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Editorial

# Clopidogrel resistance – A clear problem with an unclear solution

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Over the last decade, dual antiplatelet therapy has been shown to be of significant benefit for secondary prevention in millions of patients with acute coronary syndromes (ACS), in those undergoing percutaneous coronary interventions (PCI), and in those with atrial fibrillation unable to take warfarin.[1–3] Much like any other therapeutic agent, variability in response to clopidogrel was considered a reason for clinical failure leading to cardiovascular events; it was not until the 2006 firestorm related to late stent thrombosis that this issue underwent systematic study.[4,5] Investigations into the pharmacokinetic (PK) and pharmacodynamic (PD) properties of clopidogrel led to the uncovering of specific genetic polymorphisms such as *CYP2C19*2* and *ABCB1* involved in the metabolic conversion of the pro-drug clopidogrel into its active metabolite which finally binds to the ADP receptor responsible for the antiplatelet effect. Reduced function of these alleles has since been shown to be associated with impaired PK and PD response to clopidogrel and worse clinical cardiovascular outcomes, with those homozygous for this polymorphism faring worse than those who were heterozygous, adding further biological plausibility.[6–10] Given the large numbers worldwide who need to be on clopidogrel therapy for various secondary prevention indications, even the conservative prevalence estimates for these genetic polymorphisms on the order of 25% make it a priority for clinical research.

The study by Singh et al published in this issue of the Indian Heart Journal meta-analyzes 19,601 subjects from 14 studies and reaffirms the association between the *CYP2C19*2* polymorphism carrier status and increased risk for major adverse cardiovascular events (MACE – RR 1.28, CI 1.06–1.54; $P = 0.009$).[11] The relation also holds for the risk of myocardial infarction and stent thrombosis; however, these results need to be interpreted in the context of significant heterogeneity between studies with respect to these outcomes. There appeared to be no relation between the *CYP2C19*2* polymorphism and bleeding outcomes in their analysis. Also, they did not find an association between *ABCB1* polymorphism carrier status and risk for future MACE or bleeding outcomes. The authors attempt to put their findings in perspective by providing sensitivity, specificity, positive and negative predictive value parameters for genetic testing. The high negative predictive value of genetic testing for MACE of 92–99% is striking, while the low positive predictive value of 3–10% is quite underwhelming. The paper by Singh et al thus adds to the significant body of existing literature regarding the importance of *CYP2C19*2* polymorphisms and associated risk for cardiovascular events.

Previous large observational studies nested in mega-trials have had similar findings, though with some notable differences. Simon et al studied 2,208 acute myocardial infarction subjects in the FAST-MI trial (The French registry of Acute ST elevation or non-ST elevation Myocardial Infarction), showing that patients carrying any two of the *CYP2C19* loss-of-function polymorphisms had a significantly elevated 1-year MACE rate. A moderate association was also shown in the study for *ABCB1* carrier status and MACE.[9] Mega et al evaluated CYP450 genetic variants and their associations with MACE in 1,477 clopidogrel treated subjects from the TRITON-TIMI 38 trial (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel). *CYP2C19*2* carrier status was associated with an elevated risk for MACE and stent thrombosis, but not bleeding outcomes.[7]

While the risk associated with these *CYP2C19* polymorphisms has clearly been defined, a clear solution has been less forthcoming. Attempts at tailoring clopidogrel therapy using a platelet function guided approach have not been successful, as seen in the GRAVITAS and TRIGGER-PCI trials.[12,13] In the GRAVITAS trial (Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety), 5,429 patients on the regular clopidogrel dose underwent

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platelet function testing, and 2,214 who had high residual platelet reactivity [P2Y (12) reaction units (PRU) ≥230] were randomized to continue on the 75-mg clopidogrel dose or to receive a 600-mg loading dose and a 150-mg maintenance dose.[12] At 6 months, the composite primary end point of cardiovascular death/MI/stent thrombosis was identical in both groups, at 2.3% using the predefined cutoff of 230 PRU. This strategy was not associated with a significantly lower risk of the primary end point at 60 days or at 6 months. A *post hoc* look at a threshold of 208 PRU (informed by more recent data from the 3T/2R[14] and TRIGGER-PCI studies) showed that patients with platelet reactivity below this cutoff did have a lower risk of the primary end point both at 60 days and 6 months. In the TRIGGER-PCI trial (Testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel), stable coronary artery disease (CAD) patients with high on-treatment platelet reactivity (>208 PRU by the VerifyNow test) after elective PCI with at least one drug-eluting stent (DES) were randomly assigned to either prasugrel 10 mg daily or clopidogrel 75 mg daily. Platelet reactivity of the patients on the study drug was reassessed at 3 and 6 months. The study was stopped prematurely for futility because of a lower than expected incidence of the primary end point.[13]

