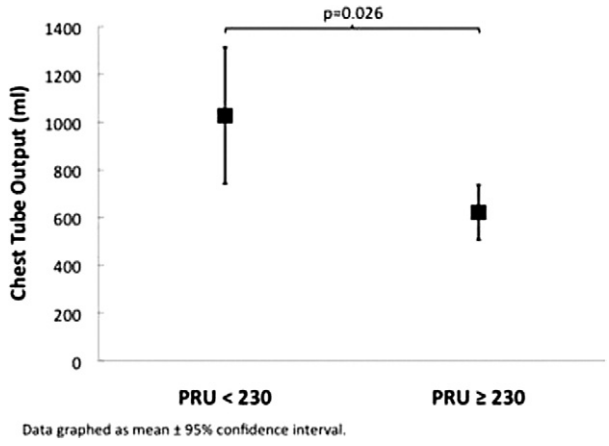
Methods: VERIFY Pre-Op TIMI 45 was a prospective study of 42 patients with indications for coronary angiography subsequently referred for CABG. All patients were therapeutic on clopidogrel. Platelet function was assessed with VerifyNow™ $P2Y_{12}$ Reaction Units (PRU). Chest tube output within 24-hours of CABG was stratified by PRU ≥ 208, ≥ 230, and ≥ 275. Results reported as mean±SD.
Results: Median time from last clopidogrel dose to CABG was 4 days (range 1 to 9 days). Patients who held clopidogrel < 4 days had lower PRU than those who held for ≥ 4 days (190±84 vs. 271±21 PRU; p=0.015). Thresholds of PRU ≥ 208 or ≥ 275 correlated with less bleeding but did not reach significance (p=0.20 and p=0.39). Patients with PRU ≥ 230 had significantly less chest tube output than those with PRU < 230 (622±220 vs. 1028±676; p=0.026) (Figure).

Figure. Perioperative Blood Loss and Platelet Reactivity.



Conclusions: The VerifyNow™ $P2Y_{12}$ platelet function assay can be used to predict perioperative bleeding in patients exposed to clopidogrel undergoing CABG. A threshold of ≥ 230 PRU is associated with less bleeding, and may assist clinicians in optimizing the timing of surgery.

TCT-723

Transferring from Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients: High on-Treatment Platelet Reactivity Analysis of the TRIPLET Trial

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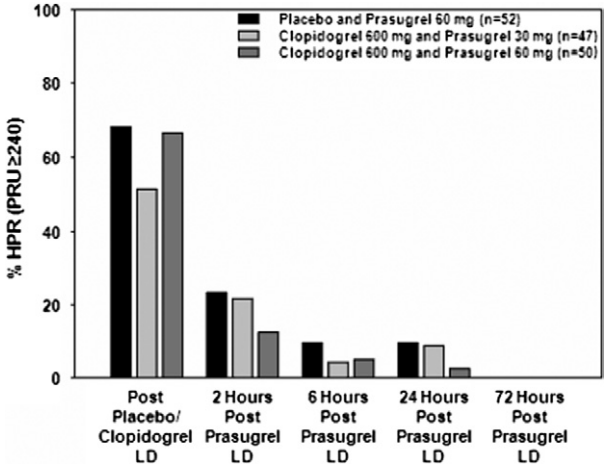
Background: High on-treatment platelet reactivity (HPR) has been identified as an independent risk factor for ischemic events in acute coronary syndrome (ACS) patients (pts). In TRIPLET, ACS pts undergoing percutaneous coronary intervention (PCI) were given a prasugrel (pras) loading dose (LD) with or without a prior clopidogrel (clop) LD. An analysis of HPR was included.
Methods: TRIPLET was a randomized, double-blind study in ACS-PCI pts on aspirin using VerifyNow P2Y12 assay to evaluate Pras with or without prior Clop in 3 arms: (1) placebo (PBO) followed by Pras 60-mg LD (2) Clop 600-mg LD followed by Pras 30-mg LD (3) Clop 600-mg LD followed by Pras 60-mg LD. Pts undergoing PCI received Pras 10-mg once daily (qd) for 2-4 days. HPR (P2Y12 Reaction Units [PRU] ≥240) were evaluated in the pharmacodynamic population within 24 hrs following the PBO/Clop LD, immediately prior to Pras LD and at 2, 6, 24, 72 hrs following Pras LDs.
Results: HPR following Clop was 58.5% in the combined Clop LD arms. No substantial difference was noted when stratified by time between the Clop and Pras LDs (< 6hrs vs ≥6 hrs). At 6 hrs in the combined Pras LD arms, HPR was 7.1%, with 0% HPR by 72 hrs. Because a high number of HPR occurred in a single site, a statistical outlier analysis was performed. When outliers were excluded, HPR occurred in 1.9% at 6 hours and in 0% by 24 hrs.
Conclusions: In TRIPLET, pts with ACS intended for PCI showed a high prevalence of HPR after Clop 600-mg LD, even when measured after 6 hrs. When Pras LD was added, HPR decreased substantially by 6 hrs and was absent by 72 hrs.



