On the cutting edge of acute coronary syndromes: adding oral factor Xa-inhibition with darexaban to dual antiplatelet therapy: the RUBY-1 trial

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This commentary refers to ‘RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome’, by Ph.G. Steg et al., on page 2541

Parenteral anticoagulants such as unfractionated heparin, low molecular weight heparins, fondaparinux, or bivalirudin are recommended in the first hours to days of an acute coronary syndrome (ACS). In the era prior to acute percutaneous coronary intervention (PCI), long-term oral anticoagulation with vitamin K antagonists (VKAs) was proven beneficial in patients with myocardial infarction (MI). However, the introduction of early PCI with stenting and the results of the CURE study boosted the use of dual antiplatelet therapy in ACS. As triple therapy with aspirin, clopidogrel, and VKA is associated with an increased risk of bleeding, the use of VKAs has never become routine therapy following ACS.

The new oral anticoagulants (direct thrombin and factor Xa inhibitors) have several advantages over VKAs. The use of VKAs is complicated by a narrow therapeutic window, a slow onset and offset, and several food and drug interactions. Moreover, it requires careful monitoring, which is not necessary with the new oral anticoagulants targeting thrombin or factor Xa. These drugs have been evaluated in the prevention and treatment of venous thrombo-embolism and in patients with atrial fibrillation. So far, results are very promising. Their potential benefit in the treatment of ACS is currently being investigated.

The RUBY-1 trial which has now been reported is a well-conducted double-blind, randomized trial evaluating the safety, tolerability, and efficacy of a new oral factor Xa inhibitor, darexaban, after ACS. Six different dosing regimens of darexaban were tested against placebo for 26 weeks in patients with ACS. The primary endpoint was the occurrence of major bleeding, but other safety measures such as liver toxicity were also investigated. As a secondary endpoint, ischaemic events were recorded.

The 1279 ACS patients were randomized as soon as possible after discontinuation of parenteral antithrombotic therapy (median randomization at day 4). More than 70% were ST-elevation MI patients and ~75% of all patients underwent PCI prior to inclusion. Median age was 56 years and only ~20% were women. More than 96% of the patients were on dual antiplatelet therapy with aspirin and clopidogrel. Patients with active bleeding during the first days were excluded, as were patients with recent stroke/transitory ischaemic attack (<12 months prior to index event) or with renal creatinine clearance of <60 mL/min.

Major and non-major clinically relevant bleeding was recorded and adjudicated by an independent committee during the 26-week study participation. In the placebo group the bleeding rate was 3.1%, of which almost all occurred within the first 90 days. Bleeding rates were higher in all darexaban groups and revealed a clear dose-response relationship (6.2, 6.5, and 9.3% for 10, 30, and 60 mg daily, respectively). In the darexaban groups, bleeding events continued to accumulate after 90 days. There was no significant difference in bleeding events for patients receiving darexaban once or twice daily. No cases of fatal bleeding or intracranial haemorrhage were reported in any study group. Adverse events leading to discontinuation of the study drug were more frequent in the groups receiving the high-dose regimen of darexaban.

No decrease in ischaemic event rates was shown with darexaban vs. placebo, but the study was underpowered to evaluate efficacy. Darexaban showed good tolerability, with no major adverse effects and with no signs of liver toxicity.

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In accordance with previous phase II trials, this study confirms that oral factor Xa inhibitors confer an excess bleeding rate when administered on top of aspirin and aspirin plus clopidogrel. In the phase II APPRAISE trial, apixaban was associated with an excess bleeding rate, particularly in patients on dual antiplatelet therapy,\(^6\) and the larger phase III study APPRAISE-2 has recently been terminated prematurely after recruitment of 7392 patients because of a significant increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischaemic events.\(^7\) With a median follow-up of 241 days, the primary safety outcome of TIMI major bleeding occurred in 1.3% of the patients who received apixaban (2.4 events per 100 patient-years) and in 0.5% of the patients who received placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.\(^7\)

Also, in the ATLAS trial, a phase II trial in which the addition of the factor Xa inhibitor rivaroxaban was tested against placebo, bleeding rates were decisive. Among ACS patients receiving either aspirin monotherapy or dual antiplatelet therapy, a dose-dependent increase in bleeding events was reported.\(^8\) However, compared with placebo, rivaroxaban was associated with a significant reduction in the secondary endpoint: the composite of death, MI, and stroke.\(^8\)

In ACS patients treated with dual antiplatelet therapy, careful dosing of factor Xa inhibitors is crucial in order to balance successfully on the cutting edge of thrombosis and bleeding. This dilemma will be emphasized in the years to come, as the more potent platelet P2Y12 inhibitors such as prasugrel and ticagrelor are entering the scene. These drugs are more efficacious than clopidogrel, but are also more prone to cause bleeding.

The RUBY-1 trial investigators wisely tested several dosing regimens of darexaban, and the results support that the lower dose should be used in future studies on ACS patients. The number of ischaemic events is highest in the first weeks to months after ACS\(^2\) and, as the excess bleeding rate with darexaban in RUBY-1 was less pronounced during the first 3 months of therapy, it might be worthwhile considering shorter treatment duration of darexaban in future ACS studies.

A large phase III trial, the ATLAS-ACS 2 TIMI 51, with the two lowest doses of rivaroxiban found in ATLAS to be associated with a trend toward improved efficacy, is currently ongoing. More than 15 000 patients will be included to evaluate if factor Xa inhibition on top of single or dual antiplatelet therapy is safe and may improve ischaemic outcome.\(^9\) Clearly, the concern is that a reduction in ischaemic events with the addition of oral factor Xa inhibition to dual antiplatelet therapy might be outbalanced by an increase in bleeding. Hopefully, future studies will enable the identification of the right combinations of drugs for the right patients in order to improve clinical outcomes further in the setting of ACS.

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References


**CARDIOVASCULAR FLASHLIGHT**

A marker of mayhem: macrovolt T-wave alternans preceding polymorphic ventricular tachycardia

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A 70-year-old male with chronic kidney failure caused by Wegener’s granulomatosis was hospitalized for a respiratory tract infection. During his stay, he experienced sudden loss of consciousness. An electrocardiogram was recorded (Figure 1A). There was an extreme lengthening of the QT interval (QTc 750 ms) and a distinct beat-to-beat alternating of the T-wave morphology. This rare phenomenon is known as macrovolt T-wave alternans. During urgent transfer to the intensive care unit, the patient developed polymorphic ventricular tachycardia which was recorded by a portable external defibrillator (Figure 1B). The episode was terminated with a precordial thump and after the intravenous injection of Mg⁡²⁺ sulfate. Two other non-sustained episodes were observed. After substituting Mg⁡²⁺, K⁺, and Ca²⁺, T-wave alternans disappeared within the hour (Figure 1C). The QT prolongation was acquired. It was induced by a combination of sotalol, moxifloxacin, and haloperidol, all known for prolonging the QT interval, together with a low serum Mg⁡²⁺ (1.64 mg/dL), K⁺ (3.7 mmol/L), and ionized Ca²⁺ (1.06 mg/dL). Within 24 h after withdrawal of the drugs, the QTc interval had already drastically shortened (Figure 1D).

This flashlight shows that macrovolt T-wave alternans is a tell-tale of acute arrhythmogenic cardiac distress. It can be easily picked up with the bare eye. This exceptional clinical phenomenon formed the basis of the development of microvolt T-wave alternans as a risk stratifier for sudden arrhythmic cardiac death.

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**Figure 1A**

**Figure 1B**

**Figure 1C**

**Figure 1D**

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