

Factor XI inhibitors in adjunct to antiplatelet therapy: the ultimate dual-pathway inhibition?

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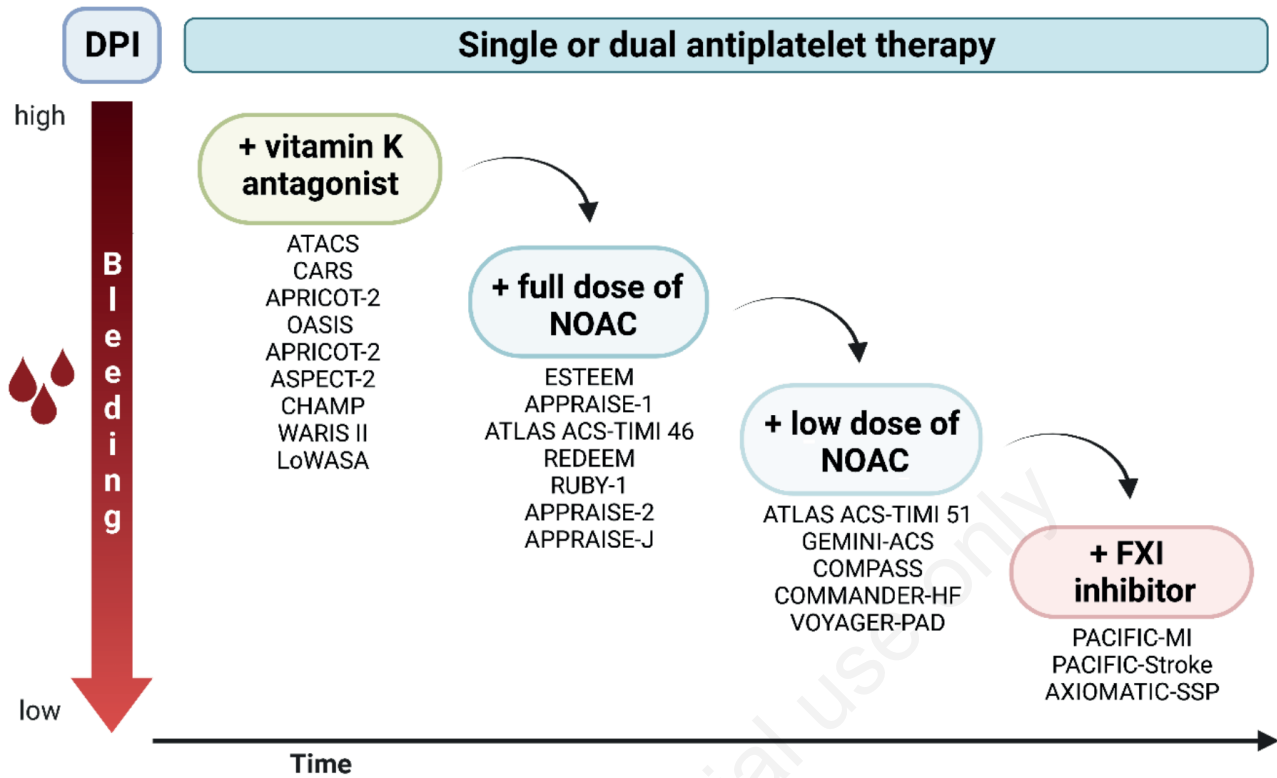
ABSTRACT

A strategy of oral anticoagulants (OAC) in addition to single or dual antiplatelet therapy, known as *dual-pathway inhibition* (DPI), has shown to reduce thrombotic events in patients with cardiovascular disease. However, despite its efficacy, its use in clinical practice has been hindered by the fact this strategy is also associated with increased bleeding, including major bleeding. The use of low dose direct oral anticoagulant (*i.e.* rivaroxaban 2.5 mg twice daily) on top of antiplatelet therapy has been associated with reduced bleeding, but some safety concerns still exists. The availability of a novel class of OACs selectively targeting the intrinsic coagulation pathway and potentially uncoupling thrombosis and hemostasis has sparked the interest towards the use of a new generation DPI strategy associated with enhanced safety. Several phase II trials using factor XI (FXI) inhibitors on top of antiplatelet therapy in patients with coronary artery or cerebrovascular disease have been recently published and others are under investigation. We here discuss the available evidence and future perspectives of DPI with FXI inhibitors in patients with cardiovascular disease.

