Options to Overcome Clopidogrel Response Variability

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Clopidogrel is one of the most frequently prescribed medications in the field of cardiovascular medicine. It is an integral component of the treatment of acute coronary syndrome (ACS) and post-percutaneous coronary intervention (PCI) patients.\(^1,2\)

Clopidogrel has a broad spectrum of use, including secondary prevention of stroke in high-risk patients,\(^3\) as an alternative for patients who are intolerant to aspirin,\(^4\) and to prevent stroke in patients with atrial fibrillation who cannot take warfarin.\(^5\) There is wide variability in the response to clopidogrel, and thus we cannot expect the same degree of platelet inhibition in all patients.\(^6,7\) Also, the onset of action of clopidogrel is slow, requiring a higher loading dose to reduce the time to full effect.\(^7\) Therefore, nearly 30% of patients treated with clopidogrel do not achieve an adequate antiplatelet response.\(^8,9\)

This is a major shortcoming of clopidogrel, and has led to various efforts to reduce the response variability and to potentiate its antiplatelet effects. The major reason for the response variability is that clopidogrel is a prodrug that requires absorption and a 2-step activation process to yield its active metabolite.\(^10,11\) Therefore, any alteration in this process can result in reduced levels of active metabolite and thus a reduced antiplatelet effect.

The response to clopidogrel is affected by genetic variations.\(^10,12\) A typical example is the effect of polymorphisms in the cytochrome P450 enzymes (which can affect metabolism),\(^13\) or the P-glycoproteins (which can affect absorption).\(^14\)

Carriers of the CYP2C19*2 allele have been shown to have a reduced response to clopidogrel and significantly worse outcomes, compared with those that do not have the allele, when treated with clopidogrel.\(^13,15\) Similarly, the FAST-MI investigators reported that among patients with acute myocardial infarction (MI), carriers of the CYP2C19 loss-of-function (LOF) alleles had a significantly greater risk of cardiovascular events.\(^16\) In that study, they also found that patients with 2 variant alleles of ABCB1 (the gene coding P-glycoprotein) were at greater risk of cardiovascular events. Others have reported the combined effects of both CYP2C19 and ABCB1.\(^17\)

In addition to genetic factors, many clinical factors are associated with high clopidogrel on-treatment platelet reactivity (OPR), such as diabetes, female sex, smoking, ACS, and body mass index.\(^18-21\) and clopidogrel is also prone to drug-drug interaction with proton-pump inhibitors\(^22,23\) and calcium-channel blockers.\(^24,25\)

**Clopidogrel Response Variability in Asia**

Although most of the data regarding clopidogrel response variability has come from Western countries, this phenomenon is not exclusive to the Western population. We reported the distribution of OPR in 1,431 consecutive Korean patients,\(^26\) and found that the mean OPR was 241.9±70.3 (P2Y12 reaction units, PRU), which is significantly higher than in previous reports from the United States.\(^27\) Furthermore, various clinical characteristics were independently associated with high clopidogrel OPR, including female sex, chronic renal disease, diabetes, mellitus, high level of high-sensitivity C-reactive protein, older age, and smoking status. Higher platelet reactivity in Asians has not only been reported in Koreans, but also in Asian Indians,\(^28\) Japanese,\(^29\) and Chinese.\(^30\)

A proposed mechanism of the heightened platelet reactivity in Asians is based on the fact that the frequency of CYP2C19 LOF polymorphism is strikingly higher in Asians than in Caucasians. In Koreans, we reported that the proportion of patients carrying at least 1 CYP2C19*2 allele was 53%, and these

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patients had significantly higher clopidogrel OPR than non-carriers. If we consider the CYP2C19*3 LOF allele, which is almost non-existent in Caucasian patients, the frequency of CYP2C19 LOF allele carriers exceeds 60% in the Korean population. The frequency of the CYP2C19 LOF allele is also very high in other East Asian populations, such as Chinese and Japanese. In Chinese, Tang et al reported that the proportion of patients carrying at least one CYP2C19*2 LOF allele was greater than 50%, and these patients were at significantly higher risk for urgent coronary revascularization compared with the wild type. In Japanese, the percentage of CYP2C19*2 LOF carriers is reported to be approximately 42%.