TCT-724

Clopidogrel Loading doses result in Favourable Changes in Nitric Oxide (NO) Metabolism in Patients with Stable Angina Undergoing Percutaneous Coronary Intervention (PCI)

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Background: Clopidogrel loading dose of 600mg is used in patients undergoing PCI and those treated for acute coronary syndromes. 600mg of clopidogrel can significantly inhibit platelet inhibition within 2 hours but also improve endothelial dysfunction in stable CAD patients via a mechanism independent of platelet function. We sought to study the effect of both acute clopidogrel 600mg loading and chronic 75mg therapy on markers of NO metabolism, vasodilatory effect and antioxidant status in these patients.
Methods: 58 CAD patients were recruited. In the clopidogrel naive group (36 subjects) blood was taken before and 2h after 600mg dose of clopidogrel and 75mg aspirin (ASA)who were attending for PCI for stable angina. We studied another cohort on chronic ASA and clopidogrel 75mg (22 subjects) after 2 months of therapy. All plasma samples were measured for NO metabolites (nitrite, nitrate and S-nitrosothiols), cGMP (a marker of vasodilatory effect) and antioxidant capacity of the plasma (ORAC index). Pearson correlation statistics were performed on all acute pre and post clopidogrel loading and chronic therapy to explore the relationships seen in NO metabolites.
Results: 2 hours after clopidogrel 600mg dose, plasma nitrite was increased from 157.1±82.4 to 194.2±87.64 nM (p=0.012), cGMP from 214.2±124.4 to 231.5±107.8 pmol/ml(p=0.05) and ORAC index from 60.66±11.45 to 64.15±10.61%(p=0.037). Acute loading - the rise in cGMP was inversely related to the total antioxidant capacity of the plasma (ORAC index)p<0.0001 also the rise in nitrite with the increase in cGMP p=0.0043. There was a weaker correlation in the rise in nitrate as a consequence of 600mg with the rise in ORAC p=0.0782. After chronic clopidogrel, nitrite was increased from 157.1±82.4 to 254.3±139.4nM(p=0.0028), as well as cGMP from 214.2±124.4 to 276.9±72.15pmol/ml(p=0.05). In both acute and chronic groups RSNO (nitrosothiol) was unchanged.
Conclusions: Patients receiving clopidogrel exhibit a time-proportional increase in NO bioavailability and effective vasodilation. Clopidogrel has beneficial effects on redox status 2 hours after 600mg. These results suggest non platelet - pleiotropic effects of clopidogrel in CAD patients.

TCT-725

Point-of-Care Genetic Testing of Eleven CYP2C19 Single Nucleotide Polymorphisms Identifies Extensive and Reduced Metabolizers of Clopidogrel With High Accuracy in Patients With Coronary Artery Disease

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Background: The clinical use of genetic testing in ACS is limited by accessibility and turn-around-time. Nanosphere Verigene® System is a novel point-of-care (POC) genetic test analyzing 11 CYP2C19 variants within 3 hours. We evaluated the accuracy of the method to identify extensive (EM) and reduced clopidogrel (clop) metabolizers (RM) in

