Effects of EDOXaban on the cellular and protein phase of coagulation in coronary artery disease patients on dual antiplatelet therapy with aspirin and clopidogrel: a randomized pharmacodynamic study

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Topic(s):
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Background: In patients on dual antiplatelet therapy (DAPT) also requiring oral anticoagulant therapy (OAC), withdrawal of aspirin therapy reduced the risk of bleeding complications without any apparent trade-off in efficacy.

Purpose: There is limited data on the pharmacodynamic (PD) effects the effects of high and low dose edoxaban regimens on platelet aggregation and clot kinetics in patients treated with DAPT as well as to assess the impact of discontinuation of aspirin therapy, which was the aim of our study.

Methods: In this prospective, randomized, open label PD investigation patients (n=75) with stable coronary artery disease on DAPT (aspirin plus clopidogrel) were randomized to DAPT plus high-dose edoxaban (60mg/od, Group A), DAPT plus low-dose edoxaban (30mg/od, Group B), or DAPT only (Group C) for 10±2 days (Phase I). Afterwards, Groups A and B interrupted aspirin and maintained single antiplatelet therapy (SAPT) with clopidogrel and edoxaban for 10±2 days, while patients in Group C maintained DAPT (Phase II). Platelet aggregation and clot kinetics were assessed at baseline, end of Phase I, and end of Phase II using thrombelastography (TEG), light transmittance aggregometry (LTA) using arachidonic acid (AA), collagen (Coll), ADP and TRAP as agonists, VerifyNow P2Y12, and serum thromboxane B2 (TxB2) assessments. High platelet reactivity (HPR) was defined as P2Y12 reaction unit (PRU) >208.

Results: Key PD findings are summarized in the Figure. Edoxaban prolonged in a dose-dependent manner speed of thrombin generation (TEG R). However, edoxaban did not impact (irrespective of dose) other markers of clot kinetics including the primary endpoint measure of TEG MA (Maximum Amplitude, a measure of clot strength). Although TEG MA was not affected by the intensity of antiplatelet therapy, showing consistent findings in patients treated with SAPT or DAPT, thrombin-mediated platelet reactivity by LTA-TRAP was significantly increased after aspirin withdrawal in patients treated with low-dose edoxaban, which was attenuated with the high-dose regimen. Although stopping aspirin therapy did not affect profiles of clot kinetics or markers of platelet reactivity specific to P2Y12 signaling (LTA-ADP and PRU), it was associated with an increase in markers sensitive to cyclooxygenase-1 (COX-1) blockade (LTA-AA, LTA-Coll, TxB2). Overall findings were consistent irrespective of HPR status at baseline.

Conclusions: Despite modulating thrombin generation, adjunctive edoxaban does not impact clot strength in DAPT-treated patients. Dropping aspirin on a background of OAC with edoxaban and P2Y12 inhibition with clopidogrel does not affect clot kinetics. However, profiles of platelet reactivity following withdrawal of aspirin therapy varies according to the intensity of OAC, which does not overcome COX-1 specific effects-induced by aspirin, suggesting that when considering a double antithrombotic treatment regimen, high-dose edoxaban
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P-values represent the comparisons across the 3 groups at each time point. Asterisks (*) identify significant differences (p<0.05) between two groups.