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RIVAROXABAN BEYOND INHIBITING THROMBOSIS: TARGETING INFLAMMATION AND ATHEROSCLEROSIS

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ABSTRACT
Recent evidence has described beneficial clinical effects among patients with stable coronary artery disease (CAD), peripheral artery disease (PAD), and/or stroke when low-dose rivaroxaban (anti-factor Xa) was added to aspirin. A decrease on atherothrombotic events was observed, in part, by optimization of vascular protection. While the function of platelets is well recognized, substantiation is being composed on the role of coagulation factors to the developments of both atherosclerosis and atherothrombosis. Coagulation factors participate importantly on thrombus formation, meaning fibrin materialization and platelet activation and aggregation. In addition, these factors facilitate numerous pathophysiologic mechanisms through activation of protease-activated-receptors (PARs). Consequently, the association of anticoagulant to antiplatelet has obtained interest in secondary prevention for CAD/PAD as residual atherothrombotic risks are reduced. In this review, based on these recent findings, we emphasize the importance of factor Xa inhibition on protease-activated receptor (PAR) inactivation. PARs participate markedly on the pathophysiology of atherothrombosis.

Key points:

- Combining low-dose rivaroxaban to aspirin improves cardiovascular outcomes in patients with stable atherosclerotic vascular disease.
- Coagulation and inflammatory pathways via factor Xa-mediated PAR activation on the arterial wall, and the resulting contribution to atherosclerosis, have been well documented.
- Rivaroxaban can experimentally attenuate miointimal formation after mechanical vascular injury.
- Inhibition of the factor Xa-PAR-2 pathway may minimize cardiac injury and dysfunction after myocardial infarction.

KEYWORDS: Rivaroxaban; atherosclerosis; inflammation; factor Xa; protease-activated receptor; coronary artery disease.

INTRODUCTION
The extensive category of clinical signs of atherothrombotic disease include coronary artery disease (CAD), peripheral artery disease (PAD), and/or stroke. Whereas the participation of platelets is well recognized, substantiation is now gathering on the involvement of coagulation proteins to the courses of atherosclerosis and atherothrombosis.

Recently, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial reported lower cardiovascular event rates among patients with stable atherosclerotic vascular disease that were treated with rivaroxaban (2.5 mg twice daily dose) plus aspirin (acetylsalicylic acid).[1] Interestingly, the dose used in this trial was lower than that used for the prevention of thromboembolic events. Nevertheless, little is known about the vascular protection mechanisms of rivaroxaban in this setting.

Outline of blood coagulation
Blood coagulation is started when the integrity of the endothelium is broken. Tissue factor (TF) and factor VIIa generate the TF-factor VIIa compound, which triggers factor X and factor IX. Factor Xa then transforms prothrombin to thrombin. The slight quantity of thrombin formed intensifies coagulation by activating factor V, factor VIII and platelets. Factor VIIIa conglomerates with factor IXa and produces the factor IXa-factor VIIIa-phospholipid compound – a main activator of factor X. Factor Xa attachs to negatively charged phospholipid surfaces (for example, activated

platelets), and composed with factor Va forms the prothrombinase compound –that transforms prothrombin to thrombin.[2] Thrombin is a vital protagonist in the coagulation course, including changing soluble fibrinogen to fibrin, triggering platelets and stimulating factor XIII to prompt fibrin cross-linking.[3] Blood-originated TF has been recognized on microparticles derivative from leukocytes and other cell varieties that are intricated in the beginning of clotting, when vessel damage is still restricted to endothelial activation.[4]

Physiological anticoagulant structures. Under physiological circumstances, clotting is firmly controlled by physiological and natural anticoagulants and the fibrinolytic system. In this order, thrombus materialization can be restricted to the site of vascular injury. The key physiological anticoagulants are antithrombin, TF pathway inhibitor (TFPI) and the protein C and protein S structures.[5]

Antithrombin impedes important clotting enzymes such as thrombin and factor Xa. In the lack of heparin, antithrombin attenuates these enzymes in a gradual and slow manner, but its action is amplified intensely in the existence of heparin.[6] TFPI is a key biological antagonist of factor Xa in the early stages of blood clotting, which acts by inhibiting the TF-factor VIIa-factor Xa compound[7], thus avoiding the making of both factor IXa and factor Xa.

