cholesterol ester (CE). The primary safety endpoint was treatment-emergent adverse events (AEs) and clinically important changes in electrocardiogram, vital signs and laboratory evaluations.
Results: A total of 32 stable patients with atherosclerosis were randomized into 4 planned dosing cohorts. All patients completed the study. MEDI6012 significantly increased the AUC0–96hr for HDL-C, HDL-CE and CE in a graded fashion with increasing doses (Figure). Furthermore, relative to placebo, MEDI6012 significantly increased HDL-C at 96 hours by 66% (95% CI 33–99, p=0.014) with the 120 mg dose and 144% (95% CI 108–181, p<0.001) with the 300 mg dose. The proportion of patients experiencing an AE were similar between placebo (3, 50%) and MEDI6012 (13, 54%). No patients experienced a severe, life-threatening or fatal AE. When the first dose was administered as an IV push (cohort 4), safety and efficacy results were consistent.

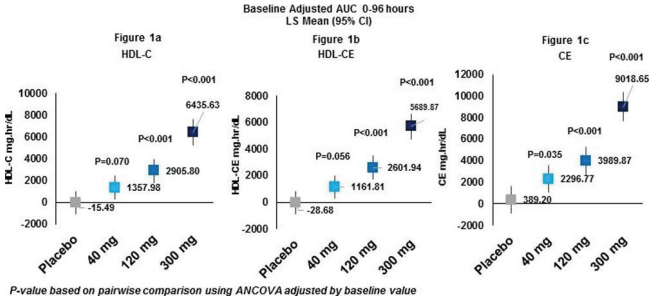

Figure 1

Conclusions: Administration of multiple ascending doses of recombinant human LCAT in patients with stable atherosclerosis was safe and well tolerated and resulted in significant dose related increases in HDL-C, HDL-CE and CE. These data support further study in patients with atherosclerosis.
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Effects of the PAR-1 receptor antagonist vorapaxar on platelet activation and coagulation biomarkers in patients with stable coronary artery disease

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Introduction: Vorapaxar is a selective antagonist of protease-activated receptor 1 (PAR-1), thereby blocking thrombin-mediated platelet activation. Although vorapaxar is likely not to affect the coagulation process directly, inhibition of platelet activation and thereby reducing the availability of a procoagulant platelet surface for the assembly of coagulation factors, might reduce the formation of thrombin and fibrin indirectly. While standard coagulation tests, like prothrombin time (PT) and activated partial thromboplastin time (aPTT), are not influenced by vorapaxar use, the effect on more specific biomarkers of coagulation is currently unknown. A reduction in platelet activation can be measured by soluble P-selectin, a plasma biomarker of in vivo platelet activation. Next to thrombin-antithrombin (TAT) complex levels, the complexes of factor IXa-antithrombin (IXa-AT) and factor Xa-antithrombin (Xa-AT) are new biomarkers of upstream coagulation activity.
Purpose: To investigate the effect of vorapaxar on biomarkers of platelet activation and coagulation activity in patients with stable coronary artery disease (CAD).
Methods: Soluble P-selectin and TAT were measured following manufacturer's instructions. Factor IXa-AT and factor Xa-AT were determined with in-house developed enzyme-linked immunosorbent assays (ELISAs). Samples were taken while on long-term treatment in a subgroup of patients with stable CAD randomized to vorapaxar or placebo on top of standard antiplatelet therapy participating in the TRA2°P-TIMI-50 trial. For this analysis, we excluded patients using anticoagulant medication during follow-up. Student's t-test and Mann-Whitney U test were used for comparison of biomarker levels between groups.
Results:. Baseline characteristics including comorbidity, prior cardiovascular disease, concomitant aspirin and clopidogrel use (99.3% and 56.3%, respectively), and other concomitant medication were well balanced between the vorapaxar-group (n=73) and placebo-group (n=62). Samples were taken after a mean study drug exposure of 904 (± 149) days. As anticipated, platelet activation was reduced in the vorapaxar-group, according to soluble P-selectin levels (ng/mL) (mean ± SD); 26.12±7.81 in the vorapaxar-group vs. 29.39±9.16 in the placebo-group (p=0.027). However, coagulation activity as measured by TAT, IXa-AT and Xa-AT was comparable in vorapaxar vs placebo group: TAT (μg/L) (median, [IQR]) 4.08 [3.20–5.01] vs. 3.88 [3.26–4.92], p=0.71; IXa-AT (pM) (median, [IQR]) 86,7 [77.2–101.3] vs. 85,5 [77.7–97.6], p=0.95; X-AT (pM) (mean ± SD) 282.1±57.4 vs. 296.4±54.6, p=0.14.
Conclusion: On top of standard antiplatelet therapy, vorapaxar reduced platelet activation as measured by a reduction in soluble P-selectin levels. We did not find an additional effect of vorapaxar on TAT, IXa-AT and Xa-AT levels in patients with stable CAD, indicating that vorapaxar does not further reduce thrombin generation via intensified platelet inhibition.

