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Pharmacogenomic Testing of Anti-Platelets Drugs and its Cost-Effectiveness

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Percutaneous Coronary Intervention (PCI) plays a vital role in the management of Acute Coronary Syndrome (ACS) patients [1]. Intensive dual anti-platelet treatment is necessary in patients received PCI. Anti-platelet agents, including aspirin, thienopyridines, and platelet Glycoprotein (GP) IIb/IIIa receptor inhibitors, have become the foundation of antithrombotic therapy [2]. Recently, observational studies documented the drug-drug interactions between clopidogrel and proton pump inhibitors (PPI) that may lead to undesirable adverse cardiovascular outcomes [3-5]. It was also suggested that H_2-receptor antagonist (H2RA) may be considered an alternative; yet its clinical efficacy is yet to be confirmed due to contradicting results from various studies [6,7].

Clopidogrel is a pro-drug that requires hepatic biotransformation by cytochrome P450 3A4 and 2C19 to an active metabolite [8]. Genetic polymorphism of the CYP 2C19 has been documented to have an impact on the metabolism of clopidogrel. Based on the metabolic activity of an individual, most of the population can be categorized as Extensive Metabolizers (EM), Intermediate Metabolizer (IM) or Poor Metabolizers (PM). The two main mutations that are related to the PM phenotype are CYP 2C19*2 and CYP 2C19*3 [9,10]. Genetic polymorphism of CYP 2C19 also demonstrated with interracial differences, approximately 2-5% of Caucasians and 11-23% of Oriental populations representing with the PM phenotype [10]. It has been documented that PMs of CYP 2C19*2 (loss-of-function allele) has a marked decrease in platelet responsiveness to clopidogrel [11,12]. It increased cardiovascular events including death (12.1% [carriers] versus 8.0% [non-carriers], Hazard ratio of 1.53; 95% CI, 1.07 to 2.19) and stent thrombosis (2.6% [carriers] versus 0.8% [non-carriers], Hazard ratio, 3.09; 95% CI, 1.19 to 8.00) than non-carriers [13]. Yet, genetic screening is not a usual clinical practice in the management of ACS patients. The situation is more problematic when patients require concurrent use of PPIs for gastrointestinal protection. The incidence of inpatient cardiac-related death was 12% in PM genotypes with concurrent use of PPI and clopidogrel compared to non-PPI users at 5% [11]. In addition, there will be additional expenditure and work force for the genetic screening. It is important to assess the cost-effectiveness of this screening before suggesting routine genetic screening to the real world cardiology practice.

Acute coronary syndrome is a major cause of mortality and morbidity in different countries including Hong Kong [14]. In our previous study, we have documented the average cost of ACS management per patient per year was US$ 10,998 using dual antiplatelet therapy [15]. In Hong Kong, it was shown that 50% of all hospitalizations of peptic ulcer bleeding were related to the use of antiplatelet agent (namely aspirin) or non-steroidal anti-inflammatory drugs (NSAIDs) [16]. In our previous one-year randomized trial of clopidogrel versus aspirin with PPI in patients with vascular diseases who had a history of peptic ulcer bleeding, we showed that the incidence of recurrent bleeding was significantly lower in the aspirin/PPI group (0.7%) than the clopidogrel group (9%) (16). Our finding was contrary to the recommendations of the American Heart Association and American College of Cardiology to use clopidogrel in patients with gastrointestinal problems [17]. In our previous study, we observed that there was 45%, 41% and 14% of Hong Kong Chinese with the EM, IM, and PM phenotypes respectively [18]. The prevalence of PM phenotype was higher than Caucasian population. Therefore, Chinese ACS patients with PM genotype on clopidogrel may have unsatisfactory clinical outcomes including Major Adverse Cardiac Events (MACE) such as Myocardial Infarction (MI), target lesion revascularizations, or death. We have conducted a cost of acute MI study in Hong Kong. The economic impact of MACE is vast and significant since our results showed that the yearly cost of acute MI management for each patient was US$ 9,383 [19].

To date, there are newer antiplatelet agents including prasugrel and ticagrelor that are not genetic dependent as compared with clopidogrel. However, the costs of these newer agents are more expensive given the availability of generic clopidogrel. It has been shown that genotype-guided antiplatelet therapy in ACS patients may be cost-effective when comparing a simulated cohort of ACS patients using either clopidogrel or prasugrel [20]. It is unknown how these newer agents impact on the clinical practice along with routine pharmacogenomics screening since most of the published articles are based on simulation rather than the real-world findings. Recently, the working group of the National Heart Lung and Blood Institute (NHLBI) reviewed three areas where pharamcogenomic applications can be applied. These 3 areas are anticoagulants, anti-platelet agents and lipid lowering agents [21]. The NHLBI noted the clinical challenges and clinical needs for cardiovascular pharmacogenomics. The gold standard to validate cardiovascular pharmacogenomics must include findings from the prospective randomized controlled trials. However, the prospective clinical trials are not possible with sustainable financial and institutional support. In addition, there is a great demand for experts in health technology assessment (HTA) and health policy for the validation of cost-effectiveness in cardiology pharmacogenomics including anti-platelet agents. The impact of HTA on health policy can be country specific and may be influenced by various clinical, political, financial and cultural factors in each country. The established platform in one country may not apply in another country.

In conclusion, pharmacogenomic screening of antiplatelet agents may improve clinical outcomes of ACS patients. However, it is

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important to establish a sustainable platform to evaluate the long-term clinical and economic impact of the translational pharmacogenomic testing of anti-platelet agents in ACS management.

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