patients [18].

In the CAPRIE study, the residual risk of atherothrombotic events with clopidogrel alone was 5.3% per year. In the CHARISMA trial, the residual risk of such events was 6.8% with clopidogrel plus aspirin, whereas, in the PEGASUS trial, it was nearly 8% after 3 years of extended treatment with ticagrelor [18–20].

DAPT was also tested in a variety of trials after percutaneous coronary interventions (PCI) with stent implantation, including drug eluting stents, to prevent recurrent coronary ischemic events and stent thrombosis. In this setting, DAPT is superior to aspirin for efficacy, at the price of increased major bleeding [21]. Trials also evaluated the duration of DAPT after the index event, challenging guidelines recommendations of 12 months of DAPT treatment duration. Reductions to 6 or even 3 months were tested pursuing best protection to ischemic events with less bleeding possible. Table 2 provides a comprehensive comparison of primary ischemic events reduction with bleeding risk for a variety of antithrombotic and anticoagulant medications in ACS and PAD trials described. In summary, these trials were in general underpowered to detect benefit, given the lower event rates observed than expected during trial design [22]. Therefore, neither single nor dual antiplatelet therapy is sufficient to protect patients from atherothrombotic events.

In arterial thrombosis, thrombin generation is triggered by tissue factor (TF) after atherosclerotic plaque rupture. Thrombin activates platelets by binding and cleaving protease-activated receptor (PAR)-1 and PAR-4. Activated platelets promote additional thrombin generation by providing a surface onto which clotting factors assemble; a process that enhances their activity by several orders of magnitude [23]. Thrombin converts soluble fibrinogen into fibrin monomers, which polymerize to form a fibrin network.

Platelet activation promotes their release of thromboxane A2 and other agonists, which activate ambient platelets. Activated platelets aggregate at the site of vascular injury and these aggregates are stabilized by the fibrin network to form a platelet-rich thrombus. Therefore, atherothrombosis is triggered by thrombin generation and platelet activation.

Recognizing the coordinated contribution of thrombin generation and platelet activation to atherothrombosis, DPI involves the co-administration of an anticoagulant to attenuate thrombin generation and aspirin to inhibit platelet thromboxane A2 synthesis [24]. When anticoagulants are administered in conjunction with aspirin, anticoagulant dosing is critical to prevent excessive bleeding. VKAs were the first anticoagulants to be evaluated in the setting of DPI. When given to MI patients in doses sufficient to produce a therapeutic international normalized ratio (INR), the combination of a VKA plus aspirin reduced recurrent MI and stroke by 44% and 54%, respectively, compared with aspirin alone. However, this benefit was offset by a 2.5-fold increase in major bleeding. Therefore, VKAs are problematic when used for DPI [4].

Direct oral anticoagulants (DOACs) were developed to overcome the limitations of VKAs. The DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. Of the DOACs, rivaroxaban is the agent that has been evaluated most extensively for DPI. The mechanism of action of rivaroxaban vascular dose targeting both coagulation and platelets – DPI - is represented in Fig. 1. Even when given in low doses (2.5 or 5 mg) to healthy volunteers, rivaroxaban attenuates thrombin generation. When given in these low doses, rivaroxaban has a half-life of 3 to 6 h, which necessitates twice-daily dosing. In contrast, with doses of 10 mg or higher, the half-life or rivaroxaban is longer, thereby permitting once-daily dosing, as depicted in Table 2. Based on this information, various doses and dose regimens of rivaroxaban were first evaluated on top of antiplatelet therapy in ACS patients [25].

2.1. ATLAS-ACS-1 TIMI 46 study

In phase II ATLAS-ACS-1 TIMI 46 study, 3491 ACS patients were randomized to varying dose regimens of rivaroxaban or placebo on top of dual or single antiplatelet therapy. Clinically significant bleeding with rivaroxaban as compared to placebo increased in a dose-dependent fashion. Rates of the primary efficacy endpoint, a composite of death, MI, stroke or severe recurring ischemia requiring revascularization, were not reduced. However, compared with placebo, rivaroxaban reduced the secondary efficacy endpoint of death, MI, or stroke compared from 5.5% to 3.9% (hazard ratio [HR] 0·69, 95% confidence interval [CI] 0·50–0·96; $P = 0·027$) [13]. The 2.5 and 5 mg twice daily doses were the rivaroxaban regimens with the best benefit-risk profiles. Consequently, these doses were carried forward into phase III.