The protein C structure is a chief physiological and natural anticoagulant route, which is triggered when thrombin attaches to thrombomodulin (TM). Triggering of protein C to activated protein C (APC) occurs mostly on the endothelium surface and triggering is increased when protein C is attached to the endothelial cell protein C receptor (EPCR). The APC-EPCR compound must detach previously so APC can attach to protein S and produce the protein S-APC compound accountable for the inactivation of factor Va and factor VIIIa. This declines the development of factor Xa-factor Va (the prothrombinase compound) and factor IXa-factor VIIIa (the intrinsic tenase compound), persuading the attenuation of clotting.[8] The attachment of thrombin to TM declines free thrombin intensities, thus inhibiting thrombin from splitting fibrinogen and activating platelets. Similarly, thrombin within the thrombin-TM compound is more subtle to inhibition by circulating antithrombin than free thrombin.[9] APC can similarly activate fibrinolysis by forming a compound with plasminogen activator inhibitor-1 (PAI-1). The function of PAI-1 is to attenuate plasmin formation, mediating inhibition of fibrinolysis (or clot dissolution). Accordingly, the suppression of this inhibitor of fibrinolysis by APC promotes additional anticoagulation.[10]

Vascular inflammation and thrombosis in atherosclerosis

Atherosclerosis is described by endothelial dysfunction alongside ongoing chronic vascular inflammation.[11,12] Attachment of monocytes to the stimulated endothelial cells of the arterial wall followed by diapedesis and differentiation into macrophages that internalize modified and oxidized LDL lipoproteins. Arterial macrophages with these features result in the configuration of foam cells which, in turn, promote fatty streak formation by vascular smooth muscle cell (VSMC) proliferation / migration as well as fibrotic cap development.[13]

The combination of foam cell lipids, smooth muscle cells and fibrous cap gradually constitutes an atheroma in the artery lumen. Instabilization and rupture of an atheroma reveals collagen and tissue factor (TF), robust activators of platelets and of the coagulation cascade, respectively, thus promoting an atherothrombotic closure of the artery. Although the participation of platelets in these events is well understood[14], important data is now being obtained on the role of coagulation proteins regarding atherosclerosis and related atherothrombosis.

Thrombosis in atherosclerosis. Atherothrombotic events initiate with the instabilization followed by rupture of an atheroma. Consequently, instant contact of potent thrombogenic content to elements of the blood happens.[15] Thrombus onset is determined by synchronized platelet and thrombin generation routes. Circulating platelets adhere to superficially expressed subendothelial collagen and von Willebrand factor (vWF), become stimulated, and then liberate ADP and thromboxane A2 (TXA2), which arouse other platelets. Stimulated platelets provoke conformational alterations in glycoprotein (GP) IIb/IIIa, which intensifies the attraction for its receptors fibrinogen and vWF, and thereby facilitates platelet aggregation. Concurrently with platelet activation and aggregation, the transmembrane receptor TF in the atheroma links to factor VII(a) in the blood and coagulation is initiated, leading to thrombin generation. Importantly, thrombin is a strategic protein that transforms fibrinogen into fibrin as well as triggers platelets through the activation of protease-activated receptors (PARs)-1 and 2. Likewise, thrombin also determines several feedback circuits that include triggering of factors V, VIII and XI to broaden even more thrombin formation. Ultimately, factor XIII is stimulated to cross-link fibrin to alleviate the clot. The expansion of coagulation requires a phospholipid surface delivering phosphatidylserine (PS) on which the intrinsic tenase (a complex of factor IXa and factor VIIIa) and prothrombinase (factor Xa and factor Va) complexes accumulate.[16] This PS surface is primarily delivered by stimulated platelets at the site of plaque rupture as platelet and thrombin pathways become linked.

Pathological analysis of the coronary artery thrombi has shown that thrombi frequently have a white, platelet-rich

crown, which develops at the site of plaque rupture, while its distal portion is colored red, reproducing its fibrin- and erythrocyte-rich appendage, once blood movement is stopped.[17] Platelets overlook this process in the first 3-4 hours, although fibrin becomes the main element afterwards. This evidence reveals that platelet and thrombin pathways are entangled in thrombus formation on an atherosclerotic setting.

