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# Is clopidogrel as the $P2Y_{12}$ inhibitor a wise choice for long-term monotherapy in patients undergoing stenting?

**Paul A. Gurbel***, MD; Udaya S. Tantry, MD

*Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD, USA*

International practice guidelines uniformly recommend dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor in patients undergoing drug-eluting stent (DES) implantation to reduce ischaemic events such as stent thrombosis. In high-risk coronary artery disease (CAD) patients, potent platelet $P2Y_{12}$ inhibitors such as prasugrel or ticagrelor are preferred whereas in stable CAD patients clopidogrel is widely used[1,2]. A shorter duration of DAPT (1-3 months) followed by mono antiplatelet therapy has been suggested based on the significantly lower incidences of stent thrombosis with second-generation DES[1,2]. A recent meta-analysis suggested that de-escalation of DAPT after 1-3 months to monotherapy with a $P2Y_{12}$ inhibitor, but not aspirin, might be a safer and equally effective strategy compared to 12 months of DAPT[3]. However, the choice of $P2Y_{12}$ receptor inhibitor has been continuously debated for stable CAD patients versus high-risk acute coronary syndrome (ACS) patients[1-3]. None of the short DAPT trials have been adequately sized to assess effects on stent thrombosis.

Since the initial demonstration of clopidogrel response variability in 2003, numerous translational research studies have repeatedly confirmed the independent association of the high platelet reactivity (HPR) to ADP phenotype with post-stent ischaemic events, particularly stent thrombosis[4-6]. It has been shown that East Asians exhibit a higher prevalence of clopidogrel non-responsiveness that is attributed to a higher prevalence of CYP 2C19 loss-of-function (LOF) allele carriage[7]. CYP 2C19 is the dominant cytochrome responsible for converting clopidogrel to its active metabolite. In studies of East Asians undergoing percutaneous coronary intervention (PCI), CYP 2C19 LOF allele carriage, as in Caucasians, has translated into more thrombotic outcomes post-stenting than in non-carriers. However, the heightened thrombotic risk associated with LOF carriage in East Asians is less than expected given the high frequency of LOF carriage. The latter phenomenon was termed as the "East Asian paradox" by our group. Moreover, higher cut-offs of HPR have been suggested in East Asian patients (252–289 $P2Y_{12}$ reaction units [PRU]) in comparison to Caucasian patients (208 PRU)[8].

In this issue of EuroIntervention, Lee et al explored the relevance of HPR to post-PCI ischaemic event occurrences in the platelet function substudy of the SMART-CHOICE trial conducted in South Korea[9]. In the SMART-CHOICE trial of 2,993 patients undergoing PCI with DES, the prevalence of 12-month major adverse cardiovascular and cerebrovascular events (MACCE) was similar between patients treated with aspirin plus a $P2Y_{12}$ receptor inhibitor for three months followed by $P2Y_{12}$ inhibitor alone, and those treated with DAPT for 12 months (2.9% versus 2.5%; p=0.007 for non-inferiority). In the original trial, 41% and 59% of patients were admitted with stable angina and ACS, respectively, whereas 78%, 18%, and 4% of patients were treated with clopidogrel, ticagrelor,

*Corresponding author: Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, 2401 W Belvedere Ave, Baltimore, MD 21215, USA. E-mail: pgurbel@lifebridgehealth.org





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and prasugrel, respectively. In the current platelet function testing (PFT) substudy, platelet reactivity was measured in 833 patients on clopidogrel therapy at 2-4 weeks after randomisation using the VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA). In this cohort of clopidogrel-treated patients, 58% and 42% of patients were admitted with stable CAD and ACS, respectively. Nearly 13% of patients on clopidogrel met the East Asian definition of HPR (PRU ≥275). It is interesting to note that in our seminal paper published 18 years ago, the prevalence of clopidogrel non-responsiveness was also 15% when assessed by ADP-induced platelet aggregation at 30 days after coronary stenting[5]. In the PFT substudy of SMART-CHOICE, patients with HPR exhibited a higher rate of MACCE compared to patients without HPR (8.7% vs 1.5%, p=0.038). There were no treatment interactions – the MACCE and Bleeding Academic Research Consortium (BARC) 2-5 bleeding rates were similar between patients treated with DAPT versus monotherapy irrespective of the presence of HPR (adjusted p for interaction=0.17 and 0.42, respectively)[9].

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In our opinion, the major concern of clopidogrel monotherapy as the sole antiplatelet strategy in patients treated with stents is a lack of antiplatelet effect in poor metabolisers and patients with HPR. The authors of the current study clearly demonstrate the clinical risk associated with HPR and should be congratulated for exploring this important relevant issue of the optimal effectiveness of long-term clopidogrel monotherapy. This study has many important implications. Significantly, the study results again reinforce the time-tested "platelet hypothesis" that states that HPR is a risk factor for post-PCI ischaemic events, and that greater platelet inhibition can reduce the risk of ischaemic events[10]. In this PFT substudy, most of the post-PCI events were observed in patients with HPR, and a higher prevalence of HPR was observed in ACS patients compared to stable CAD patients (15% vs 10%). Intriguingly, compared to patients with HPR, patients who were responders to clopidogrel had a MACCE rate that was similar to patients treated with potent $P2Y_{12}$ receptor blockers (8.7% vs 1.7% vs 2.2%, respectively). These data suggest that clopidogrel therapy in responders based on a pharmacodynamic assessment is as clinically effective as potent $P2Y_{12}$ receptor inhibitors. These results again support the finding of the TROPICAL-ACS study where de-escalation to clopidogrel in responders and treating only clopidogrel non-responders with a potent $P2Y_{12}$ receptor inhibitor provided similar clinical efficacy[11]. A final take-home message from this study may be that clopidogrel is definitely not a uniform treatment of choice for long-term therapy in the presence of an attenuated pharmacodynamic effect and elevated ischaemic risk, and clopidogrel is clinically as effective as potent $P2Y_{12}$ receptor blockers in pharmacodynamically responsive patients. The results of the PFT substudy of the SMART-CHOICE trial further support personalising antiplatelet therapy based on platelet function, rather than blanket therapy with a more potent $P2Y_{12}$ inhibitor, which is associated with more bleeding that may be particularly present in an East Asian population[6].

## Conflict of interest statement

P.A. Gurbel reports grants and personal fees from Bayer HealthCare LLC, OtiTopic Inc, Amgen, Janssen, and US WorldMeds LLC; grants from Instrumentation Laboratory, Haemonetics, Medicure Inc, Idorsia Pharmaceuticals, and Hikari Dx; personal fees from UpToDate, Inc; he is a relator and expert witness in litigation involving clopidogrel. In addition, he has two patents: Detection of restenosis risk in patients (10942192) and Assessment of cardiac health and thrombotic risk in a patient (10660942). U.S. Tantry reports personal fees from UptoDate, Inc. and AggreDyne.

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