Table 2
Comparison of primary endpoint reduction with bleeding risk for a variety of antithrombotic and anticoagulant medications in ACS and PAD trials.

Trial	Groups studied	N	Primary outcome (efficacy)	Bleeding risk (safety)
Antiplatelets				
CHARISMA (2006) (Clopidogrel for high atherothrombotic risk and ischemic stabilization, management and avoidance)	Clopidogrel vs. clopidogrel + aspirin for secondary prevention in ACS	15,603	MI, stroke, or CV death **HR (0.93 [0.83–1.05])** **No difference**	Major bleeding **RR, 1.25 (95% CI, 0.97–1.61)** **No difference**
CHARISMA (2009) PAD subgroup (Clopidogrel for high atherothrombotic risk and ischemic stabilization, management and avoidance)	PAD subgroup Clopidogrel vs. clopidogrel + aspirin for secondary prevention	3096	Adjudicated cardiovascular death, MI, or stroke **HR, 0.85 (95% CI, 0.66–1.08)** **No difference**	Adjudicated GUSTO severe bleeding **RR, 0.97 (95% CI, 0.56–1.66)** **No difference**
TRITON-TIMI 38 (2007) (Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–thrombolysis in myocardial infarction 38)	Prasugrel + aspirin vs. clopidogrel + aspirin for ACS	13,608	MI, stroke, or CV death **HR,0.81 (0.73–0.90)** **Reduced**	Major bleeding **HR, 1.32, CI, 1.03 to 1.68** **Increased**
PLATO (2009) (A comparison of ticagrelor and clopidogrel in patients with acute coronary syndrome)	Ticagrelor + aspirin vs. clopidogrel + aspirin for ACS	18,624	Death from vascular causes, MI, or stoke **HR, 0.84 (0.77–0.92)** **Reduced**	Major bleeding **HR, 1.04 (95% CI, 0.95–1.13)** **Increased**
PLATO (2015) PAD subgroup (A comparison of ticagrelor and clopidogrel in patients with PAD)	Ticagrelor + aspirin vs. clopidogrel + aspirin for PAD	1144	Death from vascular causes, MI, or stoke **HR, 0.85 (95% CI, 0.64–1.11)** **No difference**	Major bleeding **HR, 0.81 (95% CI, 0.59–1.10)** **No difference**
TRA 2P-TIMI 50 (2012) (Thrombin receptor antagonist in secondary prevention of atherothrombotic ischemic events–thrombolysis in myocardial infarction 50)	Vorapaxar + antiplatelet agent(s) vs. antiplatelet agent(s) for secondary prevention	26,449	MI, stroke or CV death **HR, 0.87 [0.80–0.94]** **Reduced**	Major bleeding **HR, 1.66; CI, 1.43 to 1.93** **Increased**
PEGASUS TIMI 54 (2015) (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)	Ticagrelor + aspirin vs. clopidogrel + aspirin for long-term secondary prevention following ACS	21,162	MI, stroke or CV death **HR, 0.84 [0.74–0.95]** **Reduced**	TIMI major bleeding **HR, 2.69 (95% CI, 1.96–3.70)** **Increased**
EUCLID (2016) Ticagrelor vs clopidogrel	Stable PAD	13,800	Adjudicated cardiovascular death, MI, or ischemic stroke **HR, 1.02 (95% CI, 0.92–1.13)** **No difference**	Adjudicated TIMI major bleeding **HR, 1.10 (95% CI, 0.84–1.43)** **No difference**
Anticoagulants				
WAVE (2007) VKA vs aspirin PAD patients	Warfarin or acenocoumarol vs aspirin, ticlopidine, or clopidogrel for PAD or carotid artery disease	2161	Coprimary 1: cardiovascular death, MI, or stroke **RR, 0.92 (95% CI, 0.73–1.16)** **No difference**	Major bleeding **RR, 3.41 (95% CI, 1.84–3.65)** **Increased**
APPRAISE-2 (2011) (Apixaban for Prevention of Acute Ischemic Events 2)	Apixaban + DAPT vs. DAPT for secondary prevention following ACS	7392	MI, stroke or CV death **HR, 0.95 [0.80–1.110]** **No difference**	TIMI major bleeding **HR, 2.59; CI, 1.50 to 4.46** **Increased**
ATLAS ACS 2- TIMI 51 (2012) (Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome–thrombolysis in myocardial infarction 51)	Rivaroxaban + dual antiplatelet therapy (DAPT) vs. DAPT for secondary prevention following ACS	15,526	MI, stroke or CV **HR, 0.84 (0.72–0.96)** **Reduced**	TIMI major bleeding **HR, 3.96; CI, 2.46 to 6.38** **Increased**
COMPASS (2017) Rivaroxaban + aspirin vs. rivaroxaban alone	CAD and or PAD	27,395	MI, stroke or CV death **RR, 0.76 [0.66–0.86]** **Reduced**	Major bleeding **HR 1.70 [1.40–2.05]** **Increased**
COMPASS (2017) PAD subgroup Rivaroxaban + aspirin vs. rivaroxaban alone	PAD	7470	MI, stroke or CV death **HR, 0.72, 95% CI 0·57–0·90** **Reduced**	Major bleeding **HR, 1.61, 95% CI 1.12–2.31** **Increased**

