Effect of evolocumab on platelet function in patients with acute coronary syndromes. An analysis of the randomized, double-blind, placebo-controlled EVOPACS Trial

K.C. Koskinas1, F. Mach2, G. Pedrazzini3, C. Mueller4, S. Cook5, C.M. Matter6, O. Muller7, J. Haener1, M. Valgimigli3, L. Raeber1, D. Heg8, S. Windecker1, J.F. Iglesias2

1Bern University Hospital, Inselspital, Bern, Switzerland
2Geneva University Hospitals, Geneva, Switzerland
3Cardiocentro Ticino, Lugano, Switzerland
4University Hospital Basel, Basel, Switzerland
5Fribourg Hospital, Fribourg, Switzerland
6University Hospital Zurich, Zurich, Switzerland
7University Hospital of Lausanne, Lausanne, Switzerland
8CTU, Bern University, Bern, Switzerland

Funding Acknowledgements: Type of funding sources: Private company. Main funding source(s): The EVOPACS trial was an investigator-initiated trial funded by Amgen.

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors substantially lower levels of low-density lipoprotein cholesterol (LDL-C) and favourably impact clinical outcomes in patients with acute coronary syndromes (ACS). Although PCSK9 inhibitors have been suggested in ex vivo studies to suppress platelet activation, the impact of evolocumab on platelet function in ACS patients receiving potent antiplatelet therapy remains largely unknown.

Methods: The EVOPACS trial was a randomized, double-blind, placebo-controlled trial assessing the use of evolocumab initiated in the acute phase of ACS. Patients presenting with ST-elevation myocardial infarction (STEMI) or Non-ST-elevation ACS (NSTE-ACS) were randomly allocated in a 1:1 ratio to either evolocumab 420mg SC or matching placebo at baseline (during hospitalization for index ACS event) and after 4 weeks. All patients received atorvastatin 40mg daily. Dual antiplatelet therapy consisting of aspirin and a potent P2Y12 inhibitor was initiated according to STEMI / NSTE-ACS guidelines, unless a less potent treatment was indicated (e.g. due to concomitant use of oral anticoagulation). Platelet function was measured at baseline (during index hospitalization) and after 8 weeks, using the Multiplate analyser. The main outcome for this analysis was the change from baseline to 8 weeks in adenosine diphosphate (ADP)-induced platelet aggregation.

Results: Serial platelet function measurements were available in 260 of all 308 enrolled patients, 124 in the evolocumab and 136 in the placebo group. Mean age was 60.2 ± 11.0 years and 83% were men. Baseline clinical characteristics were well balanced between the two treatment groups. At discharge, the proportion of patients treated with ticagrelor, prasugrel, and clopidogrel was 73%, 11%, and 9% respectively, without differences between groups. Evolocumab significantly reduced LDL-C compared to placebo at 8 weeks (difference in mean percentage change -40.75%, 95% CI -45.39 to -36.11; p < 0.001). Change in ADP-induced platelet aggregation between baseline and 8-week follow-up was -5.6 ± 23.5 U (from 24.1 ± 19.8 to 29.7 ± 25.6 U) in the evolocumab group vs. -1.7 ± 19.8 U (from 23.0 ± 14.7 U to 24.7 ± 19.1 U) in the placebo group (p = 0.13). Similar results were found in a subgroup of 189 patients (86 in the evolocumab and 103 in the placebo group) treated with ticagrelor at discharge, showing a change in ADP-induced platelet aggregation of -2.7 ± 19.5 U with evolocumab vs. -2.4 ± 19.9 U with placebo (p = 0.80).

Conclusions: In this randomized trial of ACS patients largely treated with a potent P2Y12 inhibitor, evolocumab initiated during index hospitalization on top of high-intensity statin therapy had no measurable effect on ADP-induced platelet aggregation. These findings suggest that the early therapeutic benefit of PCSK9 inhibitors in ACS patients is likely related to plaque regression/stabilization rather than changes in platelet activity.