Racial disparity with on-treatment platelet reactivity in patients undergoing percutaneous coronary intervention

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Background On-treatment platelet reactivity to clopidogrel is variable and in part genetic dependent. In African American (AA) patients, the relation between on-treatment platelet reactivity to clopidogrel and the factors that influence this interaction is unknown. The present study aims to evaluate on-treatment platelet reactivity to clopidogrel in AA patients and its interaction to race and *CYP2C19*2* loss of function mutation.

Methods The study cohort included 289 consecutive patients presenting for percutaneous coronary intervention who were entered into a prospective observational registry. *High on-treatment platelet reactivity* (HTPR) was defined as P2Y12 reaction units (PRU) ≥208 with VerifyNow P2Y12 assay and >50% by vasodilator-stimulated phosphoprotein phosphorylation assay platelet reactivity index (VASP PRI) measured 6 to 24 hours postprocedure. *CYP2C19*2* (rs4244285) genotype was analyzed by real-time polymerase chain reaction.

Results The prevalence of HTPR by both PRU (56% vs 35%, $P = .003$) and VASP PRI (67% vs 45%, $P = .002$) is more common in AAs compared with whites, respectively. African American patients had higher on-treatment mean PRU (207 ± 110 vs 160 ± 102, $P = .002$) and VASP PRI (49 ± 26 vs 38 ± 26, $P = .004$). African Americans also had a higher prevalence of *CYP2C19*2* allele carrier status compared with whites (43% vs 29%, $P = .04$). African American race ($P = .008$) and *CYP2C19*2* allele status ($P = .02$) independently had significant effects on PRU and VASP. Multivariable logistic regression analysis has shown that both *CYP2C19*2* allele carrier status and AA race were independent correlates of HTPR for PRU ≥208.

Conclusions African American patients undergoing percutaneous coronary intervention not only have a higher prevalence of HTPR to clopidogrel but also have higher *CYP2C19*2* allele carrier status compared with whites. Careful selection of antiplatelet agents should be considered in an AA population at higher risk for ischemic complications. (Am Heart J 2013;166:266-72.)

Numerous studies have shown that a tremendous variability in platelet functional response to clopidogrel and high on-treatment platelet reactivity (HTPR) in patients taking clopidogrel is associated with adverse cardiac events and periprocedural myonecrosis after percutaneous coronary intervention (PCI).[1-3] Clopidogrel as a prodrug requires the hepatic cytochrome P450–mediated conversion to an active metabolite, and its pharmacokinetic and pharmacodynamic effects can be influenced by multiple factors.[4] Several clinical, genetic, and cellular factors are involved in the clopidogrel response variability.[5-8] There are also ethnic differences in HTPR, which supports the hypothesis that genetic mechanisms are partly responsible for the variability in platelet reactivity on clopidogrel therapy.[9]

African American (AA) patients undergoing PCI have unfavorable baseline cardiovascular characteristics and are shown to have worse clinical outcomes and significantly worse long-term survival.[10,11] AA race remained an independent predictor of death and adverse cardiac outcome at 5 years' follow-up.[11] African American race is also shown to be an independent predictor of stent thrombosis (ST) after drug-eluting stent (DES) implantation, even after accounting for potential confounders such as socioeconomic status and

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comorbidities.[12] To further embark on the potential causes of this heightened risk in AA patients, we studied the relation between the on-treatment platelet reactivity to clopidogrel in conjunction to race and *CYP2C19**2 loss of function mutation.

Methods

Study population and data collection

Patients ≥18 years of age presenting for elective and urgent PCI who met the study inclusion and exclusion criteria and provided consent for the platelet reactivity and genetic testing were consecutively enrolled into a prospective, observational registry from June 2010 to February 2012. A dedicated data coordinating center performed all data management and analyses. Prespecified clinical and laboratory data during hospitalization periods were obtained from hospital medical records reviewed by independent research personnel blinded to the study objectives. Written informed consent was obtained from all patients. The institutional review boards at MedStar Washington Hospital Center and the MedStar Research Institute (Washington, DC) approved this study. No extramural funding was used to support this work.

