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ACUTE CORONARY SYNDROMES

Lackluster RUBY is received with some disappointment

Oral factor Xa inhibitors have been intensively studied over the past few years in various clinical settings that require effective anticoagulation therapy. One such factor Xa inhibitor, darexaban (also known as YM150), was tested in the setting of acute coronary syndrome (ACS) in an international phase II trial called RUBY-1. Unfortunately, the results of this trial were somewhat lackluster and it is currently unclear as to whether a phase III trial will be undertaken.

Dual antiplatelet therapy (aspirin and clopidogrel) has reduced morbidity and mortality in patients who have experienced an ACS; however, the recurrence of ischemic events in these patients still remains relatively high. As the RUBY-1 investigators highlight in their trial report, "there is evidence from several phase II studies that adding an oral anticoagulant to antiplatelet therapy in patients with recent ACS may have efficacy in the prevention of ischemic events and death compared with antiplatelet alone."

In RUBY-1, various doses and dose regimens of darexaban were compared with placebo to determine their safety and tolerability in patients who had experienced a recent ACS (within 7 days) and were taking aspirin alone (3%) or in combination with clopidogrel (97%) for the duration of the trial. Median age of the 1,258 trial participants was 56 years. The study drug was administered for 26 weeks.

The primary safety outcome—major and clinically relevant non-major bleeding events according to the modified version of the ISTH—occurred in 3.1% of the patients receiving placebo ($n = 159$), 6.8% of patients receiving darexaban 5 mg twice daily ($n = 159$; HR 2.045, 95% CI 0.81–5.15, $P = 0.129$), 5.6% of patients receiving darexaban 10 mg once daily ($n = 159$; HR 1.775, 95% CI 0.68–4.60, $P = 0.238$), 7.5% of patients receiving darexaban 15 mg twice daily ($n = 159$; HR 2.269, 95% CI 0.92–5.59, $P = 0.075$), 5.6% of patients receiving darexaban 30 mg once daily ($n = 156$; HR 1.831, 95% CI 0.71–4.75, $P = 0.213$), 11.3% of patients receiving darexaban 30 mg twice daily ($n = 153$; HR 3.796, 95% CI 1.66–8.68, $P = 0.002$), and 7.3% of patients receiving darexaban 60 mg once daily ($n = 153$; HR 2.425, 95% CI 0.98–5.97, $P = 0.054$). A statistically significant dose-response relationship was shown for the three total daily doses (10 mg, 30 mg, and 60 mg; $P = 0.009$). No cases of fatal bleeding or intracranial hemorrhage were recorded. Compared with placebo (9.7%), the number of adverse events leading to discontinuation of the study drug were increased in patients taking darexaban 30 mg once daily (17.3%), 30 mg twice daily (19.0%), and 60 mg once daily (16.3%).

Although the trial was not sufficiently powered to test efficacy, the composite of all-cause mortality, nonfatal MI, nonfatal stroke, and severe recurrent ischemia was assessed. Compared with placebo, darexaban treatment was not associated with a significantly different cumulative risk of the aforementioned events. A slight numerical decrease in risk was found for the lowest daily dose of 10 mg; however, a numerically higher risk was found with the higher doses, mostly as a result of an increased incidence of severe recurrent ischemia. As the investigators point out, though, "the CIs around these point estimates were wide".

"Given the failure of factor Xa inhibition to add benefit to dual antiplatelet therapy after ACS in the APPRAISE-2 trial," say the RUBY-1 investigators, "the validity of ... combining dual antiplatelet therapy with anticoagulant therapy after ACS remains at best uncertain." Whilst they suggest that "a phase III trial of darexaban after ACS should use doses at the lower end of the dose range (e.g. 10 mg daily)," they go on to state that "the likelihood of the success of a phase III trial with darexaban will need to be placed in the context of results of ongoing trials like ATLAS ACS-2."

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Original article Steg, P. G. *et al.* 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. *Eur. Heart J.* doi:10.1093/eurheartj/ehr334