Relative Association of Genetic Variants to Clopidogrel Responsiveness in Patients Undergoing Percutaneous Coronary Intervention

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Background
- Percutaneous coronary intervention (PCI), the implantation of stents using balloon-tipped catheters, is the most common revascularization procedure for coronary artery disease.
- Dual anti-platelet therapy with aspirin and clopidogrel (PLAVIX®) is the standard standard treatment after PCI.
- However, clinical studies have shown up to 30% of patients exhibit high post-treatment platelet reactivity (HPPR); these patients remain at risk for adverse cardiovascular outcomes (stent thrombosis, myocardial infarction, death).²⁻³
- Clopidogrel, an irreversible inhibitor of ADP P2Y12 receptors, is a pro-drug requiring biotransformation into its active metabolite.

Methods

- **Study Design**
  - Retrospective cohort study
  - Patients (n=183) analyzed from RAPID GENE randomized control trial (clinicaltrials.gov NCT01184300)
  - Consent was obtained for genotyping candidate single nucleotide polymorphisms (SNPs)

- **Inclusion Criteria**
  - < 3 months old
  - Underwent PCI in context of acute coronary syndrome (ACS) or non-ST-elevation acute coronary syndrome (NSTEMI) with a 30-day follow-up

- **Exclusion Criteria**
  - History of stroke or transient ischemic attack
  - Active infection
  - Creatinine clearance <30 ml/min
  - Severe liver dysfunction
  - Pregnancy

- **Genetic Variant**
  - 600 mg oral loading dose of clopidogrel
  - Day 0: Collect peripheral blood
  - Day 0: Platelet Reactivity (VerifyNow P2Y12 Assay)

- **Endpoint**
  - Assess association between carriage of genetic variants and platelet function

- **Genotyping**
  - CYP2C19, PON-1, ABCB1

- **HPPR**
  - PRU > 234

- **CRP**
  - ≤ 1 copy of *2
  - ≥ 1 copy of *3

- **Genotype Distribution**
  - ABCB1 TT >208
  - ABCB1 TT >234

- **Results**
  - No significant associations found between CYP2C19*3, CYP2C19*17, PON-1 QQ, and ABCB1 TT to HPPR in patients undergoing PCI who were treated with clopidogrel.

- **Conclusions**
  - CYP2C19*2 shows the strongest association to HPPR in response to clopidogrel.
  - The low prevalence of CYP2C19*3 is consistent with other studies.
  - There were no significant associations found between CYP2C19*3, CYP2C19*17, PON-1 QQ, or ABCB1 TT and HPPR.

- **Future Directions**
  - Multivariate analysis combining genetic factors and clinical risk factors (body mass index, smoking, ACS, glucose intolerance, and proton pump inhibitors).
  - Developing an algorithm that takes into account genetic and clinical risk factors to prospectively predict clopidogrel non-responsiveness.
  - Pharmacogenetic-based personalized anti-platelet therapy.

**Objective**
To investigate the relative association of other genetic variants, including CYP2C19*3, *17, PON-1 QQ, and ABCB1 TT to HPPR in patients undergoing PCI who were treated with clopidogrel.

**References**

**Acknowledgements**
NIHR Garg received funding from the Undergraduate Research Opportunity Program (UROP) through the University of Ottawa. Dr. Derek So received funding from the Canadian Institutes of Health Research and the technical support of Spartan Bioscience Inc.