Effect of low-dose rivaroxaban with low-dose aspirin vs low-dose aspirin on platelet and oxidative biomarkers: a randomized study in diabetes patients with stable peripheral or coronary artery disease

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Funding Acknowledgement:
Type of funding sources: Private grant(s) and/or Sponsorship. Main funding source(s): Investigator-initiated study funded by Bayer AG

Background: Rivaroxaban (Riva), a direct FXa inhibitor, at 2.5 mg twice-daily (bid) combined with low-dose aspirin (ASA, 100 mg once daily-od) reduced major vascular events vs. ASA alone in subjects with stable coronary artery (CAD) or symptomatic peripheral artery disease (PAD). Whether this benefit is due to the anticoagulant effect or additional FXa-mediated effects through the platelet and endothelial cell thrombin receptors is unknown. Type 2 diabetes mellitus (T2DM) is characterized by high platelet activation and oxidative stress that may contribute to increased cardiovascular risk.

Purpose: We investigated the effects of Riva (2.5 mg bid) + ASA (100 mg od) vs. ASA (100 mg od) alone on platelet and oxidative biomarkers in subjects with T2DM and stable vascular disease (stable CAD, symptomatic PAD and/or significant carotid stenosis).

Methods: In this randomized, open-label, cross-over trial, patients were randomized to continue ASA for 4 weeks and then add Riva for 4 weeks, or add Riva in the first 4 weeks and then continue with ASA alone for 4 weeks. Primary endpoints were: in vivo platelet activation and lipid peroxidation, assessed by the urinary excretion of 11-dehydro-TXB2 (TXM) and 8-iso-PGF2alpha (ISOP), respectively. Secondary endpoints included: routine coagulation tests, D-dimer, thrombin generation, serum TXB2, and Riva plasma concentrations.

Results: Seventy-six subjects (10 females) were recruited: age 68±7 years (mean±SD); BMI 27.1±3.5 kg/m²; fasting glucose 129±31 mg/dL; HbA1c 6.8±0.9%; serum creatinine 1±0.25 mg/dL; LDL-cholesterol 77±31 mg/dL. Two patients dropped out: one for benign, self-limiting hematuria, one for unwillingness to continue, 8 subjects are completing the study leaving 66 who completed the 8-week randomized treatment and showed no sequence effect. Urinary TXM and ISOP were significantly reduced by Riva+ASA vs. ASA alone: TXM was 260 [195–398] vs. 335 [225–441] pg/mg creatinine and ISOP 722 [601–991] vs. 827 [648–1350] pg/mg creatinine (median [IQR]) on Riva+ASA vs. ASA alone, respectively (p < 0.001 for paired samples). Riva plasma concentrations were 48±1.9 ng/ml at peak and 21±1.4 ng/ml at trough. The velocity of thrombin formation significantly decreased with Riva+ASA vs. ASA alone (velocity index, 46±3% vs. 83±3%; peak-height, 66±2% vs. 83±1%, respectively). aPTT levels were slightly but significantly prolonged by Riva vs. ASA alone (44±1 vs. 39±1 sec). Serum TXB2, D-dimer, von Willebrand factor, PT, fibrinogen and endogenous thrombin potential values were similar between treatments.

Conclusions: In ASA-treated subjects with T2DM and stable vascular disease, the addition of very low-dose Riva restrained incompletely suppressed lipid peroxidation and platelet activation and modified the kinetics of thrombin formation. These changes may contribute to the beneficial effects of the Riva+ASA combination.