DNA methylation of ADAMTS7 gene promoter in direct oral anticoagulant-induced bleeding in patients with atrial fibrillation

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Funding Acknowledgements: Type of funding sources: Public grant(s) – EU funding. Main funding source(s): Funding: Financial support for project IMPReS (MIS 5047189) was provided to V.G. Manolopoulos through the Program “Competitiveness, Entrepreneurship and Innovation” (NSRF 2014–2020) co-financed by Greece and the European Union (European Regional Development Fund).

Introduction: Direct Oral Anticoagulants (DOACs) are recommended as first-line treatment in atrial fibrillation (AF) patients. Despite their benefits and effectiveness, several patients experience bleeding events. No studies have addressed how epigenetic modifications may affect DOAC treatment. To fill this gap, we are conducting a study aiming to follow in time changes of DNA methylation patterns in naive AF patients starting DOAC therapy. Herein, we present our findings regarding DNA methylation analysis of ADAM Metallopeptidase with Thrombospondin Type 1 Motif 7 (ADAMTS7), a protease that acts on the cardiovascular system.

Methods: A total of 76 AF patients treated with dabigatran, rivaroxaban, or apixaban and 22 non-AF controls were included. Genomic DNA has been isolated at baseline (t0, controls and patients), and for patients at 7 (t1) and 28 (t2) days of DOAC treatment. Blood genomic DNA was isolated and bisulfite converted prior to methylation analysis. Promoter DNA methylation of ADAMTS7 was analyzed with qMSP-PCR.

Results: In our study, no major bleeding or thrombotic events were recorded. A total of 16 minor bleeding events occurred. The percentage of ADAMTS7 methylation at baseline did not differ between patients and controls (16.8% vs. 14.8%, p=0.138). In patient cohort, DOAC therapy did not alter ADAMTS7 methylation at different timepoints (16.8% at t0, 15.7% at t1 and 14.3% at t2, p=0.293 from t0 to t1, p=0.06 from t0 to t2 and p=0.205 from t0 to t1). When patients were categorized into experiencing bleeding events (cases) or not (controls), ADAMTS7 was demethylated from t0 to t2 (-3.7% in cases vs. -1.2% in controls, p=0.015) and from t1 to t2 (-2.1% in cases vs. -1.1% in controls, p=0.034). In adjusted regression analysis, bleeding was associated with ADAMTS7 demethylation ($\beta$=-2.973, 95%CI -5.481, -0.466, p=0.021).

Conclusion: This is the first study of DNA methylation on DOACs. Our findings suggest that the methylation of the promoter of ADAMTS7 is reduced when DOAC-related bleeding occurs, increasing its expression levels, and may subsequently promote hemostasis and endothelium remodeling through different pathways.