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Use of direct oral anticoagulant in ischaemic heart disease: the COMPASS study

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Despite the progress of personalized treatment and the '*target*' control of cardiovascular risk factors, as well as the widespread application of surgical and percutaneous revascularization of patients with acute coronary syndrome (ACS), 5–10% of the patients with ischaemic cardiomyopathy experience recurrent acute events every year thereafter.[1] Aspirin therapy is a mainstay of secondary cardiovascular prevention, and by itself is responsible for a 20% reduction of major cardiovascular events and a 10% reduction of cardiovascular mortality.[2] In an effort of reducing ischaemic recurrences, several modalities of antithrombotic therapy have been tried, and presently double antiplatelet treatment is recommended for 12 months after ACS.[3] When dual antiplatelet treatment is prolonged beyond the first 12 months after ACS the evidences suggest that on one hand there is a reduction of ischaemic events, but, on the other, an increase of bleeding events, without a net benefit in terms of overall and cardiovascular mortality: presently prolonged dual antiplatelet therapy is recommended, for secondary prevention, only in the subgroup of patients at high ischaemic risk and low bleeding risk.[3] Entertaining the hypothesis according to which the recurrent ischaemic event could be determined by an over activation of the coagulation cascade,[4] the role of oral anticoagulant has been explored, through the years, in secondary prevention settings.

The use of vitamin K inhibitors has been effective in reducing ischaemic cardiovascular events, but their use in clinical practice, for this indication, has been hindered by the high risk of major bleeding events.[4] The introduction of the new oral anticoagulant, with their improved safety profile, has allowed the re-introduction of a therapeutic strategy long abandoned for the excessive side effects, and its unpractical use (*Table 1*). It is interesting to notice that prevention of ischaemic cardiovascular events is inversely proportional to the drug dosage utilized (Phase 2 of the ATLAS and COMPASS studies), which are different from the dosages used for prevention of cardioembolism and deep vein thromboembolism. This observation, albeit in need of further evidence, raises the hypothesis that the efficacy of these drugs could be due to the thrombin related platelets aggregation inhibition, rather than the anticoagulant properties. On the other hand, the COMPASS study demonstrated a clear advantage over the aspirin alone strategy, where long-term dual antiplatelet treatment either failed or didn't completely prove effective[3]: this consideration along with the fact that Rivaroxaban 5 mg b.i.d. alone didn't manifest a net clinical benefit, seems to emphasize the importance of platelet inhibition and thrombin activation at multiple levels, rather than a powerful anticoagulation. The data of the study present us with the necessity to identify patients, considering also economic factors, benefitting the most from the new treatment. Finally, and considering the compliance and the side effects of multi-drug treatment, there is growing interest in the new strategies (such as GEMINI ACS-1) testing, in the immediate post-ACS period, combination therapy with $P2Y_{12}$receptor inhibitors and low dose new oral anticoagulants. The elderly population is ill suited for more powerful antithrombotic treatment in the secondary prevention of ischaemic events, where the evidence is already scant in support of low dose aspirin.[2]

Conflict of interest: none declared.

Table 1 Use of direct oral anticoagulant in ischaemic heart disease

Study	Study target	Drugs	Results	Notes
ESTEEM trial ($n = 1883$)	Patients with ACS (STEMI or NSTEMI), on aspirin therapy • Phase 2	Ximelagatran, direct factor II inhibitor	• At 6 months 26% reduction of ischaemic outcome • 97% increase of major bleeding	Drug removed from the market for hepatic toxicity
RUBY-1 trial ($n = 1279$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Darexaban, direct factor Xa inhibitor	• At 6 months no reduction of ischaemic outcome • 128% increase of major bleeding	No further studies planned
RE-DEEM trial ($n = 1861$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Dabigatran, direct factor II inhibitor	• At 6 months 77–327% increase of major bleeding according to the dose tested	No further studies planned
ATLAS-ACS-TIMI ($n = 3491$)	Patients with ACS, on aspirin or aspirin and thienopyridine • Phase 2	Rivaroxaban, direct factor Xa inhibitor	• 31% reduction of ischaemic outcome • Dose-dependent increase in bleeding episodes	
APPRAISE trial ($n = 1715$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Apixaban, direct factor Xa inhibitor	• At 6 months and at 5 mg bid 27% reduction of the ischaemic outcome • Dose-dependent increase in major bleeding episodes	Riduzione dell' outcome ischaemico more significant for aspirin only
APPRAISE 2 Trial ($n = 7392$)	High-risk patients after ACS, on aspirin and clopidogrel therapy • Phase 3	Apixaban 5 mg bid, direct factor Xa inhibitor	• Study suspended early for excessive major bleeding episodes without benefits in ischaemic outcome	
ATLAS-ACS2-TIMI ($n = 15\,526$)	Patients with ACS, on aspirin and thienopyridine • Phase 3	Rivaroxaban 2.5 mg or 5 mg bid, direct factor Xa inhibitor	• At 2.5 mg bid reduction of primary ischaemic outcome, reduction cardiovascular mortality, and total mortality, reduction intrastent thrombosis • Increase major and intracranial bleeding events, but not fatal bleeding events	
GEMINI ACS ($n = 3.037$)	Patients with ACS, on clopidogrel or ticagrelor, without aspirin • Phase 2	Rivaroxaban 2.5 mg bid, direct factor Xa inhibitor	• Compared with aspirin similar bleeding events. Ischaemic outcome similar	Study underpowered for evaluation of ischaemic events
COMPASS trial ($n = 27\,395$)	Patients with stable cardiovascular disease divided in three groups: aspirin alone, aspirin + Rivaroxaban 2.5 mg bid, Rivaroxaban only 5 mg bid • Phase 3	Rivaroxaban 2.5 mg bid +aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality • Increase of major bleeding episodes but not fatal or critical bleeding episodes	
COMPASS trial (coronaropatia) ($n = 24\,824$)	Patients enrolled in the COMPASS with stable coronary artery disease • Phase 3	Rivaroxaban 2.5 mg bid + aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality	

(continued)

Table 1 Continued

Study	Study target	Drugs	Results	Notes
COMPASS trial (malattia periferica) ($n = 7473$)	Patients enrolled in the COMPASS with stable peripheral arterial disease	Rivaroxaban 2.5 mg bid + aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Increase of major bleeding episodes but not fatal or critical bleeding episodes • Reduction of the primary outcome and reduction of acute limb ischaemia, including major amputations • Increase of major bleeding episodes but not fatal or critical bleeding episodes	

List of the published randomized studies and summary of the results.

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