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EDITORIAL COMMENT

Factor Xa Inhibition, A New Strategy for Prevention of Adverse Cardiac Remodeling in Early Stages?*

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Coagulation factors are known to play a role in wound healing by stimulating fibroblasts and are associated with tissue fibrosis (1). Factor Xa (FXa) is the key serine protease of the coagulation cascade at the point of convergence of the intrinsic and extrinsic pathways leading to the formation of thrombin and is the established target of anticoagulation therapy (1). Direct oral anticoagulants targeting FXa are widely used in clinical practice for prevention and treatment of thrombotic events. Increasing evidence suggests that FXa exerts nonhemostatic cellular effects that are mediated mainly through protease-activated receptors-1 (PAR-1) and PAR-2, which are expressed in cardiac myocytes and fibroblasts (1,2). Activation of PAR-1 and PAR-2 have been implicated in pathophysiological conditions such as atherosclerosis, inflammation, and fibrosis, raising the possibility of pleiotropic antifibrotic and anti-inflammatory cardioprotective effects of direct oral anticoagulants targeting FXa (1,2).

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In this issue of *JACC: Basic to Translational Science*, Guo et al. (2) demonstrate that in an experimental mouse model, cardiac expression of FXa was increased following transverse aortic constriction and that low dose rivaroxaban, a direct oral anticoagulant, attenuated cardiac inflammation, hypertrophy, and fibrosis. These were accompanied by favorable changes in left ventricular (LV) diastolic function, LV remodeling, and hypertrophic gene and fibrosis markers (2). In accord with former publications (3,4), Guo et al. (2) also demonstrated that FXa signaling and cardiomyocyte hypertrophy required both PAR-1 and -2 receptors. The novel findings of this study are that FXa is produced locally by the cardiac myocytes and fibroblasts in response to stress, that low-dose FXa inhibition, at a dose that does not affect systemic anticoagulation, can reduce LV hypertrophy and fibrosis, attenuate maladaptive ventricular remodeling, and improve LV diastolic function following pressure overload.

These findings further add to the growing body of evidence demonstrating the important role of FXa in maladaptive cardiac hypertrophy, fibrosis, and remodeling beyond its effects on coagulation (2–4). As shown by Guo et al. (2), PAR-1 and -2 receptors, which are required for FXa signaling, are expressed by a variety of cardiac cell types including cardiomyocytes and cardiac fibroblasts. Other studies have shown that these receptors also contribute to the infarct size, induce cardiomyocyte hypertrophy, result in proliferation of cardiac fibroblasts, and are identified as important targets for proinflammatory and fibroproliferative states (2–4). Indeed, PAR-2$^{-/-}$ mice have been shown to exhibit less cardiac dysfunction and deleterious remodeling after cardiac injury (3). FXa inhibition by rivaroxaban has also been shown to inhibit various inflammatory signal pathways, which are known to be activated in heart failure (HF) (1–3). In experimental models of pressure