stable coronary artery disease (CAD) patients by comparing the results to an established, validated laboratory-based genotyping method.
Methods: 74 stable CAD patients on clop 75 mg daily were tested by clinical nurses with no genetic laboratory experience and 1 hour of basic training on the device. The patients were defined as EM (*1/*1, *1/*17, *17/*17), RM (*1/*2A, *1/*8, *2A/*2A, *2A/*3). Genetic testing was conducted on 1 mL of whole blood using the Verigene® System and compared to an Affymetrix® DMET+ assay. Pharmacokinetic (PK) exposure to clop's active metabolite (AM) was measured and platelet reactivity (PD) was assessed with the VerifyNow™ P2Y12 system (PRU) and VASP (PRI) assays.
Results: There was an overall 99.9% concordance of marker-level data between the Verigene® and the reference (DMET+) in measuring the CYP2C19 markers of interest. There was a 100% agreement between Verigene® and the reference test in classifying the patients into established EM and RM groups. The POC assay identified 59 EM, 15 RM. The EM group had significantly lower PRU (LS means 158 vs. 212; p=0.003), and PRI (LS means 48 vs. 63, p=0.01) than RM group treated with clopidogrel 75 mg. The EM group also had significantly higher AM exposure by AUC(0-last) than the RM group (LS means 12.6 vs. 7.7; p=0.0009).
Conclusions: This is the first report of a POC genetic testing platform performing a comprehensive CYP2C19 polymorphism characterization in CAD patients and validating the genotypes against the PK and PD phenotype. There was a high concordance between the two platforms in measuring the star allele marker data. The POC genetic test identified EM and RM phenotypes based on 11 gene variants with high accuracy and predicted a reduced platelet inhibition in response to clop. A rapid, reliable POC CYP2C19 genetic test could make clop pharmacogenetic testing feasible for all patients.

TCT-726

Residual Platelet Reactivity Threshold After Clopidogrel Loading Dose to Predict Long-term Clinical Outcome in Patients with Acute Coronary Syndrome: Insights from the RECLOSE2-ACS Study

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Background: There is no consensus concerning the usefulness of routine assessment of in vitro platelet reactivity for recognition of clopidogrel nonresponders, or the method or methods that allow reliable assessment of residual platelet reactivity, and for each method the cutoff of platelet aggregation inhibition that should be used in clinical practice.
Methods: The study includes 1,789 acute coronary syndrome (ACS) patients receiving an invasive treatment and for whom platelet reactivity after a 600 mg clopidogrel loading was prospectively assessed by light transmittance aggregometry (LTA). The primary end point of the study was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke (MACE) at 2-year follow-up; the secondary end point was cardiac mortality. The sensitivity and specificity of platelet reactivity to predict both end points were calculated in a ROC curve analysis. The "optimal" cutoff value was defined by the highest Youden index value and compared with the predefined cutoff of 70% used in the main study and corresponding to the 90th percentile value derived from an healthy volunteer sample.
Results: By ROC analysis 63% resulted the optimal cutoff value to predict both MACE and cardiac death at 2 years of follow-up. A significant sensitivity improvement for the ROC-based cutoff value was revealed (32%; p<0.001). The incidence of clopidogrel nonresponders changed from 14% with the cutoff of 70% to 24% with the ROC-based cutoff. However, the increased sensitivity was reached at the price of a lower specificity and accuracy. The latter with the cutoff of 70% was 81% for MACE and 84% for cardiac death, while with the cutoff of 63% the predictive accuracy was 73% and 75%, respectively. The AUCs were nearly identical with the 2 cutoffs both for MACE (0.71; 95% CI 0.69-0.73) and cardiac death (0.79; 95% CI 0.77-0.81).
Conclusions: The cutoff of 70% as compared to the ROC-based of 63% allows the identification of a subset of patients at very high risk of cardiac death in only 14% of the studied population, making the ADP LAT test more acceptable in clinical practice for the identification of subjects at risk.

TCT-727

Meta-analysis Comparing Bleeding Rates After Low Versus High Dose Clopidogrel In Patients Undergoing Percutaneous Coronary Intervention And Receiving A Glycoprotein IIb/IIIa Inhibitor