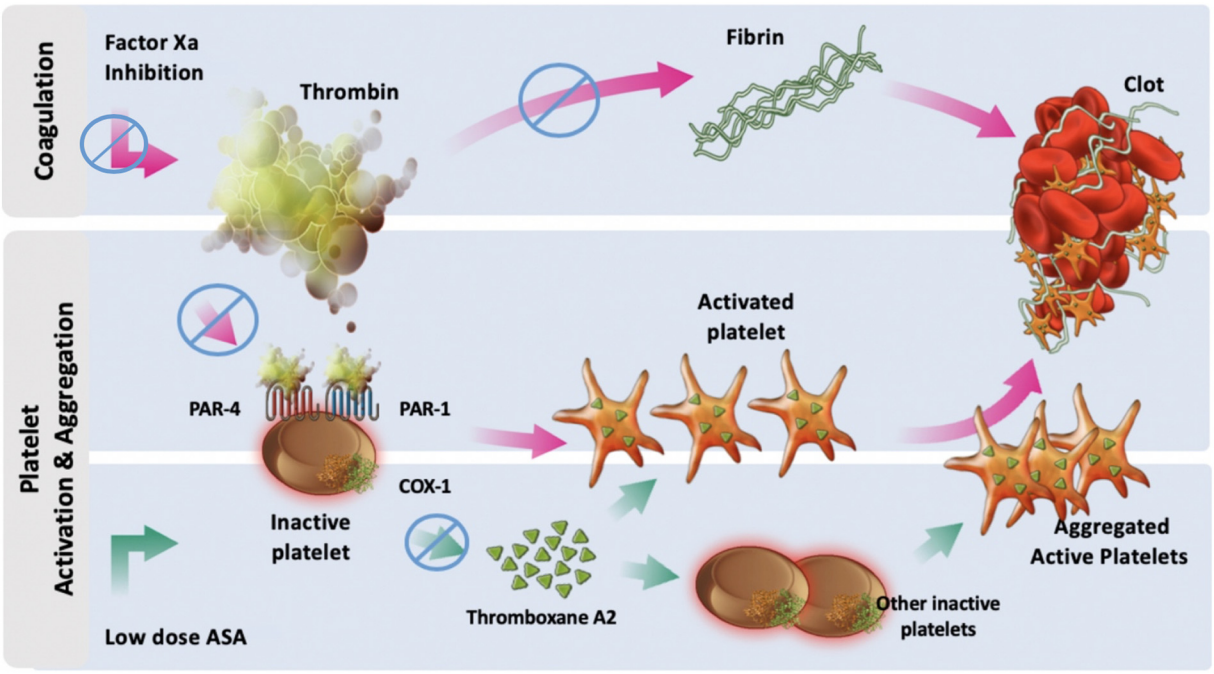

Fig. 1. The mechanism of action of rivaroxaban vascular dose targeting both coagulation and platelets. Inhibiting thrombin inhibits fibrin decreasing clot formation. Thrombin inhibition with low-dose rivaroxaban also blocks PAR-1/4, with a synergistic effect with low dose aspirin blocking COX-1, thereby attenuating TXA2 production, decreasing platelet aggregation.