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Effect of renin-angiotensin system blockade in long term outcomes following transcatheter aortic valve implantation

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Introduction: Several studies have demonstrated the benefits of transcatheter aortic valve implantation (TAVI) in high-risk and intermediate-risk patients, but there is still a gap in the evidence of pharmacological therapies with potential impact in long-term outcomes. In particular, the presence of fibrosis and myocardial hypertrophy in patients with aortic stenosis has been related to worse prognosis. Therefore, better outcomes may be achieved with the use of strategies improving cardiac remodelling by reversing fibrosis and hypertrophy. In this regard, renin-angiotensin system (RAS) blockade has been shown to have a positive impact in remodelling and in major clinical outcomes in alternative scenarios. We aimed to determine the effects of this therapy following successful TAVI procedures.
Methods: Patients from 9 institutions with severe aortic stenosis who underwent TAVI between August/2007 and August/2017 were included. All baseline clinical, echocardiographic and procedural data were prospectively recorded in a dedicated database, and pre-specified follow up was performed. Dose and type of RAS blockade therapy was also recorded. Patients were compared according to the prescription of RAS blockade or not. Only those patients surviving the in-hospital period and under continuous RAS blockade therapy for at least 1 month after TAVI were included in the treatment group. Also, a matched comparison was performed according to baseline characteristics, use of other medications, procedural approach, left ventricular ejection fraction, and residual aortic regurgitation degree.
Results: A total of 1980 patiens were included. Mean age of the study population was 81.3±9.1 years and 65.3% were males. STS and EuroSCORE-II mean values were 7.2±1.3 and 6.5±2.4%, respectively, with 35.5% of diabetes mellitus, 13.9% of prior myocardial infarction, and left ventricular ejection fraction <40% in 32.6%of the patients. Of them, 706 (59.5%) received RAS blockade therapy after the procedure. At a median follow up of 3 years post-TAVI, the RAS blockade group had significantly lower cumulative mortality than the no-RAS blockade group (9.5% vs 16.5%; log-rank test, p=0.001). After matching, RAS blockade therapy was still associated with significantly lower mortality (HR, 0.581; 95% CI 0.310 to 0.893; p=0.002). In addition, the rates of myocardial infarction, new-onset atrial fibrillation, stroke, and re-admission due to heart failure remained lower in the RAS blockade group for the entire cohort and the matched one.
Conclusions: Post-TAVI RAS blockade therapy is associated to lower all-cause mortality at 3-year follow up and presents a global cardiovascular protective effect irrespective of the left ventricular ejection fraction and the residual aortic regurgitation. An ongoing randomised controlled trial (RASTAVI Study, NCT03201185) will help to determine the accuracy of these findings.
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Nicorandil plays a protective role against pressure-overload-induced cardiac dysfunction via alleviating myocardial apoptosis and improving energy metabolism

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Background: As one of most important metabolic sensors, ATP-sensitive potassium channels (KATP) could regulate cellular activity to meet energetic demands. It has also been demonstrated that KATP plays a cardioprotective role on cardiac dysfunction. However, there are few studies to clarify whether KATP opener could directly improve left ventricular remodeling and heart failure caused by systolic overload.
Objectives: This experimental study was designed to clarify the effect and mechanism of nicorandil (a KATP opener) on cardiac dysfunction and left ventricular remodeling in transverse aortic constriction (TAC) mice model.
Methods: Mice TAC models were developed and observed at 4 weeks after operation. In nicorandil treatment group, nicorandil was injected intraperitoneally daily for 2 weeks from the third week of TAC operation. Cardiac function and left ventricular diameters were detected by echocardiography. In order to neutralize the