Dual Pathway Inhibition of Coagulation and Inflammation With Rivaroxaban: A New Therapy Paradigm Against Atherosclerosis

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This Commentary relates to the article by V. Russo et al on pages 129-133.

Right is right even if no one is doing it; wrong is wrong even if everyone is doing it.

Saint Augustine

Atherosclerosis is the chronic pathophysiological substrate for coronary artery disease (CAD) and peripheral artery disease (PAD), and its many clinical consequences, which include chronic ischemic syndromes, acute cerebral or cardiac ischemia, as well as sudden cardiac death.[1] This condition is characterized by endothelial injury, low-grade inflammation, lipid accumulation, and plaque formation within the intima of the vessel wall.[2] The rupture of an atherosclerotic plaque is a predominant cause of acute atherothrombotic events and consequent vessel occlusion, leading to cardiovascular (CV) events, and indeed, CAD and PAD share a common pathophysiology and risk factors (eg, smoking, dyslipidemia, hypertension, and diabetes mellitus).[3,4]

Clinical guidelines for the management of CAD and PAD have been developed by several societies and organizations. The main goals in these guidelines are to provide symptom relief, to salvage limbs in patients with PAD, and to prevent future CV events. Recommendations for the secondary prevention of CV events include the control of modifiable CV risk factors (eg, diabetes mellitus, hypertension, and smoking) through lifestyle changes and pharmacologic therapy. Moreover, the use of antithrombotics is recommended for most patients.[5]

Coagulation processes and atherosclerogenesis are closely related by the presence of specific coagulation proteins inside the atherosclerotic lesion, such as tissue factor (TF) and factor VII (FVIII). These factors are expressed on macrophage and vascular smooth muscle cell membrane within the atherosclerotic lesion, and they participate in proatherogenic processes such as inflammation and angiogenesis.[6] Moreover, the interaction between these 2 factors constitutes the catalytic complex for thrombin and fibrin synthesis.[7] Furthermore, the concomitant presence of proinflammatory molecules (eg, tumor necrosis factor-α [TNF-α], interleukin-1, and interleukin-6 [IL-6]) may enhance this procoagulant condition because anticoagulant proteins such as thrombomodulin and the endothelial cell protein C receptor are downregulated by inflammation.[4] In particular, IL-6 is strongly associated with CV events. Thus, increased coagulation activity, possibly due to a chronic inflammatory state, may reduce plaque stability and increase the risk of plaque rupture.

Rivaroxaban is an oral, selective direct inhibitor of factor Xa. Numerous clinical trials have analyzed the efficacy and safety of rivaroxaban in the treatment of thromboembolic

Received for publication October 19, 2022; accepted October 22, 2022.

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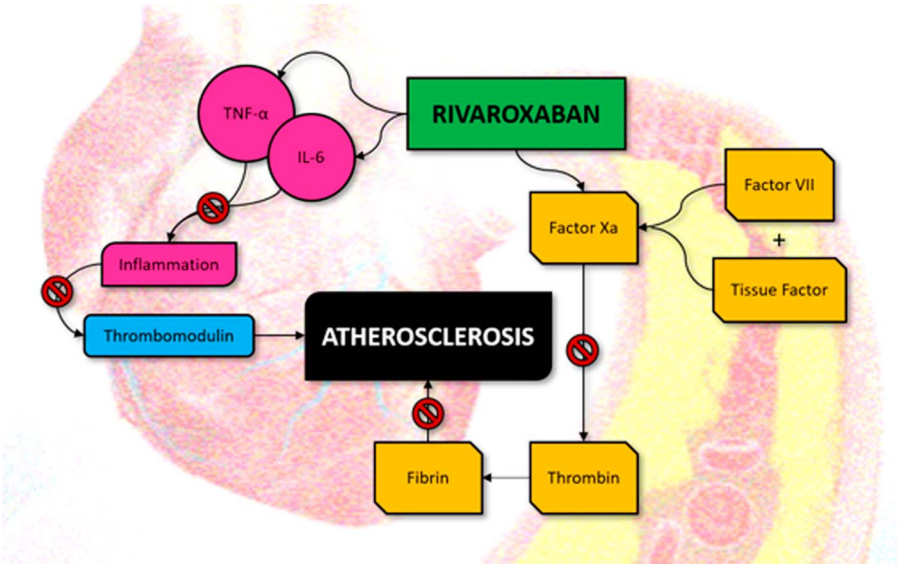

FIGURE 1. Pleiotropic anti-inflammatory and anticoagulant effects of rivaroxaban on atherosclerosis. IL = interleukin; TNF = tumor necrosis factor.