The relationship among decreased response to clopidogrel, genetic risks, and clinical outcome also holds true in Asians, similar to Western populations. In the CROSS VERIFY cohort, we found that because Koreans as a population have a higher mean OPR, the best cut-off value to discriminate patients with high OPR is higher in Koreans. Nevertheless, the positive relationship between high OPR and adverse clinical outcome, including cardiac death, MI and stent thrombosis, is significant regardless of the definition of high OPR (cut-off value 235 or 275 PRU) in addition, the carrier status of CYP2C19 is also associated with outcome in Asians. From the SKY registry we reported that carriers of the CYP2C19*2 allele had a 2.6-fold risk for the occurrence of cardiac death and MI. In Chinese, it has also been reported that carriers of the CYP2C19*2 LOF allele have a significantly higher risk of stent thrombosis after PCI. In Japan, there was an interesting optical coherence tomography study by Sawada et al, who found that carriers of the 2C19*2 LOF allele had greater occurrence of intra-stent thrombosis formation, suggesting that genetic risk may be associated with greater thrombotic risk. In summary, the scope of the problem with clopidogrel response variability, high OPR, and genetic risks associated...
with CYP2C19 LOF polymorphisms seem to be at least as significant, if not more significant, in the Asian population as in Western countries. In addition, the positive relationship between these risks and thrombotic outcome seems to hold true in the Asian population.

**Options for Overcoming Clopidogrel Response Variability**

Having explained the problems associated with clopidogrel response variability, and that this is very much an issue in the Asian population, we need to find measures to overcome it. Figure summarizes the action mechanisms of the drugs covered in this review. Clopidogrel, prasugrel, and ticagrelor all act through the platelet P2Y12 receptor, whereas cilostazol inhibits the degradation of cyclic adenosine monophosphate (cAMP). There are many novel agents under development, but to be pragmatic, we will discuss only the options that are available at present in Asian countries.

**Option 1: Increasing the Dose**

One possible solution to overcome the decreased response to clopidogrel is to increase the dose: (1) increase the loading dose from 300 mg to 600 mg, or (2) increase the maintenance dose from 75 mg to 150 mg. There have been several studies that have shown the benefit of a higher loading dose. Gurbel et al showed that increasing the initial loading dose of clopidogrel significantly reduced the risk of a poor response to the drug.\(^{35}\) A loading dosage of 600 mg led to an earlier, stronger, and more sustained inhibition of platelet function.\(^{37,38}\) In the Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA) trial,\(^{39}\) a small group of 255 patients were randomized to different loading doses of clopidogrel (600 mg vs. 300 mg) before PCI. At 30 days, there was a significant reduction in the rates of death, MI, and target vessel revascularization in the 600-mg group.

The data are not as convincing with regard to increasing the maintenance dose. In the OPTIMUS trial,\(^{40}\) patients with diabetes or coronary artery disease were randomly assigned to either 75 mg or 150 mg of clopidogrel maintenance therapy. The double-dose clopidogrel group had significantly increased inhibition of maximal platelet inhibition to both 5 and 20 μmol/L stimulation of adenosine diphosphate (ADP). This strategy was first tested clinically in the CURRENT-OASIS 7 trial, which randomized patients with ACS to standard dose of clopidogrel against a 1-week duration of double-dose (150 mg/day) of clopidogrel. The overall trial, which had over 25,000 patients, including both those undergoing PCI and medical therapy, double-dose clopidogrel did not significantly reduce the occurrence of the primary outcome of cardiovascular death, MI, or stroke (hazard ratio (HR), 0.94; 95% confidence interval (CI) 0.83–1.06; P=0.30).\(^{41}\) However, in the 17,263 patients in the PCI subgroup, double-dose clopidogrel resulted in a 14% relative reduction in the risk of the primary outcome and a 46% reduction in the risk of stent thrombosis.\(^{42}\) In the GRAVITAS trial, patients with high clopidogrel OPR (defined as \(\geq 230\) PRU on Verify Now P2Y12 measurement), were randomized to 6 months of the standard dose vs. double-dose maintenance clopidogrel. The primary outcome, which was cardiovascular death, MI or stent thrombosis, was not significantly different between the 2 treatment groups (HR 1.01; 95%CI 0.58–1.76; P=0.97), suggesting that in stable low-risk patients undergoing elective PCI, doubling the dose of clopidogrel does not have additive benefit over standard dose clopidogrel, even in those with documented high OPR to clopidogrel.\(^{43}\) In a post-hoc analysis, the investigators showed that patients with the CYP2C19 LOF allele generally did not respond well to doubling the dose of clopidogrel, which was still insufficient to adequately inhibit platelet function (unpublished data, presented at the American College of Cardiology 2011 Scientific Sessions). This was confirmed in the recent ELEVATE TIMI-56 trial, which measured platelet reactivity at different maintenance doses of clopidogrel. Those investigators found that in heterozygotes of the CYP2C19*2 polymorphism, the response was comparable to that of non-carriers when the dose of clopidogrel was tripled (225 mg) or quadrupled (300 mg). However, among homozygotes even the highest maintenance dose (300 mg) did not result in adequate platelet inhibition in certain patients.\(^{44}\)