Dual pathway inhibition

The persistence of elevated rates of ischemic recurrences, despite the use of antiplatelet therapy in patients with cardiovascular disease (CVD), together with the understanding of the pivotal role of coagulation factors on thrombo-inflammatory processes involved in the pathogenesis of atherosclerosis and its complications have represented the rationale for the use of oral anticoagulants (OAC) in addition to standard antiplatelet therapy, a strategy known as *dual-pathway inhibition* (DPI).^{1,2} Over the years, a DPI strategy has been tested using different OAC regimens (Figure 1). Thus far, a DPI with a low dose of a direct OAC (DOAC, *i.e.* rivaroxaban 2.5 mg twice daily) has been associated with the most favorable safety and efficacy profile, although the reduction of ischemic events occurred at the expense of increased major bleeding, underscoring the need to identify alternative targets.³

The recent development of a novel class of OACs, selectively targeting the intrinsic coagulation pathway, has been proposed as an opportunity to uncouple thrombosis and hemostasis.⁴ To this extent, several molecules with different routes of administration and mechanisms of action, ranging from gene silencing to the direct inhibition of factor XI (FXI) by monoclonal antibody or small molecules have been developed over the last few years.^{5,6} Early phase II trials have suggested FXI inhibitors to be an effective and potentially safer strategy compared with low-molecular-weight-heparin or a DOAC among patients undergo-



DPI, dual-pathway inhibition; NOAC, novel oral anticoagulants; FXI, factor XI.

Figure 1. Temporal evolution of dual-pathway inhibition.

ing total knee arthroplasty or with atrial fibrillation (AF), respectively.^{5,7} The favorable safety profile of this novel class of OAC has stimulated interest towards their use in high risk scenarios, including those that have traditionally exposed patients to an increased risk of bleeding such as in patients treated with other antiplatelet agents (*i.e.*, DPI). The first phase II trials using a DPI strategy with FXI inhibitors have been recently published and others are under investigation.

Dual pathway inhibition with FXI inhibitors

Specifically, PACIFIC-MI randomized 1601 patients with recent (<5 days) acute myocardial infarction treated with standard dual antiplatelet therapy (DAPT, prasugrel/ticagrelor 80%, clopidogrel 20%) to oral asundexian 10, 20, or 50 mg or placebo once-daily (od). Of note, asundexian 20 and 50 mg correspond to the therapeutic dose used for stroke prevention in patients with AF. At 1 year, there was no difference in ischemic or bleeding events with any dose of asundexian compared with placebo.⁸ PACIFIC-Stroke found similar results at 26 weeks in 1880 patients with acute (<48 hours) non-cardioembolic ischemic stroke randomized to either oral asundexian 10, 20, or 50 mg or placebo od. All patients were treated with standard of care antiplatelet therapy (aspirin alone 57%, DAPT with clopidogrel 43%, lasting in average 70 days).⁹ Finally, no differences in

bleeding and ischemic events at 90 days were also found in the AXIOMATIC-SSP trial randomizing 2366 patients with non-cardioembolic ischemic stroke or transient ischemic attack (TIA) to milvexian at the dose of 25 mg od, 25 mg bis in die (bid), 50 mg bid, 100 mg bid, 200 mg bid or placebo. Background antiplatelet therapy consisted in DAPT with clopidogrel for the first 21 days followed by aspirin alone.

Although these phase II trials were underpowered for clinical outcomes, especially efficacy events, and larger phase III trials are warranted to support the efficacy of DPI with FXI inhibitors in different clinical scenarios, the observed safety profile – including in patients treated DAPT with prasugrel/ticagrelor – in the individual trials appears promising. Nevertheless, a recent meta-analysis pooling data from phase II trials and performing a pre-specified analysis according to the dose of the FXI inhibitor used on top of antiplatelet therapy found that, compared with placebo, DPI may increase the risk of bleeding, including major bleeding, especially when high doses are used.¹⁰ Indeed, large scale phase III clinical testing will allow to better unravel both safety and efficacy data associated with DPI using FXI inhibitors in combination with standard-of-care antiplatelet treatment regimens.^{5,7} The LIBREXIA-ACS trial (NCT05754957) is aiming at randomizing 16,000 ACS patients receiving antiplatelet therapy standard-of-care to either milvexian orally or placebo and will provide important information on the safety and efficacy of DPI in the ACS setting. Indeed, an important component of this trial

will be the understanding of the safety and efficacy of milvexian according to antiplatelet treatment regimens which may vary over the course of the study time course (up to 42 months) in line with recent updates in the field.¹¹ Similarly, other studies will be evaluating DPI using FXI inhibitors in combination with standard-of-care antiplatelet treatment regimens in other clinical setting. Among patients with recent acute ischemic stroke or high-risk TIA, LIBREXIA-STROKE (NCT05702034) will randomize 15,000 patients to either milvexian or placebo and OCEANIC-STROKE (NCT05686070) will randomize 9300 patients to either asundexian or placebo, in addition to single or DAPT.¹²

Conclusions

Overall, a DPI strategy using a FXI inhibitor in adjunct to antiplatelet therapy may represent a paradigm shift for the treatment of high-risk patients with cardiovascular and cerebrovascular disease, with the potential to reduce the risk of thrombotic complications while mitigating the risk of bleeding which has been the major drawback of more aggressive antithrombotic combination strategies. Ongoing trials will unravel the safety and efficacy of FXI inhibitors in adjunct to antiplatelet therapy in various clinical scenarios and define whether this will constitute the ultimate DPI strategy.

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