Contribution of coagulation proteins in the atherosclerosis progression. Various coagulation proteins have been associated in pro-inflammatory conditions, such as atherosclerosis. TF is known to be the main intrinsic trigger of the coagulation cascade and is encountered in atheromas, specifically on the surface of macrophages and VSMC − coexistent with factor VII. Patients with acute coronary syndromes present markedly higher levels of TF in lesions than patients with stable CAD.[18] TF, thrombin, factor X and FXII activities were meaningfully greater in atherogenetic lesions than in stable progressive atherosclerotic lesions. Moreover, intrinsic thrombin potential and thrombin-antithrombin (TAT) complex levels suggest a procoagulant condition of atherogenetic lesions as compared to stable progressive atherosclerotic lesions. Furthermore, individuals with subclinical atherosclerosis, such as advanced carotid intima media thickness (IMT), an association between TF and IMT as indicator of early atherosclerosis has been shown.[19]

The existence of coagulation constituents in atheromas suggests, to some extent, the contribuition of coagulation proteins in plaque thrombogenicity. Moreover, some of these coagulation proteases, like thrombin and factor Xa, may transform atherogenesis up to the condition of atherothrombosis. Since coagulation proteins are more existent in initial atherosclerotic lesions compared to progressive atherosclerotic lesions[20], suggests that these proteins contribute to the initial development of atherosclerosis, rather than just thrombus formation in unstable plaques.

Role of factor Xa-protease-activated receptor pathway in atherosclerosis and inflammation

Besides their roles in coagulation, the TF-VIIa complex, factor Xa and thrombin all can signal through activation of PARs, and thereby, thrombotic and inflammatory pathways are connected. Interestingly, cross talk between thrombotic and inflammatory pathways via factor Xa-mediated PAR activation on the arterial vessel wall and heart, and the resulting contribution to atherosclerosis, has been well documented.[21,22] Through PAR-activation, the blood proteases from the coagulation system are involved in several pathophysiological processes, comprising leukocyte recruitment, vascular remodeling, angiogenesis and inflammation, which each participate importantly with atherogenesis.[23]

The PARs is the family of G protein-coupled, seven transmembrane domain receptors. Four members of the PAR family have been cloned (PAR 1-4) and are widely expressed in various cell types within the cardiovascular system. Both PAR-1 and PAR-2 are expressed on vascular endothelium, smooth muscle cells and cardiomyocytes.

Importantly, factor Xa activates both PAR-1 (expressed in platelets and vascular cells) and PAR-2 (expressed in vascular cells, but not in platelets), while it has no effect on PAR-3 or PAR-4. Numerous studies have reported various physiological roles of PARs.[24] Recent studies have suggested that factor Xa, or its major receptor PAR-2, plays an important role in the pathophysiology of inflammatory diseases.[25,26]

The endothelium, platelets, pro-inflammatory cytokines and chemokines, and several serine proteases (e.g., tissue factor, factor Xa, thrombin), via the activation of PARs, are major points in for the promotion of inflammation and leukocyte recruitment, which results in the initiation of atherosclerosis[27]; see Figure 2.

Furthermore, activated factor X plays an important role in the pro-inflammatory responses through PARs in many cell types involved in the initiation and progression of atherosclerosis such as monocytes/macrophages, endothelial cells and smooth muscle cells[28], in addition to platelets and fibroblasts. In fact, PAR-2 deficiency is associated with attenuation of atherosclerosis and may reduce lesion progression by blunting monocyte infiltration.[29]

Anticoagulation properties of rivaroxaban

Rivaroxaban is an oral, direct factor Xa inhibitor that targets free and clot-bound factor Xa and factor Xa in the prothrombinase complex. Factor Xa is an important constituent of the coagulation cascade and other biological and pathogenic activities that are known goals for appropriate antithrombotic management.[30] See Figure 1.

Rivaroxaban, as well as other direct anticoagulants, was developed recently to over come the limitations of traditional anticoagulants such as vitamin K antagonists (VKAs). VKAs have been the only oral anticoagulants accessible for clinical practice for many years. Although efficient, VKAs have a slow beginning and ending of effect, several drug-drug and food-drug interactions, and an erratic pharmacodynamic reaction that demands regular coagulation monitoring and dose tuning.[31]

Appealingly, direct factor Xa inhibitors as antithrombotic agents proposes selective, effective and orally active treatment with respect to the other established anticoagulants.[32] Particularly, rivaroxaban is absorbed promptly, with full blood concentrations being obtained 2-4 hours after oral consumption.[33]

Notably, factor Xa plays an important role in blood coagulation and is activated by both the intrinsic and

extrinsic coagulation pathways. Factor Xa directly converts prothrombin to thrombin via the prothrombinase complex, leading to fibrin clot formation and activation of platelets by thrombin.[34]