2.2. ATLAS-ACS-2 TIMI 51 trial

This double-blind, placebo-controlled phase III trial randomized 15,526 ACS patients to receive oral rivaroxaban (2.5 mg or 5 mg twice daily) or matching placebo on a background of DAPT for around 13 months, but up to 31 months. Compared with placebo, both doses of rivaroxaban significantly reduced the primary efficacy endpoint, a composite of cardiovascular death, MI, or stroke (HR in the combined rivaroxaban group, 0.84; 95% CI, 0.74 to 0.96; $P = .008$). In contrast to the twice daily 5 mg dose of rivaroxaban, the twice daily 2.5-mg dose reduced the rates of cardiovascular death (2.7% vs. 4.1%, $P = .002$) and all-cause death (2.9% vs. 4.5%, $P = .002$). Overall, rivaroxaban significantly increased the rates of major bleeding from 0.6% to 2.1% ($P < .001$) and intracranial hemorrhage from 0.2% to 0.6% ($P = .009$) as compared to placebo. No significant increase in fatal bleeding was observed (0.3% vs. 0.2%, $P = .66$). Rivaroxaban 2.5 mg twice-daily dose led to fewer fatal bleeds as compared to the 5-mg twice-daily dose (0.1% vs. 0.4%, $P = .04$) [26]. On the basis of these findings, the 2.5 mg twice daily dose of rivaroxaban was licensed in Europe for use on top of DAPT in high-risk ACS patients.

The importance of using low doses when DOACs are combined with antiplatelet therapy is highlighted by the findings of the APPRAISE 2 trial. When apixaban, at the full therapeutic dose of 5 mg twice daily, was compared with placebo on top of antiplatelet therapy in ACS patients, the trial was stopped early after recruitment of 7392 patients because of increased major bleeding (including intracranial bleeding) with apixaban and no reduction in recurrent ischemic events [27].

With the benefit of lower doses of rivaroxaban established, the utility of DPI was evaluated in a number of phase III studies, the largest of which was the COMPASS trial.

2.3. COMPASS trial

The multinational, randomized, prospective, placebo-controlled Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [12] enrolled 27,395 patients with stable CAD or PAD. Patients received either oral rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban alone (5 mg twice daily), or aspirin alone (100 mg once daily) for a median duration of 23 months. The primary efficacy endpoint (a composite of cardiovascular death, stroke, or MI) was lower in the rivaroxaban plus aspirin group as compared to the aspirin-alone group (4.1% and 5.4%, respectively; HR, 0.76; 95% CI, 0.66 to 0.86; $P < .001$; $z = -4.126$). Major bleeding was higher in the rivaroxaban 2.5 mg twice a day plus aspirin group (3.1% and 1.9%, respectively; HR, 1.70; 95% CI, 1.40 to 2.05; $P < .001$). The majority of bleeds were gastrointestinal. Rates of intracranial or fatal bleeding were not significantly increased in the rivaroxaban-plus-aspirin and aspirin-alone groups. The rate of death was lower in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (3.4% and 4.1%, respectively; HR, 0.82; 95% CI, 0.71 to 0.96; $P = .01$). In contrast to the results with rivaroxaban-plus-aspirin, the rate of the primary efficacy outcome was not reduced in the rivaroxaban-alone group compared with the aspirin-alone group, but there were more major bleeding events in the rivaroxaban-alone group.

The finding that cardiovascular outcomes were lower with rivaroxaban (2.5 mg twice daily) plus aspirin than with aspirin alone or rivaroxaban alone supports the DPI hypothesis that a strategy that combines a low-dose of an anticoagulant to attenuate thrombin generation with aspirin, which blocks thromboxane A2 synthesis, is superior to single pathway inhibition. Furthermore, when the findings of the COMPASS trial are considered in the context of those of the ATLAS and APPRAISE trials, it is clear that optimal combination therapy requires the use of the lowest effective dose of the anticoagulant.

COMPASS CAD subgroup: out of 27 395 patients that were enrolled to the COMPASS trial, 24 824 patients had stable CAD. Rivaroxaban 2.5 mg twice a day in addition to aspirin reduced the primary composite outcome as compared to aspirin alone (347 [4%] of 8313 vs 460 [6%] of 8261; HR = 0.74, 95% CI 0.65–0.86, $P < .0001$). Rivaroxaban 5 mg twice daily with no associated aspirin therapy did not decrease the prespecified primary efficacy outcome when compared with aspirin alone treatment (411 [5%] of 8250 patients vs 460 [6%] of 8261 patients; HR = 0.89, 95% CI 0.78–1.02, $P = .094$). This combination of rivaroxaban and aspirin led to more major bleeding than aspirin in single therapy (263 [3%] of 8313 patients vs 158 [2%] of 8261patients;