**Option 2: Adding Cilostazol as a Third Agent**

Cilostazol is a reversible phosphodiesterase 3 inhibitor that exerts antiplatelet effects through increasing the intracellular cAMP level.\(^{45,46}\) The addition of cilostazol to conventional dual antiplatelet therapy (DAT), so-called triple antiplatelet therapy (TAT), has shown various benefits. It is well known that cilostazol inhibits smooth muscle proliferation in addition to inhibition of platelets.\(^{46}\) In a combined analysis of the DECLARE-DIABETES and DECLARE-LONG studies, TAT significantly reduced the risk of target lesion revascularization by 55% (HR 0.45, 95%CI 0.26–0.78, P=0.004).\(^{47}\) In a meta-analysis of randomized trials, Tamhame et al reported that cilostazol significantly reduces the risk of restenosis in patients undergoing PCI compared with conventional DAT.\(^{48}\)

Regarding platelet function, TAT has been shown to be superior to standard DAT in various high-risk subgroups, such as diabetics,\(^{49,50}\) and those with known resistance to clopidogrel.\(^{41,51}\) In addition, we reported that cilostazol reduced the mean OPR and the frequency of high OPR in carriers of the CYP2C19 LOF allele.\(^{52}\) An interesting observation is that in previous studies the enhanced antiplatelet effects of TAT were not associated with increased bleeding compared with standard DAT,\(^{53–56}\) which may be explained by the lack of influence of cilostazol on the thrombin-mediated hemostatic mechanism.\(^{57}\)

Although TAT consistently enhances platelet inhibition compared with standard therapy, whether TAT reduces thrombotic outcomes is controversial. In the DES registry, TAT was shown to reduce ischemic cardiovascular events,\(^{54}\) and in a large acute MI registry from Korea, it was reported that TAT reduced not only major adverse cardiac events by 26%, but also significantly reduced the risk of all-cause death and cardiac death.\(^{58}\) However, in the CILON-T randomized trial, TAT did not improve clinical outcomes compared with conventional DAT in mostly stable patients undergoing elective PCI.\(^{59}\) In the post-hoc analysis, we reported that platelet function was a major determinant of outcome, suggesting that if OPR was sufficiently lowered, there is a possibility for improvement in outcome.\(^{56,58}\) We are currently performing a randomized trial in almost 4,000 all-comers undergoing drug-eluting stent implantation to compare the net clinical outcome between TAT and double-dose clopidogrel therapy for 1 month (the HOST-ASSURE Trial, clinicaltrials.gov, NCT01267734). It will be interesting to test TAT against an increased dose of clopidogrel, because the use of cilostazol is much more widespread in East Asia compared with the USA and Europe.

**Option 3: Switching to Newer P2Y12 Antagonists**

A third option is to switch from clopidogrel to the newly released, more potent P2Y12 antagonists. Many new agents are in development, but at present only prasugrel and ticagrelor...
lor are commercially available in certain parts of the Asia-Pacific region, and their use is supported by positive data from large-scale pivotal phase 3 studies.59,60 These 2 new drugs have greater platelet inhibiting potency than clopidogrel, less inter-patient variability, and faster onset of action.51,62 In addition, the clinical effect of the newer drugs is not affected significantly by genetic variations known to influence outcome with clopidogrel.63,64 However, both agents are more prone to bleeding complications.

