Material and methods: The investigator-initiated TROPICAL-ACS trial randomized 2610 biomarker-positive ACS patients 1:1 to either standard treatment with prasugrel (10 or 5 mg/d, control group) or to a platelet function testing guided de-escalation of antiplatelet treatment with a switch to clopidogrel (75 mg/d, guided de-escalation group). This study design enabled a diurnal comparison of on-prasugrel vs. on-clopidogrel treatment platelet reactivity under steady-state conditions. For 2526 ACS patients (97%), both the exact time of blood sampling and the ADP-induced platelet aggregation value (assessed in units on the Multiplate analyzer) were available. These patients constitute the study cohort for this pre-specified analysis.
Results: The mean age of patients was 58.6 (±10.1) years and 535 (21.2%) were female. Platelet function in patients on clopidogrel (n=1265) was subject to significant diurnal variability (p=0.019) with a peaking of platelet reactivity in the early morning hours (5–10 am). In prasugrel treated patients (n=1261) there was no sign for diurnal variability (p=0.174) (see Figure).

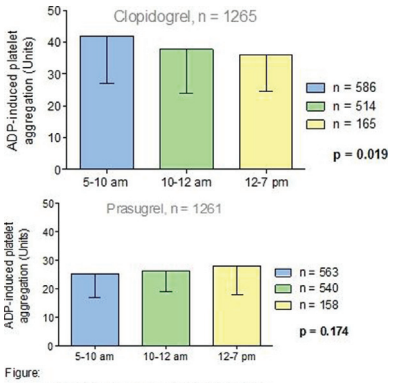

Figure:
Median with IQR of ADP-induced platelet aggregation, according to time of day in ACS patients on clopidogrel or prasugrel. P-values derive from Kruskal-Wallis test

Conclusions: The potent ADP receptor inhibitor prasugrel is not subject to diurnal variability while we observed a significant diurnal variability of on-clopidogrel platelet reactivity in ACS patients. The clinical impact of this observation may differ for patients with and without an adequate response to clopidogrel treatment and the issue of diurnal variability of platelet reactivity in ACS patients undergoing PCI warrants further investigation.
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5916
Platelet function testing predicts bleeding complications in elderly patients admitted for an acute coronary syndrome: insights from the ANTARCTIC trial

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Background: Elderly patients are at high-risk of bleeding complications, particularly in the setting of acute coronary syndrome treated with an invasive strategy. Treatment adjustment by platelet function testing (PFT) failed to improve clinical outcomes in the randomized ANTARCTIC trial.
Purpose: This pre-specified sub-study aims at determining the predictive value of PFT on occurrence of bleedings.
Methods: We analyzed the 877 patients over the age of 75 years included in the ANTARCTIC trial and randomized to a strategy of dose or drug antiplatelet therapy adjustment or a conventional "one size fits all" strategy without PFT. In the monitoring group, patients received prasugrel 5mg daily after coronary stenting and PFT was done 14 days after randomization and repeated 14 days after treatment adjustment. Occurrence of clinically relevant and major bleeding according to different classifications was collected up to one year. Correlation between PFT and bleeding complications was analyzed.
Results: Clinically relevant bleedings (Bleeding Academic Research Consortium types 2, 3 or 5) were frequently observed (20.6%, n=181 patients) with one third of bleeding events occurring in the first month. Cutaneous and gastro-intestinal bleedings were the two predominant complications. In the monitoring group, after final adjustment, the treatment given for one year was: prasugrel 5mg (55%), clopidogrel 75mg (39%) or prasugrel 10mg (4%). The main predictive factors of major bleedings in multivariate model were age>85 years [adj.HR (95% CI): 2.48 (1.25; 4.91); p=0.0093] and hemoglobin level (per gram of decrease) [adj.HR (95% CI): 1.45 (1.18; 1.79); p=0.0004].
The first PFT at 14 days was not predictive of bleeding complications (HR (95% CI): 0.99 (0.96; 1.03); p=0.62). However, the last PFT was an independent predictive factor of clinically relevant bleedings (adj.HR (95% CI): 0.95 (0.90; 0.99); p=0.017).
Conclusion: Clinically relevant bleedings were frequently observed in elderly patients in the setting of acute coronary syndrome. Platelet function testing did not improve clinical outcomes but identified the bleeding risk of these patients when the chronic treatment was installed.

