Treating the Unstable Atherosclerotic Plaque by Targeting Activated Factor X

– Anticoagulation and Beyond –

Julian Friebe, MD; Marco Witkowski, MD; Ursula Rauch, MD

During the past decades several attempts have been made to reduce cardiovascular morbidity and mortality. Unfortunately, a high disease burden still covers the developed world and is rapidly emerging in the developing countries, with all the characteristics of an epidemic. Despite intensive work in trying to prevent post-event pathological remodeling and many efforts made to improve patients' outcomes, the data are sobering.^{1,2} Therefore, prevention of major

cardiovascular events has to be the primary focus.

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Atherosclerosis is characterized as a chronic inflammatory disease. The complex network of both innate and adaptive immunity plays a significant role in the development and progression of atherosclerotic plaques. Rupture or erosion of these

Figure. Potential targets of protease-activated receptors (PAR) 1 and 2 in the context of plaque destabilization. DC, dendritic cell; Mφ, macrophage; TF, tissue factor.

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Division of Cardiology, Charité - University Medicine Berlin, Berlin, Germany

Mailing address: Ursula Rauch, MD, Division of Cardiology, Charité - University Medicine Berlin, CBF, Hindenburgdamm 30, 12200 Berlin, Germany. E-mail: ursula.rauch@charite.de

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plaques is the primary underlying cause of the superimposed luminal thrombosis that is responsible for the onset of acute coronary syndrome (ACS). During the acute phase of ACS, anticoagulants such as fondaparinux, in combination with platelet inhibitors, are used to reduce thrombus-related events. Activated factor X (FXa) has a central role in the hemostatic cascade by promoting the production of thrombin.¹⁻³

In this issue of the Journal, Zuo et al conclude that the selective FXa inhibitor, fondaparinux, promotes the stability of atherosclerotic lesions in apolipoprotein E-deficient (ApoE^{-/-}) mice. Interestingly, they observed this effect as independent of the ability of fondaparinux to reduce thrombin activity itself.⁴

Previous studies proclaimed that besides its effects on hemostasis, FXa mediates a complex downstream cascade, directly or indirectly effecting endothelial, tissue- or immunological processes.^{5,6} In their study, Zuo et al argue that reduced endothelial activation might reduce immune cell infiltration, thereby removing the inflammatory burden (indicated by reduced inflammatory cytokines) and finally leading to plaque stabilization. Indeed, they were able to show that in ApoE^{-/-} mice, fondaparinux decreased endothelial adhesion molecules, reduced immune cell content and suppressed the expression of inflammatory cytokines within atherosclerotic plaques. Those authors also suggest a role of protease-activated receptors (PARs) 1 and 2 in this process.⁴ PAR1 and PAR2 belong to a family of G-protein-coupled receptors and are expressed on a wide range of cells. They have been shown to be involved in several physiological and pathological immunological and cardiovascular processes. Because of their interaction and receptor dimerization it is not easy to separate both pathways from each other and ascribe a precise mechanism to either PAR1 or PAR2.⁷ In a mouse model of CVB3-induced myocarditis, PAR1 and PAR2 differentially regulated the innate immune response via TLR3.^{5,7,8} Therefore, PARs are assumed to be the link between coagulation and inflammation (Figure).⁹

Immune cell infiltration of the arterial wall is the initial step in the inflammatory cascade. And it has been shown that rupture-prone plaques are associated with increased inflammation.^{1,2} But despite its effect on plaque inflammation and stability, Zuo et al were unable to show that fondaparinux remarkably decreased atherosclerotic progression in ApoE^{-/-} mice.⁴

One explanation might be that they administered fondaparinux at a point where plaques had already developed. As this reflects a more clinical approach, such as in ACS events, it would be of interest whether fondaparinux might be also be able to prevent plaque formation. Evidence comes from a study where 6-week-old ApoE^{-/-} mice were parallel fed with a pro-atherosclerotic Western diet and the FXa inhibitor rivaroxaban. During that study, Hara et al were able to show a resulting decrease in plaque burden and they also suggested a PAR-mediated effect.¹⁰ The COMPASS trial will now evaluate whether rivaroxaban plays a role in secondary prevention of major cardiovascular events in patients with known coronary or peripheral artery disease.¹¹

