Lack of Rebound in Platelet Reactivity Following Cessation of Prasugrel or Clopidogrel in Type 2 Diabetes Mellitus Patients With Coronary Artery Disease: Insights from OPTIMUS-3

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OBJECTIVE

- Measure platelet reactivity rebound after a one-week washout period following cessation of prasugrel or clopidogrel

Study Design

- Randomized, double-blind, crossover design with a 2-week washout period between study drugs in patients with diabetes mellitus and CAD. Patients remained on aspirin (75-325 mg/day) throughout the study.

METHODS

- **Sample Collection**
  - Venous blood samples were collected at predefined time points into 3.2% citrate tubes.
  - Platelet function was measured by the following methods:
    - In citrated whole blood using VerifyNow® P2Y12 (Accumetrics®)
      - Data recorded as P2Y12 Reaction Unit (PRU)
    - Device-reported % inhibition
    - In platelet-rich plasma using LTA (5 and 20 µM ADP) with a platelet aggregometer (Chrono-Log) at room temperature
      - VASP phosphorylation was measured by a whole blood flow cytometric assay using a Platelet VASP kit (Biocytex®)
      - Reported as platelet reactivity index (% PRI)
  - Time points for rebound analysis:
    - Platelet function was assessed at baseline and after a 7-day washout period
    - Baseline measurements were obtained prior to drug administration and after a 14-day (2 week) washout period prior to crossover to other study drug

Inclusion/Exclusion Criteria

- **Inclusion criteria**
  - Patients between 18 and 75 years of age with diabetes mellitus and CAD; on chronic aspirin therapy, with no increased risk of bleeding (weight ≤60 kg, no history of transient ischemic attack, or ischemic or hemorrhagic stroke)
- **Exclusion criteria**
  - Defined need for thienopyridine therapy, including but not limited to: s12 months of an ACS event

RESULTS

Figure 1. Patient Disposition

- **Enrollment (n=35)**
- **Randomization**
  - Prasugrel 60 mg LD/10 mg MD
  - Clopidogrel 600 mg LD/150 mg MD

The study used a crossover design allowing for evaluation of platelet reactivity rebound during the washout phase.

- **Statistical Analysis**
  - A linear mixed-effect model was used with treatment group, sequence (i.e., carryover effect), and treatment group by sequence (i.e., period) as fixed effects
  - Least-squares estimates for each treatment group and the difference in treatment group means were presented with a 95% confidence interval (CI)
  - Platelet rebound was prospectively defined as a ≥20% increase in baseline platelet function measured 7 days following cessation of study drug. A cut-off value of 20% was chosen because it is outside the range of (-8.3 ± 10.2, 32 -4.6 ± 9.4, 32) µ ADP) for ADP-induced platelet aggregation and defines the upper limit of normal variability. Based on the average platelet survival time, after cessation of drug for 1 week, new fully functional platelets would be the majority of circulating platelets. Results following 2 weeks of washout period are also presented.
  - All statistical analyses were performed with SAS software (version 9.1; SAS Institute)

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CONCLUSIONS

- No evidence of platelet rebound after discontinuation of prasugrel or clopidogrel, as measured by multiple platelet function methods, was found in this population of patients with diabetes mellitus and CAD.

DISCLOSURES

- Drs. Angiolillo, Badimon, Saucedo, Frelinger, and Michelson report grant support from Daiichi Sankyo, Inc. and Eli Lilly and Company. Drs. Angiolillo, Badimon, Frelinger, and Michelson report receiving consultancy fees from Daiichi Sankyo, Inc. and Eli Lilly and Company. Dr. Angiolillo reports receiving honoraria from Daiichi Sankyo, Inc. and Eli Lilly and Company. Drs. Jakubowski, Zhu, Ojeh, and Effron are employees of and report equity ownership or stock options in Eli Lilly and Company. Dr. Baker is an employee of Daiichi Sankyo, Inc.