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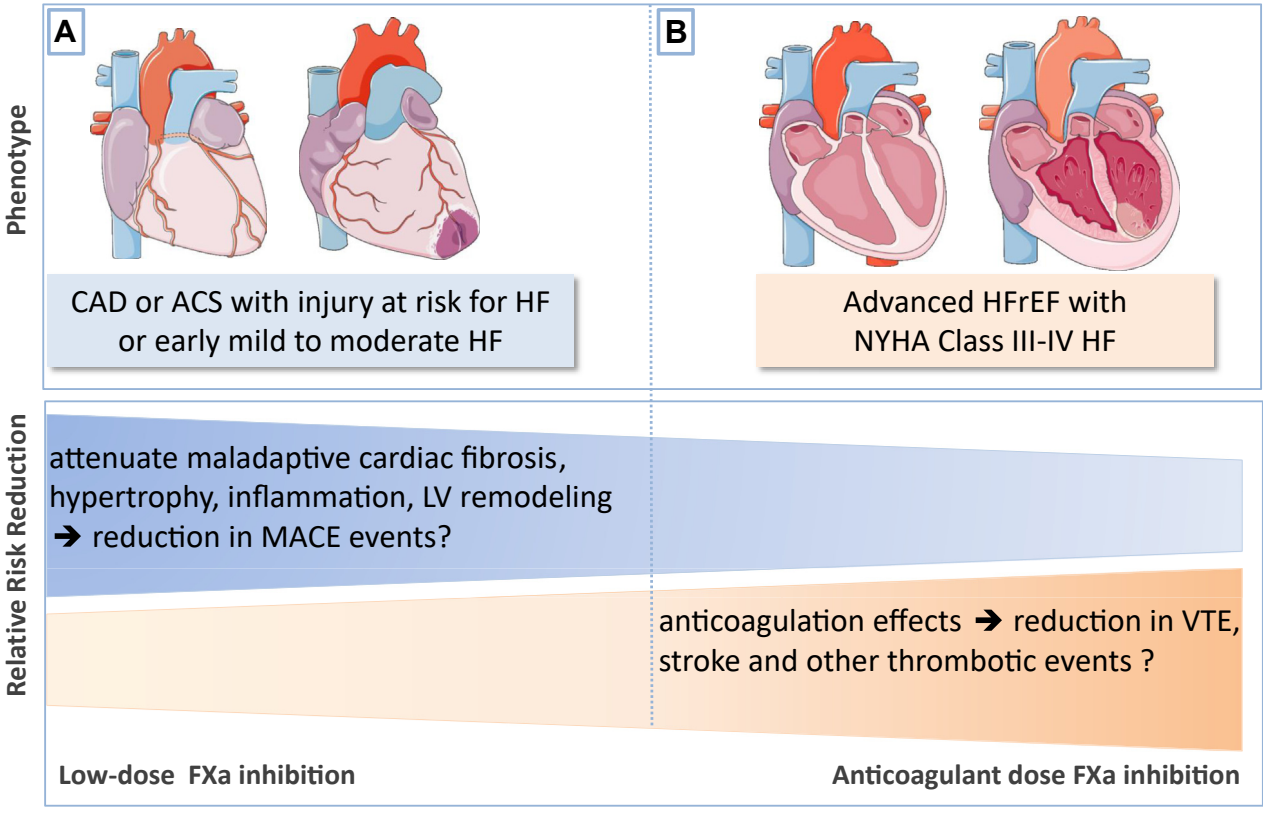
FIGURE 1 Conceptual Diagram of the Beneficial Effects of Low-Dose FXa Inhibition



Conceptual diagram of the beneficial effects of low-dose factor Xa (FXa) inhibition **(blue),** which may result in reduction in major adverse cardiovascular events (MACE) by attenuation of maladaptive cardiac fibrosis, hypertrophy, inflammation, and left ventricular (LV) remodeling in early phenotypes such as patients with coronary artery disease (CAD), acute coronary syndrome (ACS) without or with mild to moderate heart failure (HF) **(A),** but not in advanced phenotypes of heart failure with reduced ejection fraction (HFrEF) and New York Heart Association (NYHA) functional classes III and IV HF **(B).** In advanced HF phenotypes, rather than a low dose, an anticoagulant dose of FXa inhibition **(orange)** may be important to reduce venous thromboembolic events (VTE), thrombotic events, and stroke, which awaits validation by large-scale clinical trials. Heart clipart images adapted from Servier Medical under a Creative Commons Attribution 3.0 Unsupported License (https://creativecommons.org/licenses/by/3.0/).

overload, overexpression of inflammatory mediators was reversed with rivaroxaban, accompanied by reversal of atrial and ventricular remodeling and reduction of atrial fibrillation burden (4).