HR = 1.66, 95% CI 1.37–2.03, $P < .0001$). Bleeding was higher in the rivaroxaban alone group as compared to the aspirin alone group (236 [3%] of 8250 patients vs 158 [2%] of 8261 patients; HR = 1.51, 95% CI 1.23–1.84, $P < .0001$). A combination of rivaroxaban and aspirin reduced the mortality rates when compared with aspirin alone (262 [3%] of 8313 patients vs 339 [4%] of 8261 patients; HR = 0.77, 95% CI 0.65–0.90, $P = .0012$). In addition to a significant net benefit in favor of rivaroxaban plus aspirin, deaths were reduced by 23% [28].

COMPASS PAD subgroup: COMPASS enrolled 7470 patients with PAD. Compared with aspirin alone, rivaroxaban-plus-aspirin reduced the composite of cardiovascular death, MI, or stroke from 7% to 5% (HR 0.72, 95% CI 0.57–0.9; $P = .0047$), and major adverse limb events including major amputation from 2% to 1% (HR 0.54, 95% CI 0.35–0.82; $P = .0037$) [29]. In contrast, compared with aspirin, rivaroxaban alone did not significantly reduce the composite endpoint (7% and 6%, respectively; HR 0.86, 95% CI 0.69–1.08; $P = .19$), although the rate of major adverse limb events including major amputation was lower with rivaroxaban alone than with aspirin (1.6% and 2%; HR 0.67, 95% CI 0.45–1.00, $P = .05$). Major bleeding rates were higher with rivaroxaban in combination to aspirin than with aspirin alone (3% and 2%, respectively; HR 1.61, 95% CI 1.12–2.31, $P = .0089$); most of the excess bleeds were gastrointestinal as observed in the overall population [30].

2.4. Other studies using low-dose rivaroxaban

2.4.1. COMMANDER-HF

Low-dose rivaroxaban was compared with placebo in heart failure patients with reduced ejection fraction in the COMMANDER HF trial. Despite not showing benefits in this population in reducing the primary efficacy endpoint of death of any cause, MI or stroke (25% vs 26.2%, HR = 0.94; 95% [CI], 0.84 to 1.05; $P = .27$), there was no increase in bleeding in this fragile population (hazard ratio, 0.80; 95% CI, 0.43 to 1.49; $P = .48$) [14].

2.4.2. VOYAGER PAD

The ongoing VOYAGER PAD trial is comparing rivaroxaban with placebo in 6500 symptomatic PAD patients undergoing surgical and/or endovascular revascularization. Oral rivaroxaban 2.5 mg twice daily or matching placebo, on top of background therapy with aspirin (100 mg daily) are the studied treatments. The pre-specified primary efficacy endpoint was defined as a composite of MI, ischemic stroke, cardiovascular death, acute limb ischemia, and major amputation of vascular etiology, whereas the primary safety endpoint is major bleeding. Results are expected for 2019 [11].

2.5. COMPASS results from a clinical practice perspective

Overall, COMPASS is a very positive trial. The benefits were consistent in patients with CAD and PAD and the benefit was highest in those with the greatest degree of atherosclerosis. Patients with polyvascular disease (CAD + PAD) benefit the most. Given that these patients have higher baseline risk, the absolute risk reductions (ARR) are expectedly greater. When comparing patients with ≥2 vascular beds versus 1 vascular bed, the AAR is 6.02% versus 1.36%, which translates into 60 events prevented versus 14 events prevented per 1000 patients treated over 30 months. In general, number of vascular events prevented in the higher-risk patient subsets were higher in comparison to lower-risk, and ranged from 30 to 60 per 1000 patients treated and followed for 30 months [31].

The downside of intensifying the antithrombotic regimen is more bleeding. Physicians will have to balance bleeding risk with ischemic events risk. Patients that bled in the past or at risk of severe bleeding are unlikely to receive such therapy. The benefit of the combination of rivaroxaban 2.5 mg twice daily and aspirin was consistent across subgroups of the COMPASS trial; however, it would be sensible to target the populations at highest risk because they will derive the greatest absolute benefit.

