

Editorial

Gene Guided Therapy for ACS Patients Undergoing Percutaneous Coronary Intervention

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The presence of the CYP2C19 gene is a predictor of adverse cardiac outcomes in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) with clopidogrel treatment [1]. Newer and more potent antiplatelet agents reduce rates of adverse cardiac outcomes, but at the cost of an increased risk of bleeding [2]. To date, antiplatelet therapy guided by platelet function studies has not been proven to be effective in reducing cardiac events; however, several trials regarding gene guided antiplatelet therapy are now ongoing. While the results of these trials are pending, several issues for gene guided anti-platelet therapy will be discussed.

Relationship between the CYP2C19 gene and cardiovascular outcomes

In studies with healthy volunteers, tests have shown that CYP2C19 *2 allele carriers harbor relatively lower active-metabolite concentrations (32.4%) and platelet function (25%) [3]. In TIMI-TRITON 38 [4], allele carriers were at a higher risk of ischemic events (HR 1.53) and stent thrombosis (HR 3.09), while Sibbing et al. [5], also reported higher incidence of stent thrombosis in carriers (HR 3.81). Among the 2C19 gene carrier types, double carriers (homozygotes) have higher event rates than single carriers (heterozygotes) (HR 1.81 vs 1.61). In a meta-analysis, Hulot et al. [6], reported that these gene carriers had HR values of 3.45 for stent thrombosis and 1.79 for death. The presence of a gain-of-function SNP (CYP2C19 *17) is associated with an increased risk of bleeding in homozygous patients [7]

CYP2C19 carrier prevalence among ethnic groups

Higher rates of 2C19 gene carriage have been identified in people of East Asian descent, when compared to their Caucasian counterparts. In our data set (n=244), 60% of patients were carriers of the *2 and *3 alleles, a higher incidence than would be expected for Caucasians (Table 1) [8]. In addition, the *3 allele is rare in Caucasians but was detected in 18% of our patients, whereas only 2-3% harbored the *17 allele. Likely due to the high incidence of *2 and *3 alleles and lower incidence of *17 alleles, an increased frequency of high platelet reactivity (HPR) and elevated mean PRU levels occurred in our East Asian patients during and post-PCI (with higher cutoff for HPR: 272) [9].

Platelet function-guided therapy in PCI patients

The GRAVITAS trial [10] was a platelet function-guided PCI study using the VerifyNow P2Y12 test. In the 12-24 h post-PCI period, patients with PRU values above 230 were randomized into high-dose or standard-dose clopidogrel groups. This study did not detect any differences in cardiovascular adverse outcomes, partly due to the very low incidence of cardiac events in the entire patient population. Similarly, the TRIGGER-PCI study [11], using prasugrel instead of high-dose clopidogrel, did not show any statistical differences. A more complicated platelet function-guided trial, ARCTIC [12], also failed to show any positive clinical results. Therefore, platelet function testing during PCI is not recommended in current practice guidelines (IIb recommendation, 2012 PCI updated guideline) [13].

The GRAVITAS [10] and TRIGGER-PCI trials [11] aimed to detect reductions in HPR, but these studies did not use a reloading approach or include high risk, acute phase patients. Therefore, we are currently conducting a study to involve early manipulation of HPR using a more potent agent before or during PCI using VerifyNow PRU values (PRAISE-HPR, NCT01609647) [14].

Gene-guided therapy

Gene-guided therapy is another option for ACS or high-risk PCI patients. However, the procedure can take a day or longer using current facilities at many PCI sites. Recent POC (point-of-care) gene technology has sought to address this problem with the shortening of 2C19 gene carriage confirmation time to within 1-2 hours. Therefore, ASCPT guidelines [15] suggest this approach for ACS patients or those undergoing elective PCI. Although current ESC guidelines [16] recommend the routine use of new potent antiplatelet agents such as prasugrel or ticagrelor, current ACC/AHA guidelines [17] have yet to reflect these changes.

To further investigate these issues, our current study involves early manipulation of HPR using a more potent agent prior to PCI, and reflecting each patient's 2C19 gene carrier status (PRAISE-GENE study, NCT01641510).

Table 1: Frequencies of CYP2C19*2 and *3 minor alleles and phenotype prevalence in various ethnic groups:

	*2 Allele frequency	*3 Allele frequency	% IM	% PM	%(IM+PM)
Caucasian	0.14	0.0	24	2	26
African	0.14	0.0	24	2	26
Asian	0.27	0.09	46	10	56
DAUH Data	0.25	0.10	47	11	58

IM: Intermediate metabolizer-*1/*2 and *1/*3 genotypes; **PM:** Poor metabolizer-*2/*2,*3/*3, and *2/*3 genotypes. **DAUH:** Dong-A University Hospital

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References

- Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ*. 2011; 343: d4588.
- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357: 2001-2015.
- Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009; 360: 354-362.
- Sorich MJ, Vitry A, Ward MB, Horowitz JD, McKinnon RA. Prasugrel vs. clopidogrel for cytochrome P450 2C19-genotyped subgroups: integration of the TRITON-TIMI 38 trial data. *J Thromb Haemost*. 2010; 8: 1678-1684.
- Sibbing D, Stegheer J, Latz W, Koch W, Mehilli J, Dörrler K, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J*. 2009; 30: 916-922.
- Hulot JS, Collet JP, Silvain J, Pena A, Bellemain-Appaix A, Barthélémy O, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol*. 2010; 56: 134-143.
- Gurbel PA, Tantry US, Shuldiner AR. Letter by Gurbel et al Regarding Article, "Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement". *Circulation*. 2010; 122: e478.
- Beitelshees AL, Horenstein RB, Vesely MR, Mehra MR, Shuldiner AR. Pharmacogenetics and Clopidogrel Response in Patients Undergoing Percutaneous Coronary Interventions. *Clin Pharmacol Ther*. 2011; 89: 455-459.
- Zhang HZ, Kim MH, Jeong YH. Predictive values of post-clopidogrel platelet reactivity assessed by different platelet function tests on ischemic events in East Asian patients treated with PCI. *Platelets*. 2013. [Epub ahead of print].
- Matthew Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, et al. Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention The GRAVITAS Randomized Trial. *JAMA*. 2011; 305: 1097-1105.
- Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol*. 2012; 59: 2159-2164.
- Collet JP, Cayla G, Cuisset T, Elhadad S, Rangé G, Vicaut E, et al. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J*. 2011; 161: 5-12.e5.
- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011; 124: e574-651.
- Lee DH, Kim MH, Park TH, Park JS, Park K, Zhang HZ, et al. Comparison of prasugrel and clopidogrel reloading on high platelet reactivity in clopidogrel-loaded patients undergoing percutaneous coronary intervention (PRAISE-HPR): a study protocol for a prospective randomized controlled clinical trial. *Trials*. 2013 28; 14: 62. doi: 10.1186/1745-6215-14-62.
- Johnson JA, Cavallari LH, Beitelshees AL, Lewis JP, Shuldiner AR, Roden DM. Pharmacogenomics: application to the management of cardiovascular disease. *Clin Pharmacol Ther*. 2011; 90: 519-531.
- Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34: 2949-3003.
- Jneid H, Anderson JL, Wright RS, Adams CD, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2012; 126: 875-910.