Importantly, these beneficial effects appear to be time- and phenotype-sensitive. In a coronary infarct mouse model, rivaroxaban attenuated cardiac dysfunction and infarct expansion only when rivaroxaban was administered immediately after coronary ligation, but not when administered several days after surgery, underlining the importance of presence of FXa inhibition at the time of cardiac injury (3). These findings may provide some insights into the disparate outcomes seen with low-dose FXa inhibition in recent clinical trials in different phenotypes of patients (5–8).

In the recent clinical trials, lower doses of rivaroxaban in combination with antiplatelet agents, have been reported to reduce the risk of death from cardiovascular causes, myocardial infarction, and stroke in patients with acute coronary syndrome or stable coronary artery disease (5–7), but not in patients with a recent worsening HF with reduced ejection fraction (EF)(8).

In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial (6),

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patients with stable atherosclerotic disease with no HF or mild to moderate HF were enrolled, but patients with New York Heart Association functional class III or IV HF or LVEF <30% were excluded. By post hoc analysis, in the subset of patients with HF, compared with those patients without HF, rivaroxaban and aspirin resulted in a similar relative, but higher absolute risk reduction in major adverse cardiovascular events and mortality events. Results were similar in subgroups of patients with EF <40% versus ≥40% (7).

Combination therapy of rivaroxaban with aspirin was also tested in the ATLAS ACS 2 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome) trial, in which patients were enrolled early after acute coronary syndrome (5). ATLAS ACS 2 demonstrated significant reductions in major adverse cardiovascular events and all-cause mortality with low-dose rivaroxaban. In the subset of patients with HF at randomization, major adverse cardiovascular events benefits were amplified, with a 41% relative risk reduction compared with risk reduction for patients with and without HF who took the placebo. In addition, patients with HF had a 57% relative mortality reduction, with low-dose rivaroxaban compared with placebo (5).

Compared with these studies, lack of benefit with low-dose rivaroxaban in the COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial (8) in patients with coronary artery disease, low EF (≤40%), and recent HF exacerbation was surprising, and was attributed to the advanced HF phenotype with higher event rates related to cardiovascular and HF mortality than antithrombotic event rates.

Although the patient populations in COMMANDER HF, ATLAS ACS-2, and COMPASS were somewhat different, when taken together, the results suggest that low-dose rivaroxaban appears to preferentially benefit those patients with early, mild to moderate HF who do not have decompensated HF or advanced HF with reduced EF (5–8). Experimental studies also suggest that anti-Xa treatment strategy may have a role in early stages of myocardial injury and LV dysfunction (3). These findings imply that advanced HF with significant LV dysfunction may be too late for antifibrotic and anti-inflammatory effects of these agents to result in meaningful reductions in clinical outcomes.

In summary, FXa is expressed by cardiac cell types including cardiomyocytes and cardiac fibroblasts and appears to play an important role in maladaptive cardiac hypertrophy, fibrosis, and remodeling beyond its effects on coagulation (1,2). Experimental evidence support the role of low nonanticoagulation dose FXa inhibition in patients who are at risk or early HF, possibly with ongoing myocardial injury, in whom early strategies to halt or prevent maladaptive signaling for fibrosis, inflammation, or remodeling may be cardioprotective (1–4) (**Figure 1**). Lack of benefit in clinical trials with decompensated HF with reduced EF patients (8) suggest that in more advanced chronic HF patients with possibly "burnt-out" myocardium, with significant myocyte loss, hypertrophy, fibrosis, and remodeling, low-dose FXa inhibition may not be adequate to halt or change maladaptive signaling and might result in significant cardiovascular benefit. In such patients, the antithrombotic doses of FXa inhibition may be more important for reduction of thrombotic events, but this approach awaits validation from prospective large-scale studies (**Figure 1**). Finally, the timing of FXa inhibition needs attention in further studies. It is not clear whether FXa inhibition needs to be started early during myocardial injury before LV dysfunction ensues in stage A HF or whether it can prevent or attenuate maladaptive remodeling in stage B or early stage C HF with mild to moderate HF symptoms.

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