Prasugrel, which shares a similar structure to clopidogrel, is a specific and irreversible antagonist of the platelet ADP P2Y12 receptor.65 However, it only requires a 1-step activation mechanism, and thus has a more predictable metabolism than clopidogrel. In preclinical studies, prasugrel was 10–100-fold more potent in inhibiting ex vivo platelet aggregation and in vivo thrombus formation compared with clopidogrel and ticlopidine, respectively.66 In addition, the genetic risk factors that affect clopidogrel do not seem to significantly alter the metabolism and pharmacodynamic effect of prasugrel.67 In the initial phase 2 study, the JUMBO TIMI-26 trial, prasugrel showed a higher degree of platelet inhibition and a more rapid onset of action than clopidogrel,68 which was the basis for the TRITON TIMI-38 trial, the pivotal phase 3 trial.69 In that trial, prasugrel significantly reduced the risk of the composite of cardiovascular death, MI and stroke at the price of an increased risk of bleeding. However, the overall net clinical benefit favored prasugrel, and was more pronounced in the STEMI69 and diabetes subgroups.70 An important observation from the study was that there were 3 groups that did not significantly benefit from prasugrel: (1) patient >75 years of age, (2) those with bodyweight <60 kg, and (3) those with a prior history of stroke or transient ischemic attack, which are labeled as absolute or relative contraindications of prasugrel by most regulatory agencies.71 One criticism of the TRITON TIMI-38 trial is that prasugrel was not compared against a higher loading dose and higher maintenance dose of clopidogrel. However, this was studied in the PRINCIPLE TIMI 44 trial, where prasugrel 60 mg loading with 10 mg maintenance resulted in greater platelet inhibition than doubling the loading and maintenance doses of clopidogrel.72

In contrast to prasugrel, which is a thienopyridine, ticagrelor is a new class of drug that inhibits the P2Y12 receptor. It is a cyclopentyl-triazolo-pyrimidine derived from adenosine triphosphate, and is not a produg, thus not requiring activation through metabolism in the body as do clopidogrel and prasugrel.73,74 It is a reversible agent and needs to be given twice daily. Ticagrelor also has a very fast onset of action, more potent antiplatelet effect, and a more predictable response compared with clopidogrel.75 In the PLATO trial, which compared ticagrelor with clopidogrel in 18,624 ACS patients treated with medical therapy, PCI, or bypass surgery, ticagrelor significantly reduced the risk of death from vascular causes, MI or stroke by 16%, with significant reductions in the risk of the individual endpoints of death from any cause, death from vascular causes, MI, and stent thrombosis.60 The reductions in death observed in the PLATO trial are the first in antiplatelet therapy, and whether this is a chance finding or an important ancillary effect of ticagrelor needs to be studied in more detail in the future. Although the predefined major bleeding endpoint was not different between the 2 groups in PLATO, major bleeding not related to bypass surgery was significantly higher in the ticagrelor group. Moreover, the antiplatelet effect of ticagrelor was similar regardless of the response state to clopidogrel,76 suggesting that ticagrelor may be a good option for those with a poor response to clopidogrel. Also, the rapid onset and offset of action of ticagrelor make it a good therapeutic option for patients before bypass surgery or those awaiting non-cardiac surgery.77

Conclusion

The issue of response variability to clopidogrel has gained great interest recently and may pose a threat to the treatment of ACS patients and high-risk patients undergoing PCI. Many clinical and genetic factors have been postulated to be associated with the variability. Moreover, this may be as important if not more important in Asian populations, than in Western patients, considering the higher mean platelet reactivity and greater frequency of genetic risk factors affecting clopidogrel response. Various methods can be used to overcome this issue, including increasing the dose of clopidogrel, adding cilostazol as a third agent, and switching from clopidogrel to more recently developed agents such as prasugrel or ticagrelor. Although the newer agents definitely have greater antiplatelet effects and are less susceptible to inter-patient variability, the benefits come at the increased risk of bleeding. Therefore, balancing the risk of thrombosis and bleeding in choosing the appropriate strategy for the individual patients is necessary.

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