events, confirming its therapeutic window and predictable anticoagulant effect.[8] Moreover, some preclinical evidence on ApoE$^{-/-}$ mice showed that rivaroxaban may induce atherosclerotic lesion stabilization by reducing serum levels of proinflammatory cytokines such as TNF-α and IL-6, in addition to inhibiting the activation of macrophages.[9] Furthermore, treatment with rivaroxaban resulted in a significant reduction in levels of biomarkers of coagulation and inflammation in patients with atrial fibrillation (AF) on rivaroxaban therapy in a clinical setting.[10]

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was designed to test the hypothesis that rivaroxaban in combination with aspirin or by itself is more effective than aspirin alone in preventing cardiovascular events in patients with stable atherosclerotic vascular disease.[11] In their prospective observational study, Russo et al enrolled patients with an established diagnosis of CAD and/or PAD based on COMPASS study inclusion and exclusion criteria. Eligible patients were treated with aspirin (ASA) 100 mg once daily (OD) and rivaroxaban 2.5 mg twice daily (TD). Although rivaroxaban resulted in a reduction in levels of inflammatory biomarkers in patients with atrial fibrillation (AF), little to no data are available on the anti-inflammatory effects of rivaroxaban 2.5 mg TD and aspirin 100 mg OD in patients with CAD or PAD to date.

Russo et al[12] showed that in the study population dual pathway inhibition with low dose rivaroxaban and aspirin in patients with established diagnosis of CAD and/or PAD was associated with a reduction in serum levels of some inflammation markers, such as IL-6 and fibrinogen. Moreover, this combined therapy showed little to no impact on hemoglobin values and renal function markers. These findings support the hypothesis of a pleiotropic anti-inflammatory effect of rivaroxaban, in addition to its anticoagulant effect, and partially explain the positive results of COMPASS trial for reduction of cardiovascular events in patients with stable atherosclerotic vascular disease. The association of anticoagulant and antiplatelet drugs at the standard dose has always been contraindicated because it increased bleeding risk without actual benefits for reducing thrombotic risk. Nevertheless, the COMPASS trial put this combination therapy into a new perspective, by adjusting the dose of rivaroxaban and by highlighting its anti-inflammatory properties, fundamental to reduce the procoagulant state. In this issue, Russo et al applied the criteria expressed in the COMPASS trial and partially explained why such dual pathway inhibition holds the promise of the reduction of cardiovascular risk in patients with CAD or PAD.

It is then now clear that these preliminary results may suggest a physiopathological rationale for using dual pathway inhibition treatment in patients with myopericardial inflammatory diseases or oxidative stress–based cardiovascular disease, such as atherosclerosis.

REFERENCES

1. Saglietto A, Manfredi R, Elia E, et al. Cardiovascular disease burden: Italian and global perspectives. *Minerva Cardiol Angiol.* 2021;69:231–240.
2. Ambrosini S, Mohammed SA, Costantino S, et al. Disentangling the epigenetic landscape in cardiovascular patients: a path toward personalized medicine. *Minerva Cardiol Angiol.* 2021;69:331–345.
3. Bauersachs R, Zeymer U, Brière JB, et al. Burden of coronary artery disease and peripheral artery disease: a literature review. *Cardiovasc Ther.* 2019;2019:8295054.
4. Borissoff JI, Heeneman S, Kilinç E, et al. Early atherosclerosis exhibits an enhanced procoagulant state. *Circulation*. 2010;122:821–830.
5. Montalescot G, Sechtem U, Achenbach S, et al; ESC Committee for Practice Guidelines. ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34:2949–3003.
6. Wilcox JN, Smith KM, Schwartz SM, et al. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci U S A.* 1989;86:2839–2843.
7. Smith EB, Thompson WD. Fibrin as a factor in atherogenesis. *Thromb Res.* 1994;73:1–19.
8. Turpie AG, Kreutz R, Llau J, et al. Management consensus guidance for the use of rivaroxaban–an oral, direct factor Xa inhibitor. *Thromb Haemost.* 2012;108:876–886.

9. Hara T, Fukuda D, Tanaka K, et al. Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice. *Atherosclerosis*. 2015;242:639–646.
10. Kirchhof P, Ezekowitz MD, Purmah Y, et al. Effects of rivaroxaban on biomarkers of coagulation and inflammation: a post hoc analysis of the X-VeRT trial. *TH Open*. 2020;4:e20–e32.
11. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330.
12. Russo V, Fabiani D, Leonardi S, et al. Dual pathway inhibition with rivaroxaban and aspirin reduces inflammatory biomarkers in atherosclerosis. *J Cardiovasc Pharmacol.* 2022. In press.