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Editorial

Gene Guided Therapy for ACS Patients Undergoing Percutaneous Coronary Intervention

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Editorial

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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