Procedures and adjunctive medical therapy

Percutaneous coronary intervention was performed according to guidelines current at the time of the procedure. All patients received a 600-mg loading dose of clopidogrel ≥6 hours before platelet reactivity testing or a 75-mg maintenance dose for ≥5 days before testing. All patients received aspirin 325 mg 6 to 24 hours before testing. After the procedure, aspirin was prescribed indefinitely; and clopidogrel was prescribed for a minimum of 1 month in patients receiving bare metal stents for elective PCI, and for 12 months in patients receiving DES and in all patients with acute coronary syndrome. Patients who received the glycoprotein IIb/IIIa inhibitor eptifibatide <8 hours before platelet reactivity testing were excluded (no patients received abciximab or tirofiban); as were patients on warfarin, nonsteroidal anti-inflammatory drugs, and those who had a contraindication to aspirin or clopidogrel. Patients known to be pregnant; those with a history of bleeding diathesis, active bleeding, platelet count $<100 \times 10^9$/L, or hematocrit <25%; and those who had received a blood transfusion in the preceding 10 days were also excluded.

Platelet function testing

All patients underwent platelet reactivity testing with the VerifyNow P2Y12 and aspirin assays (Accumetrics, San Diego, CA) and vasodilator-stimulated phosphoprotein phosphorylation (VASP) analysis (FACSCalibur flow cytometer, BD Biosciences, San Jose, CA). The objective was to assess on-treatment platelet reactivity measured 6 to 24 hours after PCI. Whole blood samples were drawn through a ≥18-gauge needle into 3.2% sodium citrate tubes including 1.8-mL Greiner tube for the VerifyNow assay.[13] The platelet reactivity testing was performed within 3 hours of blood sampling.

VerifyNow P2Y12 assay (Accumetrics) was performed by the addition of whole blood to dedicated cartridges containing fibrinogen-coated beads, 20 μmol/L of ADP as agonist, and 22 nmol of prostaglandin E1 (to reduce the nonspecific contribution of P2Y1 receptors). This point-of-care system uses turbidimetric optical detection to measure changes in light transmittance that result from clumping of the fibrinogen-coated beads. These changes are reported as P2Y12 reaction units (PRU). The VerifyNow aspirin assay was performed in a similar manner but used arachidonic acid as the agonist; this result is reported as aspirin reaction units (ARU).

The VASP analysis (FACSCalibur flow cytometer, BD Biosciences) was performed using the PLT VASP/P2Y12 assay. First, whole blood was incubated with ADP with or without prostaglandin E1. A monoclonal antibody to label the VASP protein in its phosphorylated state was added. This antibody was then stained with a fluorescein reagent (BioCytex, Marseille, France), which can be detected as mean fluorescence intensity (MFI) by flow cytometry. The ratio $100 \times (MFI^{PGE1} - MFI^{ADP+PGE1})/MFI^{PGE1}$ was then calculated to estimate the ratio of activated versus nonactivated platelets. This value is reported as the platelet reactivity index (PRI).

*CYP2C19**2 (rs4244285) DNA extraction and genotyping

DNA was extracted from whole blood using the manufacturer's instructions for the Gentra Puregene blood kit (Qiagen, Valencia, CA). Genotyping of *CYP2C19**2 (rs4244285) for the extracted DNA was completed in this study using a TaqMan allelic discrimination assay (AssayID: C__25986767_70; Life Technologies, Carlsbad, CA). Polymerase chain reactions (PCRs) followed standard conditions as recommended by the manufacturer. Briefly, 5 ng of DNA, 900 nmol/L primers, 200 nmol/L probes, and TaqMan Genotyping Universal PCR Master Mix (Life Technologies) and genomic DNA were mixed for a final volume of 10 μL and added to either a 9700 or a 2320 Thermocycler (Life Technologies). The PCR profile was 10 minutes at 95°C (denaturation), 44 cycles of 15 seconds at 92°C, and 1 minute at an annealing temperature of 60°C. Fluorescence ratios and allele calling were completed using a Life Technologies 7900HT system with SDS software (version 2.4). Several steps confirm quality control of the genotyping: the use of negative controls, sequence-confirmed positive control with known genotypes for each plate, and genotyping of replicate samples (5% of total). In addition, SNPs are also checked for Hardy-Weinberg equilibrium. All results were confirmed with manual checking by a technician.

Definitions

High on-treatment platelet reactivity was defined based on multiple recent publications on platelet reactivity, as PRU ≥208 for VerifyNow P2Y12 and PRI >50% for VASP.[14,15] Race determination was based on self-identification on the patient's response at the time of the admission. *Q-wave myocardial infarction* was defined as an elevation of creatine kinase–MB ≥2 times the upper normal value in the presence of new pathologic Q waves (>0.4 second) in ≥2 contiguous leads of the electrocardiogram. *Non–Q-wave myocardial infarction* was defined as typical ischemic chest pain and/or ST-segment and/or T-wave abnormalities with a creatine kinase-MB increase ≥2 times the reference values without any new pathologic Q waves. *Target lesion revascularization* (TLR) was defined as clinically driven revascularization of the index lesion.

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