Data from both preclinical and clinical studies have confirmed that factor Xa is a viable target for effective anticoagulation. Rivaroxaban has shown similar or improved efficacy and safety profiles compared with conventional anticoagulants, such as the VKAs (e.g. warfarin) and low molecular weight heparin, in clinical studies across several thromboembolic indications.[35]

Distinct from VKAs, rivaroxaban has revealed to have foreseen pharmacodynamics and pharmacokinetics, a reduced chance for drug-drug interfaces, and are available at secure doses without the prerequisite for usual coagulation checking. Rivaroxaban has been ratified by the regulatory officials for the therapy of particular thromboembolic pathologies. Principal indications for rivaroxaban are prevention of venous thromboembolism in adults enduring hip or knee surgery, prevention of systemic arterial embolism and stroke in adults with non-valvular atrial fibrillation, and overall prevention and treatment of deep vein thrombosis and/or pulmonary embolism.

Likewise, rivaroxaban is now approved in European countries for the prevention of atherothrombotic complications among patients that present an acute coronary syndrome, combined with antiplatelet therapy such as aspirin with or without clopidogrel.[36]

Concomitantly, preclinical studies have already provided evidence for the pleiotropic effects of direct Xa inhibition beyond anticoagulation, including anti-inflammatory and protective activities in insulin resistance[37], atherosclerotic plaque development[38] and restenosis.[39]

Taken together, rivaroxaban may exhibit atheroprotective anti-inflammatory effects at a relatively low concentration and at which it may not affect deeply the systemic coagulation system. This article provides a summary of the vascular protection profile of rivaroxaban. These effects may in part explain the potential beneficial aspects of rivaroxaban, established in stable atherosclerotic patient populations.

Rivaroxaban inhibits miointimal thickness after percutaneous coronary intervention

Angioplasty, especially with stent implantation for coronary artery disease, is now established as a therapeutic strategy of great benefit.[40] However, restenosis remains the main limitation of percutaneous coronary intervention (PCI).[41] Excessive miointimal hyperplasia after vascular injury contributes to restenosis after angioplasty.[42] Both monocyte/macrophage-dependent inflammation and vascular smooth muscle cell (VSMC) proliferation play causal roles in this disease process through multiple cellular and molecular mechanisms.[43] Accordingly, the pro-inflammatory response is an important mechanism of miointimal hyperplasia.

Interestingly, Hara T et al demonstrated that rivaroxaban could experimentally attenuate miointimal formation after mechanical vascular injury.[44] Rivaroxaban reduced macrophage accumulation in the neointima in injured arteries after a week of experimental arterial manipulation. Rivaroxaban treatment also reduced the expression of inflammatory mediators, such as monocyte chemoattractant protein-1, interleukin-1β, tumor necrosis factor-α, transforming growth factor-β1 and granulocyte-macrophage colony stimulating factor in the injured artery. Appropriately, the expressions of PAR- 1 and PAR-2 in the injured arteries were higher compared to non-injured arteries. These data suggests that rivaroxaban treatment may attenuate the development of miointimal proliferation after mechanical vascular injury, such as in PCI, by inhibiting the factor Xa-PARs pathway.

Rivaroxaban modulates atherogenisis and plaque rupture

Rivaroxaban, besides its well-established anti-thromboembolic effects, also exerts atheroprotective actions by attenuating vascular inflammation. Rivaroxaban modulates atherosclerotic plaque progression and rupture by inhibiting pro-inflammatory activation of macrophages.[45] Recent experimental evidence has shown that chronic administration of rivaroxaban downregulates expression of inflammatory mediators and promotes plaque stability.[46] In endothelial cells, Factor Xa triggers nuclear factor κB, the release of interleukins-6 and -8, and monocyte chemotactic protein-1, which provides leukocyte recruitment. Most of these responses are interceded through PAR-2 activation although some evidences presented minimal contribution of PAR-1.[47]

Several clinical trials have reported that patients with coronary artery disease treated with rivaroxaban experienced fewer cardiovascular events compared to controls.[48] Importantly, when added to customary antiplatelets, rivaroxaban significantly reduced the probability of combined endpoints after an acute coronary syndrome.[49]

These results may explain partly the results of recent clinical trials, which reported lower cardiovascular event rates among patients with atherosclerotic vascular disease treated with rivaroxaban.

