Perspectives and Future Directions of Anticoagulant Therapy in Coronary Artery Disease Patients

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Abstract

Antiplatelet agents are routinely used to treat patients with chronic atherosclerotic coronary artery disease. Treatment with the addition of a low dose of rivaroxaban as dual-pathway inhibition (DPI) decreases ischaemic events at the expense of increased bleeding. At present, the balance between thrombotic and bleeding risks must be carefully weighed up when considering DPI. However, with the introduction of activated coagulation factor XI inhibitors, which have fewer bleeding effects, the use of DPI in patients with atherosclerotic cardiovascular diseases could be extended.

Keywords

Anticoagulation, atherosclerosis, thrombosis, antiplatelet

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The use of antiplatelet agents to prevent ischaemic events in atherosclerotic cardiovascular diseases is well established. Coagulation pathways are involved in platelet activation and contribute to thrombus formation irrespective of whether this is within the arterial or venous circulation. The usefulness of oral anticoagulants (OACs), particularly non-vitamin K antagonist OACs (NOACs), in atherosclerotic diseases has been investigated over the past decade.

The AFIRE study compared rivaroxaban alone with rivaroxaban in combination with an antiplatelet agent as an antithrombotic therapy in stable coronary artery disease (CAD) complicated by non-valvular AF.[1] NOAC alone was non-inferior to NOAC plus antiplatelet agents in terms of efficacy for preventing ischaemic events, and was superior in terms of safety regarding bleeding events.[1] For patients with CAD in the chronic phase complicated by AF or other indications for OAC, the guidelines strongly recommend an OAC/NOAC alone without antiplatelet agents.[2,3] These findings suggest that anticoagulation therapy can prevent atherosclerotic vascular events as well as thromboembolic events.

CAD and AF share many risk factors: hypertension, diabetes, sleep apnoea, obesity and smoking. Moreover, inflammation plays a causative role in both diseases. The number of patients with CAD who develop latent or paroxysmal AF will increase with societal ageing, even though patients may have sinus rhythm at baseline. Looking beyond AF, it seems rational to find a role for OAC/NOAC as an antithrombotic therapy for CAD patients without AF.

Bleeding events are significantly higher when NOACs are used in patients with CAD at the dosages indicated for AF. Among available NOACs, rivaroxaban at a lower-than-usual dose (2.5 mg twice daily) is the only one approved for the prevention of atherothrombotic cardiovascular events.

The ATLAS-TIMI study showed that adding a smaller dose of rivaroxaban to an antiplatelet agent for the secondary prevention of atherosclerotic cardiovascular events in patients with acute coronary syndrome (ACS) shortly after onset prevented the composite endpoint of cardiovascular death, MI and stroke.[4]

In the COMPASS study, dual-pathway inhibition (anticoagulation: low-dose rivaroxaban plus an antiplatelet) was effective in reducing ischaemic events in patients with stable, high-risk atherosclerotic vascular disease.[5] There was an increase in major and intracranial bleeding but no increase in fatal bleeding.

A meta-analysis of seven randomised controlled trials also showed that dual-pathway inhibition (anticoagulation: low-dose rivaroxaban plus an antiplatelet) was effective in reducing ischaemic events, albeit with increased bleeding, in patients with atherosclerotic vascular disease who were in sinus rhythm and for whom OAC/NOACs have no other indication.[6]

Asundexian, a novel NOAC, is a small molecule that selectively inhibits activated coagulation factor XI (XIa) and is rapidly absorbed orally with a half-life similar to that of conventional NOACs.

In the PACIFIC-AF trial, a phase II randomised controlled study designed to examine the incidence of bleeding during treatment and determine the optimal dose of asundexian in AF patients at risk of stroke, asundexian at dosages of 20 mg and 50 mg once daily was associated with a significantly lower bleeding rate than apixaban.[7]

The PACIFIC-AMI trial, presented at the 2022 European Society of Cardiology Congress, compared the pharmacodynamics, safety and efficacy of three asundexian dosages (10 mg/day, 20 mg/day and 50 mg/day) with a placebo in post-ACS patients treated with dual antiplatelet therapy (aspirin and a $P2Y_{12}$ inhibitor).[8] Asundexian reduced the activity of factor XIa in a dose-dependent manner, and this activity was almost completely inhibited by 50 mg/day of asundexian.

Dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) and triple therapy with added OAC/NOAC are associated with more bleeding events, which limits the duration of triple therapy from 1 week to up to 1 month after revascularisation for ACS.[3] However, patients treated with asundexian did not show an increase in the risk of bleeding at 1 year follow-up after ACS with triple therapy, and there were no further safety issues. Moreover, because there was no reduction in ischaemic events, efficacy was considered neutral.

Over the past decade, several new paradigms have arisen. Improvements in stent quality have reduced the frequency of stent thrombosis, and the advent of new $P2Y_{12}$ inhibitors has led to more potent antithrombotic effects. Therefore, the incidence of ischaemic thrombotic events after PCI interventions in atherosclerotic vascular disease has decreased.

In future, in line with personalised therapy, it will be important to search for and identify the categories of patients who can benefit from dual pathway inhibition (antiplatelet plus anticoagulation), balancing ischaemic and bleeding risks. Choice of antiplatelet agents (i.e. aspirin versus $P2Y_{12}$ inhibitors) is an important consideration. Since thrombotic and bleeding risks change over time, time-dependent indications of dual pathway inhibition must be considered.

As Asians bleed more frequently than western patients, the usefulness of factor XIa inhibitors may need to be examined in the context of ethnic differences.[9] Dual pathway inhibition is currently associated with increased bleeding risks in patients with CAD and sinus rhythm. However, such risks will decrease if factor XIa inhibitors are introduced, and this strategy may be developed in the future.

In the PACIFIC-AMI study, asundexian neither increased the risk of bleeding nor reduced the risk of thrombotic events; however, the study was not a true efficacy study. Therefore, further research is needed to identify categories of patients with CAD who could benefit from this agent.

It is also mandatory to select patients at a higher risk of thrombotic events, such as those with ACS soon after onset and people with diabetes or chronic kidney disease, who could be a preferred target for the administration of factor XIa inhibitors together with antiplatelet agents, without increasing bleeding and with fewer ischaemic events. ❑

1. Yasuda S, Kakita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;381:1103–13. https://doi.org/10.1056/NEJMoa1904143; PMID: 31475793.
2. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289–367. https://doi.org/10.1093/eurheartj/ehaa575; PMID: 32860058.
3. Arbelo E, Dagres N. The 2020 ESC atrial fibrillation guidelines for atrial fibrillation catheter ablation, CABANA, and EAST. *Europace* 2022;24:ii3–7. https://doi.org/10.1093/europace/euab332; PMID: 35661865.
4. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9–19. https://doi.org/10.1056/NEJMoa1112277; PMID: 22077192.
5. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–30. https://doi.org/10.1056/NEJMoa1709118; PMID: 28844192.
6. Galli M, Capodanno D, Benenati S, et al. Efficacy and safety of dual-pathway inhibition in patients with cardiovascular disease: a meta-analysis of 49 802 patients from 7 randomized trials. *Eur Heart J Cardiovasc Pharmacother* 2022;8:519–28. https://doi.org/10.1093/ehjcvp/pvab043; PMID: 34146091.
7. Picconi JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet* 2022;399:1383–90. https://doi.org/10.1016/S0140-6736(22)00456-1; PMID: 35385695.
8. Rao SV, Kirsch B, Bhatt DL, et al. A multicenter, phase 2, randomized, placebo-controlled, double-blind, parallel-group, dose-finding trial of the oral factor XIa inhibitor asundexian to prevent adverse cardiovascular outcomes after acute myocardial infarction. *Circulation* 2022;146:1196–206. https://doi.org/10.1161/CIRCULATIONAHA.122.061612; PMID: 36030390.
9. Tamargo J, Kaski JC, Kimura T, et al. Racial and ethnic differences in pharmacotherapy to prevent coronary artery disease and thrombotic events. *Eur Heart J Cardiovasc Pharmacother* 2022;8:738–51. https://doi.org/10.1093/ehjcvp/pvac040; PMID: 35848895.