2.5.1. CAD patients with recent ACS

In patients with ACS, DAPT remains the standard of care. Since the benefit of DAPT decreases over time, it is our opinion patients could be transitioned from DAPT to DPI after 6 to 12 months of the index event [32].

2.5.2. Stable CAD

The benefit of combination therapy with rivaroxaban 2.5 mg bid and aspirin over aspirin alone does not decrease over time as observed with DAPT as compared to aspirin alone. Furthermore, the increased risk of major bleeding with rivaroxaban plus aspirin over aspirin alone was only evident during the first year of therapy. Consequently, the net benefit of DPI over aspirin increases over time. Therefore, DPI is an appealing alternative to aspirin for most CAD patients [32].

2.5.3. PAD

Patients with PAD are at a particularly high risk of CV events. Guidelines suggests monotherapy (aspirin or clopidogrel) for patients with symptomatic PAD. Due to the consistency of the benefit of rivaroxaban plus aspirin over aspirin alone in the COMPASS trial, PAD patients are amongst those who benefited most from combination therapy [12,31].

2.5.4. Stroke

The COMPASS trial excluded patients with stroke within the previous year and those with a history of any hemorrhagic or lacunar stroke. Nonetheless, a total of 1032 patients in COMPASS had a history of non-lacunar ischemic stroke. Rivaroxaban plus aspirin reduced significantly ischemic or unspecified strokes (the majority were lacunar strokes) as compared to aspirin alone (0.7% vs 1.4%, HR 0.51, 95%CI 0.38–0.68). A stroke subgroup analysis of COMPASS showed that fewer patients had strokes in the rivaroxaban plus aspirin group than in the aspirin group (83 [0.9% per year] versus 142 [1.6% per year]; HR 0.58; 95% CI, 0.44 to 0.76; $P < .0001$). Ischemic/uncertain strokes were reduced by nearly half (68 [0.7% per year] versus 132 [1.4% per year]; HR, 0.51; 95% CI, 0.38–0.68; $P < .0001$) by rivaroxaban in combination with aspirin in comparison with aspirin alone. This effect was also observed on patients with prior stroke [33]. The current standard care for ischemic stroke prevention of recurrence is either aspirin or clopidogrel, or aspirin in combination to dipyridamole. Additional trials are needed to determine how DPI compares with such therapy.

2.5.5. Polyvascular disease

Polyvascular disease refers to patients with CVD involving more than one vascular bed (CAD, PAD, or cerebrovascular disease). The current standard of care is aspirin or clopidogrel monotherapy with DAPT reserved for selected high-risk patients with CAD. In COMPASS, the majority of patients with polyvascular disease had concomitant CAD and PAD. The risk of ischemic events was higher in patients with polyvascular disease than in those with CAD alone and in the polyvascular disease subgroup, rivaroxaban plus aspirin significantly reduced cardiovascular events compared with aspirin alone (5.7% vs 8.4%, RR 0.67, 95%CI 0.52–0.87). Due to their high risk of cardiovascular events, patients with polyvascular disease are likely to benefit most from DPI [12,31].

2.5.6. Vascular risk sub-group analysis

According to the REACH score (REduction of Atherothrombosis for Continued Health), high-risk patients with vascular disease were those with 2 or more vascular beds affected, history of heart failure (HF), or renal insufficiency. The CART (Classification and Regression Tree) analysis identified as high-risk patients with 2 or more vascular beds affected, history of HF, or diabetes. A combination of rivaroxaban plus aspirin reduced MACE and MALE incidence by 25% (4.48% vs. 5.95%,

HR 0.75; 95% CI 0.66 to 0.85), with a nonsignificant 34% increase in severe bleeding (HR 1.34; 95% CI 0.95 to 1.88) [31]. The identification of this subset of higher vascular risk patients 2 or more vascular beds affected, HF, renal insufficiency, or diabetes will further help clinicians refining its strategies finding the correct candidates for DPI treatment.

3. Conclusions and future directions

In the COMPASS trial, DPI was superior to aspirin alone in patients with CAD and PAD. The 18% mortality reduction with DPI is a unique finding that has not been demonstrated with other intensified antithrombotic regimens. Therefore, DPI represents a paradigm shift for secondary prevention. Successful translation of the results of the COMPASS trial into clinical practice depends on identifying high-risk patients who will benefit most from DPI. Such patients include those with polyvascular disease, symptomatic PAD and those with other high-risk features such as diabetes and renal impairment.

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