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The Influence of Smoking Status On The Pharmacodynamics of Prasugrel and Clopidogrel: The PARADOX Study

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Background: Analyses from clinical outcome studies including CAPRIE, CURE, CREDO, CLARITY-TIMI 28, and CHARISMA demonstrate that nonsmokers experience less or no benefit from clopidogrel (Clop) treatment as compared with smokers, who have robust treatment benefit. Moreover, the efficacy of double dose clopidogrel was confined to smokers in the PCI cohort of the CURRENT trial. However, there are no prospective studies evaluating the effects of smoking status on Clop and prasugrel (Pras) pharmacodynamics (PD).

Methods: PARADOX was a prospective, double-blind, placebo-controlled study of 56 nonsmokers and 54 smokers with stable CAD on aspirin therapy randomized to Clop (75 mg qd for 10 d) or Pras (10 mg qd for 10 d) and crossed-over after 14 d washout. The co-primary objectives were PD of: 1) Clop nonsmokers vs. Clop smokers and 2) Clop nonsmokers vs. Pras smokers. PD was assessed using VerifyNow (VN)-P2Y12 assay and VASP PRI.

Results: VN-P2Y12 % Inhibition and PRU results are shown in the Figure. VASP PRI results were consistent with the VN-P2Y12 assay results.

Conclusions: PARADOX is the first prospective study to demonstrates that the antiplatelet effect of Clop is less in nonsmokers than smokers whereas smoking status does not influence the antiplatelet effect of Pras. Pras has significantly greater antiplatelet effect than Clop regardless of smoking status. Clop nonsmokers demonstrate greater platelet reactivity than any other group. The PD findings of PARADOX provide a mechanism to explain the results of analyses from randomized trials demonstrating less or no clinical benefit of Clop treatment in nonsmokers.

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Major Adverse Cardiac Events Associated With Discontinuation Of Clopidogrel Treatment Within The First Year After Coronary Stent Implantation In Western Denmark

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Background: The clinical importance of adherence to the recommended duration of dual antiplatelet therapy after coronary stent implantation is difficult to assess in real-life settings, and limited data are available.

Methods: In Western Denmark, we followed 13,001 patients treated with bare metal stent (BMS: n = 8847) or drug-eluting stent (DES: n = 4154) implantation between 2002 and 2005. We obtained 1-year data on clopidogrel prescription fillings and major cardiac adverse cardiovascular events (MACE) by linkage of national registries. Dual antiplatelet treatment with aspirin and clopidogrel was recommended for 1 year after stent implantation by November 2002. MACE was defined as cardiac death, myocardial infarction, or definite stent thrombosis.

Results: Discontinuation of clopidogrel was common in both the BMS and DES groups, and 70%, 73%, and 73% used clopidogrel for more than 9 months in 2003, 2004, and 2005, respectively. Discontinuation of clopidogrel within the first 6 months was not significantly associated with an increased risk of MACE after BMS implantation (<3 month of treatment: hazard ratio (HR) = 1.33, 95% confidence intervals (CI) 0.77-2.29; >3-6 months clopidogrel: HR = 1.35, 95% CI 0.85-2.14), whereas clopidogrel discontinuation after DES implantation was associated with a higher rate of MACE (<3 month of treatment: HR = 1.99, 95% CI 0.47-8.42; >3-6 months clopidogrel: HR = 2.61, 95% CI 1.31-5.21). Discontinuation after >6 months was associated with a non-significant 37% increased rate of MACE for BMS (HR = 1.37, 95% CI 0.86-2.18), but not DES (HR = 0.95, 95% CI 0.50-1.82).

Conclusions: Discontinuation of clopidogrel was frequently encountered within the first year after coronary stent implantation in spite of a general recommendation of clopidogrel treatment for 1 year. Discontinuation of clopidogrel was, although non-significantly, associated with a 35% increased rate of MACE within one year after BMS implantation. In comparison, clopidogrel discontinuation after DES implantation was associated with a markedly 2-fold increased HR, but only within the first 6 month after implantation.

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Incremental value of platelet reactivity over a risk score of clinical and procedural variables in predicting bleeding events after percutaneous coronary intervention

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Background: Bleeding events after percutaneous coronary intervention (PCI) are associated with increased risk of death at long-term follow-up. Increasing evidence suggests that platelet reactivity (PR) may reliably predict bleeding. Aim of the present study was to investigate the potential incremental value of PR in predicting bleeding events in patients undergoing PCI via the femoral approach over a validated bleeding risk score (BRS) of clinical and procedural variables (bleedingriskscore.org).

Methods: A total of 800 patients undergoing elective PCI via the femoral approach were included in this study. PR was measured immediately before PCI with the VerifyNow (VN)-P2Y12 assay. Calculation of the BRS included the following variables: age, gender, in-hospital aortic balloon pump, glycoprotein IIb/IIIa inhibitors, chronic kidney disease, anemia, low-molecular-weight heparin in 48h pre-PCI Bleeding events were monitored up to 30 days after PCI and defined according to the Thrombolysis in Myocardial Infarction (TIMI), Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) and Bleeding Academic Research Consortium (BARC) bleeding definitions.

Results: A total of 28 (3.5%) TIMI, 44 (5.5%) BARC class ≥2 and 32 (4%) REPLACE-2 bleedings occurred. Both BRS (area under the curve [AUC] 0.717 for TIMI, 0.733 for BARC class ≥2 and 0.719 for REPLACE-2 bleedings) and PR (AUC 0.729 for TIMI, 0.776 for BARC class ≥2 vs. 0.722 for REPLACE-2 bleedings) showed high discriminatory power for bleeding events according to all definitions. However, when combined together, they resulted in a significantly increased discriminatory power (TIMI: AUC 0.818, p = 0.002 vs. BRS alone; BARC class ≥2: AUC 0.812, p = 0.002 vs. BRS alone; REPLACE-2: AUC 0.813, p < 0.001 vs. BRS alone).

Conclusions: Platelet reactivity has incremental predictive value on bleeding events after PCI via the femoral approach over a validated risk score of clinical and procedural variables.