The concept that lowering PRU or achieving adequate platelet inhibition might be a dose issue receives mechanistic credence from the ELEVATE TIMI-56 (Escalating Clopidogrel by Involving a Genetic Strategy) study.[15] Mega et al studied 333 patients who were genotyped and then received various maintenance doses of clopidogrel depending on genotype for four 14-day treatment periods. The 247 non-carriers of a loss-of-function *CYP2C19*2* allele received clopidogrel doses of 75 mg and 150 mg daily (two periods each), while the 86 carriers (80 heterozygotes, six homozygotes) received doses of 75 mg, 150 mg, 225 mg, and 300 mg daily. At the end of each study period, platelet function testing was performed with both VASP and VerifyNow assays. When treated with a standard clopidogrel maintenance dose of 75 mg daily, both *CYP2C19*2* heterozygotes and homozygotes had significantly higher on-treatment platelet reactivity than did non-carriers. Among *CYP2C19*2* heterozygotes, each 75-mg increase in clopidogrel dose led to an approximate 8% to 9% absolute reduction in the platelet-reactivity index. At the end of the study period, 52% of *CYP2C19*2* heterozygotes were non-responders (≥230 PRU) with 75 mg of clopidogrel, while only 10% were non-responders with 225 or 300 mg ($P < 0.001$ for both). In *CYP2C19*2* homozygotes, even with 300 mg daily of clopidogrel, mean VASP PRI was 68.3% (95% CI 44.9%–91.6%) and mean PRU was 287.0 (95% CI 170.2–403.8). Thus, among patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in *CYP2C19*2* heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in non-carriers; in contrast, for *CYP2C19*2* homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition. What remains to be shown, however, is translation of this mechanistic benefit into reduction in clinical outcomes with an acceptable bleeding risk in a large randomized trial.

On the other hand, trials studying the efficacy of clopidogrel versus placebo do not show any effect modification by genotype. In the CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) which enrolled subjects with clinically evident cardiovascular disease or multiple risk factors and randomized them to clopidogrel versus placebo added on to background therapy with aspirin, genotyping data was examined in 4,819 subjects.[16] Carriers of *CYP2C19* loss-of-function alleles did not have an increased rate of ischemic events, but did have a significantly lower rate of any bleeding (HR for bleeding: 0.80, 95% CI 0.69–0.93, $P = 0.003$). Similar results were seen in the analysis from the CURE/ACTIVE genetic sub-study.[17] Among 5,059 genotyped patients with ACS in the CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events), clopidogrel as compared with placebo significantly reduced the rate of the primary efficacy outcome, irrespective of the genetic polymorphism carrier state (HR with clopidogrel for carriers, 0.69; 95% CI 0.49–0.98; HR among non-carriers, 0.72; 95% CI 0.59–0.87). The effect of clopidogrel on bleeding did not vary according to genotypic subgroups. Among 1,156 genotyped patients with atrial fibrillation in the ACTIVE trial (Atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events), there was no evidence of an interaction with respect to either efficacy or bleeding outcomes between the study treatment and the metabolizer phenotype, loss-of-function carrier status, or gain-of-function carrier status. It follows from these data that genotyping is not really useful if the choice is between placebo and standard clopidogrel dosing.

Why the disconnect? As shown elegantly by Shuldiner et al, the *CYP2C19* polymorphisms are not associated with baseline platelet aggregation or response to aspirin, but only affect aggregation in response to clopidogrel.[18] In addition, it is possible that a proportion of the excess risk associated with the polymorphism may be independent of clopidogrel and may have to do with potential effects on the metabolism of other cardiovascular drugs. Importantly, the genetic polymorphisms explain only a small part of the clopidogrel resistance story; drug compliance, body mass index, diabetes, smoking, use of proton pump inhibitors, and the presence of acute coronary syndromes all contribute to the variability in clopidogrel effect.[19]

Given the current state of the data especially regarding outcomes related to a genotyping strategy, we are in agreement with the authors' cautious optimism regarding the larger uptake of genetic testing. One might argue that therapy with ticagrelor or prasugrel has been clearly shown to be superior to clopidogrel even in responders and data exist to clearly demonstrate that both these drugs provide efficacious platelet inhibition in carriers of the clopidogrel platelet resistance polymorphisms.[20,21] This then seems like the "easy" solution to the clopidogrel variability problem. This easy solution, however, carries a hefty price tag, especially when one considers the generic availability of clopidogrel. Clopidogrel will most likely continue to be a part of the antiplatelet armamentarium for some time into the future and dose titration or selective use, with the option to switch to more potent agents when needed, may be a choice for the clinical community.[22] Availability of point of care rapid testing as

shown in the RAPID GENE study (ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy Based on GENetic Evaluation) may make this strategy feasible and cost-effective.[23] Large randomized, controlled trials will be needed to validate the effectiveness and/or cost-effectiveness of such an approach before routine use. Meanwhile, as wisely concluded by the authors and indicated in the ACC PCI guidelines, routine genetic testing for clopidogrel resistance cannot be advised.[24]

## Disclosure

Dr. Deepak L. Bhatt discloses the following relationships – Advisory Board: Medscape Cardiology; Board of Directors: Boston VA Research Institute, Society of Chest Pain Centres; Chair: American Heart Association Get With The Guidelines Science Subcommittee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today Intervention), WebMD (CME steering committees); Research Grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda. He was the international Principal Investigator for the CHARISMA Trial and the CHARISMA Genetics Study.

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