A main limitation of studies using atherosclerosis models in mice is the comparison of merely plaque development in mice that have been fed a Western diet and unstable plaques in humans where exacerbation is causing ACS. Of course there exist several evaluated indicators categorizing plaque as rupture prone, but we have to be careful in translating these data directly from mice to human and vice versa.¹¹ Furthermore, it has to be mentioned that neither the plaque burden nor immune cell infiltration itself are critical. The qualitative plaque composition and its stability seem to be the most important factors. Therefore, we have to be careful comparing inflammation with

disease progression, because the system is much more complex.

Interestingly, despite its inability to quantitatively influence the plaque load in mice, fondaparinux significantly increases the fibrous cap thickness and decreased necrotic core ratio, suggesting a plaque stabilizing capacity. In this context the authors of the present study highlighted the role of extracellular matrix (ECM) modulation in atherosclerotic plaques through fondaparinux application by collagen accumulation.⁴ This raises the question whether other organs might be affected by enhanced collagen deposition as well and if a benefit in plaque stability would have adverse effects by promoting profibrotic processes; for example, in the heart muscle. We were able to show that FXa inhibition by fondaparinux improves myocardial function during CVB3-induced myocarditis in mice.⁹ Further evidence for a protective role of FXa inhibition in ECM remodeling processes comes from studies in which rivaroxaban was able to positively influence post-infarct remodeling; further trials, such as COMMANDER HF, are ongoing.¹¹⁻¹³ This just illustrates the complex character and interaction of coagulation and inflammatory mechanisms by FXa (Figure).

Other questions rising are the right timing, dosing and duration of FXa inhibitor therapy. During ACS, a once initiated thrombotic stimulus at the index event may persist for a longer period and promote long-lasting hemostatic activation.¹⁻³ As therapy with anticoagulants in current clinical practice is mainly restricted to the acute phase of ACS, an inadequately controlled pro-coagulant state might be the consequence, suggesting a need for prolonged FXa inhibition.³

The main problem that has to be discussed is the potential increase in major bleeding complications. Recent randomized controlled trials such as ATLAS ACS-TIMI 51 have shown that the addition of new anticoagulants on top of standard therapy in the setting of ACS was able to reduce ischemic events, although a dose-dependent increase in bleeding complications could be observed. As a result, rivaroxaban has recently been approved for secondary prevention in adult patients who have had biomarker-confirmed ACS. In contrast, treatment with dabigatran resulted in a higher myocardial infarction rate - at least in some studies. Thus far, the interactions with the patient's immune system have not been understood. However, fondaparinux has been shown to be a promising therapy concerning efficacy and safety in ACS and was recommended as a first-choice anticoagulant in the current ACS guidelines of the ESC.^{11,14,15} Zuo et al used a relatively high concentration of 5 mg/kg once daily in mice compared with the 2.5 mg once daily recommended in the guidelines.⁴ Until now it has not been known if the effects of FXa-inhibitors with doses that are applied during ACS or in the context of prevention are primarily related to thrombin inhibition or rather secondarily via inhibition of PAR-mediated plaque destabilizing pathways. Still, a proper balance between the anti-ischemic effects and bleeding risk is crucial.

Taking these data together, FXa inhibitors seem to be ideal therapeutic candidates during ACS, not least because of their ascribed pleiotropic effects. The challenge of recent cardiac imaging is to accurately detect and discriminate vulnerable from stable plaques in vivo. Unfortunately, in vivo data of the plaque stabilization capacity of FXa inhibitors are missing.¹⁶ It remains open if potential plaque stabilization by FXa inhibitors in humans would also have effects on patients' outcomes. Based on this we conclude that further studies are necessary to identify the patients who are at a high risk of plaque rupture or erosion and might therefore benefit from FXa inhibition to primarily or secondarily prevent ACS.

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