5917
Comparison of platelet inhibition in patients with ST-elevation myocardial infarction vs. non-ST elevation myocardial infarction after a loading dose of swallowed vs. chewed ticagrelor

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Background: The pathogenesis of both ST-elevation (STEMI) and non-ST-elevation Myocardial Infarction (NSTEMI) involves coronary thrombosis over a ruptured atherosclerotic plaque, yet the reason for the different extent of coronary thrombosis in the two syndromes is largely unknown. Furthermore, recent studies showed that STEMI is associated with delayed and reduced platelet response to a novel P2Y12 antagonists loading dose (LD). It was suggested that delayed gastric absorption accounts for the delayed response in STEMI.
Methods: In this study we prospectively compared platelet inhibition in response to a ticagrelor LD in consecutive STEMI (N=73) vs. NSTEMI (N=41) patients, when a ticagrelor LD (180 mg) was swallowed (TS) or chewed (TC) in order to "bypass" any potential effect of delayed in gastric absorption on platelet response. Platelet reactivity was determined in response to ADP by VerifyNow and expressed as PRU at admission, (before ticagrelor LD) and 1 hour later.
Results: There were no differences in baseline characteristics between STEMI and NSTEMI patients. Platelet reactivity was higher at 1 hour in STEMI vs. NSTEMI regardless of whether ticagrelor was swallowed (175±93 vs. 115±85, p=0.03) or chewed (126±93 vs. 46±54, p=0.001). Among STEMI patients with a chewing vs. swallowing a ticagrelor LD, it accelerated the inhibition of platelet aggregation (IPA) over the first hour (42% vs. 14%, p<0.05), probably by bypassing the delayed GI absorption. Yet, only among patients who chewed the LD, the IPA at 1 hour was significantly higher in NSTEMI vs. STEMI (83% vs. 52%, p=0.001), figure.

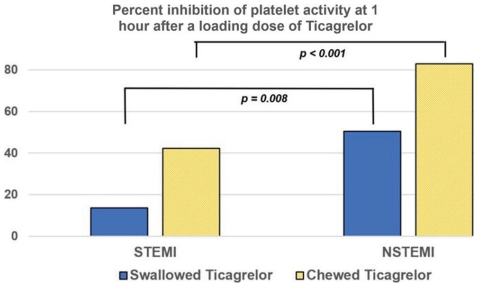

Figure 1

Conclusions: Our findings suggest that beyond the delayed gastric absorption of ticagrelor, which contributes to delayed response to P2Y12 antagonists in STEMI, STEMI as compared with NSTEMI is also associated with intrinsic platelet hyporesponsiveness that might be related to the extent of thrombus formation between these two syndromes.

5918
Influence of intravenous fentanyl versus morphine on ticagrelor absorption and platelet inhibition in patients with ST-segment elevation myocardial infarction undergoing primary PCI

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Background: Recent evidence demonstrates that intravenous (IV) morphine significantly reduces absorption and delays onset of action of oral P2Y12 receptor antagonists in patients with STEMI undergoing pPCI. The question of whether this potential drug-drug interaction represents a class effect common to all opioid receptor agonists including fentanyl remains uncertain.
Purpose: To assess the influence of IV fentanyl compared with morphine on pharmacokinetics (PK) and pharmacodynamics (PD) of ticagrelor and its active metabolite (AR-C124910XX) in patients undergoing pPCI for STEMI.
Methods: Single-center, prospective, open-label, randomized controlled study that randomly assigned in a 1:1 ratio patients with STEMI undergoing pPCI to receive IV fentanyl or morphine following pre-hospital 180 mg loading dose (LD) of ticagrelor (ClinicalTrials.gov Identifier: NCT02531165). PK/PD analyses were per-