Editorial to accompany Rao et al

Factor XIa inhibition – a novel alternative antithrombotic strategy for high-risk ACS patients?

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Despite revascularisation and optimal secondary prevention, including dual antiplatelet medication (DAPT), patients with acute coronary syndrome (ACS) remain at risk of recurrent ischemic events, with up to 7% risk of recurrent myocardial infarction at 3 years.[1] To address this residual risk, prior studies have investigated the benefit of increasing the intensity of antithrombotic medication, through the addition of an oral anticoagulant (Factor Xa inhibitor or vitamin K antagonist) to antiplatelet therapy.[2, 3] While studies have generally shown a significant reduction in ischemic events with this approach, it came at a significant cost of excess major haemorrhage. Even the addition of very low dose rivaroxaban at 2.5 mg or 5 mg twice daily to DAPT in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2- TIMI 51) study was associated with a significantly increased risk of major bleeding including intracranial haemorrhage.[2] Thus, there remains an important unmet need for an antithrombotic agent which reduces ischemic risk without increasing bleeding, especially where dual pathway inhibition (especially with increasingly potent antiplatelet agents) is increasingly considered to reduce arterial thromboembolism.[4]

Asundexian is a novel, orally bioavailable inhibitor of FXIa.[5] Factor XI (FXI) deficiency in humans and experimentally-induced in animals is associated with reduced risk of ischemic stroke and venous thromboembolism, but unlike Factor VIII or Factor XI deficiency, spontaneous bleeding is rare and bleeding in response to trauma or surgery is much milder. Interestingly, a recent retrospective cohort study reported that when matched to a general population, patients with any FXI deficiency are at higher risk of severe bleeding (adjusted HR 2.56, 95% CI 1.13 – 5.81) and clinically relevant non-severe bleeding (adjusted HR 1.45, 95% CI 1.08-1.97).[6] Most cases were post-procedural hence highlighting low likelihood of spontaneous bleed; however, when stratified by severity of deficiency, partial FXI deficiency was associated with an increase in severe bleeding whereas severe FXI deficiency was not, further highlighting the observed differences may be due to potential overlaps between haematological conditions rather than observing a dose related FXI deficiency response[6.]

Factor XIa inhibition therefore appears a potentially attractive avenue to achieve additional antithrombotic effect without compromising haemostasis[7, 8]. In the recently published phase 2 trial in patients with atrial fibrillation, asundexian was associated with significantly lower rates of major bleeding compared with apixaban, with near complete FXIa inhibition. [9] Other Factor XIa inhibitors such as IONIS-416858 and AB023 are in development, or tested in various clinical settings.[10]

In this issue of Circulation, the investigators of the PACIFIC-AMI trial report on the pharmacodynamics, safety and efficacy of adding asundexian to DAPT in patients with a recent myocardial infarction.[11] In this phase 2, randomised double-blind trial, patients with ACS considered at high ischemic risk (defined as at least one of age ≥65 years; prior MI; prior peripheral arterial disease; diabetes mellitus; prior coronary artery bypass grafting) and without increased bleeding risk, were randomised within 5 days of the index ACS event to asundexian 10, 20 or 50 mg or placebo once daily for up to 12 months. The majority of patients received prasugrel or ticagrelor as the $P2Y_{12}$ inhibitor, in addition to aspirin, and nearly all patients underwent revascularisation with PCI.

Whilst asundexian achieved dose-dependent inhibition of FXIa, with >90% inhibition with the 50mg dose, there was no difference in the main safety outcome of Bleeding Academic Research Consortium type 2, 3, or 5 bleeding comparing all pooled asundexian doses with placebo. In terms of the efficacy outcome of the composite of cardiovascular death, myocardial infarction,

stroke, or stent thrombosis, although there were numerically fewer events observed as asundexian dose increased, none of the asundexian groups had event rates lower than placebo.

The Phase II study is important, showing the apparent safety of asundexian in addition to DAPT in ACS, although the lack of signal for reducing ischemic events is disappointing. However, the apparent safety yet the numerically fewer ischemic events seen with the 50 mg asundexian dose is encouraging and suggests the need to properly evaluate the potential ischemic benefit of this dose. That would be best demonstrated in a population at high ischemic risk, and the population in PACIFIC-AMI with an average age of 68 years, with only half the patients experiencing ST-segment elevation, may not have been truly representative of that. Given the reassuring safety profile, a future large Phase 3 trial should focus on high ischemic risk patients, without excluding those considered at increased risk of bleeding. As the authors alluded to in their discussion, there may perhaps be a role in augmenting clinical outcomes in patients at both high bleeding *and* ischemic risk.

The study also raises a number of new questions. What is the optimal level of FXIa inhibition required to achieve desired outcomes? Is it all or nothing or can this be tailored to a patient's risk profile? What should the optimal treatment duration be? A short course to alleviate the initial highest risk period or given its relatively safe profile, even in addition to DAPT, a prolonged period of treatment beyond the first year of ACS? Could it be used as a substitute for conventional DAPT post ACS – single antiplatelet with FXIa inhibitor? If so, should that be aspirin or a $P2Y_{12}$ inhibitor? Would there be ethnic differences in sensitivity to this new class of drugs, particularly to the risk of bleeding? [12]

We congratulate the investigators in presenting this much-welcomed novel therapeutic agent as an addition to the antithrombotic armamentarium in ACS, which appears not to increase bleeding complications, a common shortfall with modern era antithrombotic therapy.[13] Although more data on both safety and efficacy are required, we can exercise cautious optimism in the application of Factor XIa inhibition in ACS and other therapeutic areas, offering patients potential tailored antithrombotic therapy commensurate with their risk profile. Indeed, the Factor XIa inhibitors are being investigated as thromboprophylaxis for stroke prevention in atrial fibrillation and secondary prevention of stroke.

As with all new drug therapies, more information leads to more questions. We look forward to future phase III studies using FXIa inhibition in ACS patients, to assess whether this therapeutic option can reduce thrombotic events in those at high ischemic risk, whilst avoiding excess bleeding.

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