Rivaroxaban reduces cardiac impairment in experimental myocardial infarction

Bode et al sophisticatedly demonstrated that early administration of rivaroxaban preserves cardiac function in mice after left anterior descending artery (LAD) ligation.[50] Rivaroxaban increased the prothrombin time

and inhibited the formation of intravascular thrombi in mice subjected to LAD ligation. Wild-type mice receiving rivaroxaban immediately after surgery had similar infarct sizes at day 1 as controls but exhibited significantly less impairment of cardiac function at day 3 and beyond compared to the placebo group. Rivaroxaban also inhibited the expansion of the infarct. Also, rivaroxaban did not significantly affect the expression of inflammatory mediators or a neutrophil marker. Delaying the start of rivaroxaban administration until 3 days after surgery failed to preserve cardiac function. In addition, rivaroxaban did not reduce cardiac dysfunction in PAR-2−/− mice.

Likewise, in a similar mouse model of myocardial infarction induced by permanent ligation of LAD, PAR-2 deficiency attenuated heart remodeling and improved heart function independently of its contribution to the size of the initial infarct.[51] Thus, hypothetically, inhibition of the factor Xa-PAR-2 pathway may minimize cardiac injury and dysfunction after myocardial infarction; see Figure 3.

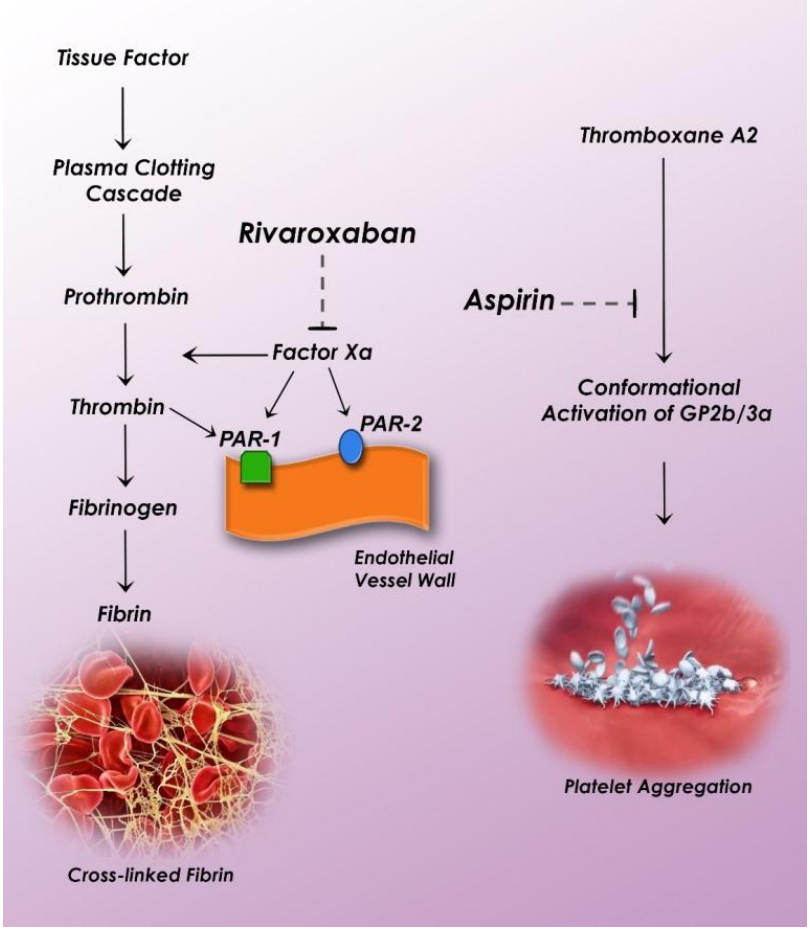

Figure 1: The figure depicts the targets of rivaroxaban and aspirin to inhibit blood coagulation and platelet aggregation during and after thrombus formation.

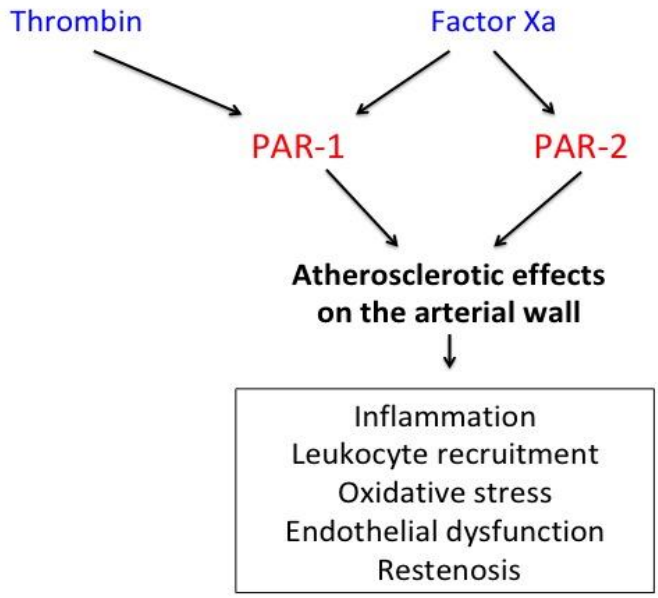

Figure 2: Representation of cellular locations of PAR-1 and PAR-2 and the potential effects of thrombin- or factor Xa-mediated PAR activation on the arterial wall and the heart, and the resulting contribution to atherosclerosis.