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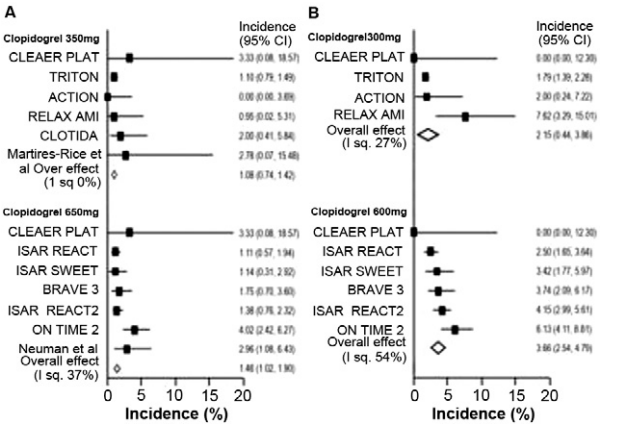
Background: Glycoprotein IIb/IIIa inhibitors (GPI) are widely used during percutaneous interventions, particularly in the setting of high clot burden, slow flow, or no reflow. While the safety of a 300 mg clopidogrel loading dose in conjunction with GPI therapy has been established, the safety of a 600 mg clopidogrel load has not been defined.
Methods: We searched PubMed, Cochrane, and ClinicalTrials.gov for studies that involved PCI in patients treated with a GPI plus either 300 mg or 600 mg of clopidogrel. We excluded studies that involved oral or intracoronary GPI therapy and/or thrombolysis.
Results: Our study included 15 trials and 12,114 patients. Major bleeding incidence ranged from 0% to 10.36% with 300 mg of clopidogrel versus 1.11% to 7.52% with 600 mg of clopidogrel. Minor bleeding incidence ranged from 0% to 25.69% with 300 mg of clopidogrel and from 0% to 6.13% with 600 mg of clopidogrel. After excluding trials that did not define bleeding based on TIMI criteria, the pooled incidence of major bleeding was 1.08 (95% CI, 0.74 to 1.42)% for the 300 mg clopidogrel group and 1.46 (95% CI, 1.02-1.90)% for the 600 mg clopidogrel group (p=0.91) (Figure 1A). The pooled incidence of TIMI minor bleeding was 2.15 (95% CI, 0.44 to 3.86)% for the 300 mg group and 3.66 (95% CI, 2.54 to 4.79)% for the 600 mg group (p=0.46) (Figure 1B).



Conclusions: Among patients undergoing PCI and receiving a GPI, the incidence of bleeding is low and similar after a 300 mg or 600 mg clopidogrel loading dose.

TCT-728

Clinical presentations, antiplatelet strategies and prognosis of patients with stent thrombosis: an observational study of 140 patients

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Background: Until now there has been scarce evidence regarding an optimal antiplatelet strategy and clinical outcomes for patients who had suffered from stent thrombosis (ST).
Methods: 140 patients who suffered from stent thrombosis were prospectively registered. Patients received dual (aspirin and 150mg clopidogrel, N=66) or triple (additional cilostazol, N=74) antiplatelet therapy at the physician's discretion. Thereafter platelet reactivity and one year clinical outcomes were analyzed. The primary outcome included the composite of cardiac death, non-fatal myocardial infarction (MI) or stroke at one year.
Results: MACE developed in 41 (29.3%) patients, consisting of 31 (22.1%) cardiac death, 9 (6.4%) non-fatal MI and 1 (1.4%) stroke. Recurrent definite and probable ST according to ARC definition was observed in 8 (5.7%) and 14 (10.0%) patients, respectively. Triple therapy was associated with significantly lower platelet reactivities (50.2±17.8, % vs. 59.6±17.2, %, P=0.002) compared to high dose dual antiplatelet therapy. However, the incidence of primary events (24.3% vs. 34.8%, P=0.172) did not differ between triple and dual antiplatelet therapies. High on-treatment platelet reactivity (HR: 8.35, 95% CI: 2.234~30.867, P=0.002) and diabetes (HR: 3.732, 95% CI: 1.353~10.298, P=0.011) were independent predictors of primary events.
Conclusions: Patients who suffered from stent thrombosis have a poor prognosis even after revascularization with intensive antiplatelet therapy. Triple antiplatelet therapy was more effective in reducing on-treatment platelet reactivity, compared to high dose dual antiplatelet therapy.

TCT-729

Discontinuation of Long-Term Clopidogrel Therapy is Associated with Death and Myocardial Infarction after Saphenous Vein Graft Percutaneous Coronary Intervention

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[1]Kaiser Permanente, Los Angeles, CA, [2]Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY, [3]Cardiovascular Research Foundation, New York, USA

Background: The timing and incidence of adverse events by different durations of clopidogrel therapy after SVG PCI remain unknown. The primary objective of this study was to investigate the risk associated with cessation of long-term clopidogrel therapy after SVG PCI.
Methods: This is a cohort study of patients undergoing SVG PCI from 2000-2009 followed for death or MI after stopping clopidogrel. A piecewise exponential survival model was used to generate adjusted incidence rate ratios comparing the 0-90 day and 91-365 day intervals after clopidogrel cessation. A multivariate Cox regression model was constructed to obtain risk-adjusted instantaneous incidence rates using kernel hazard functions.