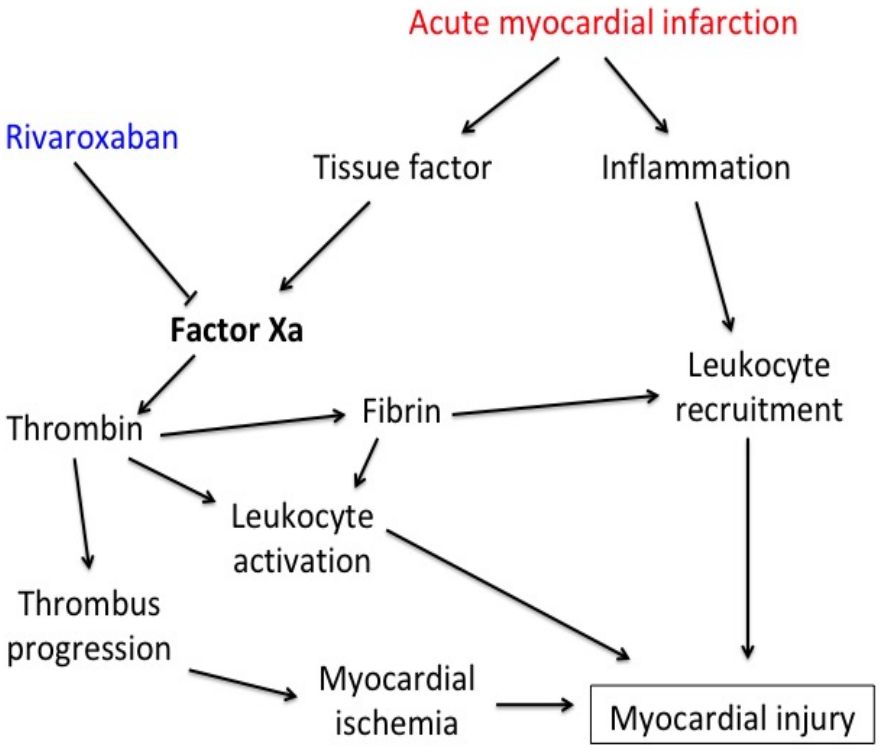

Figure 3: Rivaroxaban potentially reduces myocardial injury after an experimental myocardial infarction by distinct pathophysiological mechanisms.[32]

CONCLUSION

Coagulation proteins, such as factor Xa, possess an important participation in the onset of atherothrombotic events in patients with established atherosclerotic disease. In the process of atherothrombosis, vascular inflammation as well as the generation of thrombin facilitates fibrin production and platelet activation. Factor Xa-mediated PAR activation, in part, mediates this atherothrombotic process. Experimental and clinical data strongly suggest that the inhibition of factor Xa by rivaroxaban, and subsequent PAR inactivation, induces significant vascular protection. These findings have important implications on future directions of the management of patients with CAD/PAD. Mainly, on patients that have high residual risk of atherothrombotic complications, despite standard therapy with antiplatelet.

Importantly, the pleiotropic effects postulated by inhibition of factor Xa by rivaroxaban, and thereby PAR inactivation, in the human vasculature need yet to be elucidated. Prospective investigations are warranted to evaluate the role of thrombi-inflammation attenuation in the management of atherosclerotic disease.

Abbreviations

CAD, coronary artery disease
PAD, peripheral artery disease
PAR, protease-activated-receptor
COMPASS trial, Cardiovascular Outcomes for People Using Anticoagulation Strategies trial
VKAs, vitamin K antagonists
VTE, venous thromboembolism
DVT, deep vein thrombosis
PE, pulmonary embolism
PCI, percutaneous coronary intervention
VSMC, vascular smooth muscle cell
LAD, left anterior descending artery

Declarations

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Competing interesting. The authors have no conflicts of interest.

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