EDITORIAL COMMENT

Cilostazol—A Forgotten Antiplatelet Agent, But Does it Even Matter?*

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Cilostazol is a phosphodiesterase III inhibitor that has antiplatelet effects due to subsequent increases in cyclic adenosine monophosphate within platelets (1). This agent also provides vasodilation, improves endothelial function, inhibits vascular smooth muscle cell growth, inhibits neointimal hyperplasia, and seems to reduce the risk of restenosis and major adverse cardiac events (MACE) after percutaneous coronary interventions (PCI), without significantly increasing major hemorrhagic events, and has potential cardiovascular protection in patients with acute myocardial infarction (MI) and acute coronary syndromes (ACS) (1–4).

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 adenosine receptor antagonist has become the standard of care following PCI and ACS. Typically, aspirin has been combined with clopidogrel, but both of these agents have substantial risk of resistance (5,6), especially in certain populations. The Asian population and those from Korea, as in the present study, may be particularly resistant to clopidogrel’s antiplatelet effects, with a greater prevalence of high on-treatment platelet reactivity (HOPR), which is associated with an increased risk of MACE following PCI (7). One potential way to overcome the HOPR with clopidogrel is to use double-dose clopidogrel antiplatelet therapy (DDAT) in patients undergoing PCI and those with ACS.

Another potential alternative to DDAT is triple antiplatelet therapy (TAPT), adding cilostazol to aspirin and clopidogrel, which may offer advantages by reducing HOPR in the settings of PCI and ACS without the increased risk for a major hemorrhagic event (8,9). In particular, those with multivessel disease, HOPR on DAPT, and others who are at high risk of MACE or stent thrombosis show a more favorable response when placed on TAPT as compared with DAPT.

Several clinical trials and meta-analyses have suggested that TAPT was superior to DAPT in patients with ACS (10,11). In long-term studies comparing TAPT with DAPT, TAPT had a 32% reduction in all-cause mortality following PCI (12). Several systematic reviews and meta-analyses have found that TAPT is more effective than DAPT in reducing the risk of restenosis by nearly 50%, need for recurrent revascularization by 40% to 60%, and MACE by nearly 30%, without increasing the risk of major hemorrhagic events (13–15).

In the present study in this issue of JACC: Cardiovascular Interventions, Park et al. (7) assessed 1-month duration TAPT (aspirin, clopidogrel, and cilostazol) versus DDAT (aspirin and double-dose clopidogrel) in 3,755 patients (two-thirds with ACS) undergoing PCI with drug-eluting stents, and found that TAPT was noninferior to DDAT. This study, however, was probably underpowered, as the investigators admit, as the primary endpoint occurred in only 23 patients (1.2%) on TAPT and 27 patients (1.4%) in the DDAT group. Despite lower HOPR with TAPT, major bleeding was the same in both arms. Total endpoints, including nonfatal MI (7 vs. 13), stroke (2 vs. 3), stent thrombosis (definite or probable; 4 vs. 7), and all-cause mortality (9 vs. 11) were all lower with TAPT. In total, major endpoints favored TAPT versus DDAT (22 events vs. 34 events), although by our Forest plot, this was still not statistically significant (p = 0.11), indicating the less than ideal power of the study, thus representing the major study limitation. Other study limitations were that more patients on TAPT had peripheral arterial disease and more DDAT patients had prior MI and were older. Also, allocated therapy was given significantly more often with TAPT, and patients were more adherent on TAPT than DDAT. The study also had a short follow-up (1 month), and Koreans as a population have HOPR with the frequency of the CYP2C19 loss of function allele being greater than 60% (7).

The strength of the study was that it was multicenter, randomized, and blinded.

Although this study may provide some support for TAPT being on even par versus DDAT, one could question the clinical significance of this finding and even ask, “Does it even matter?” In the United States, for example, many interventional cardiologists prefer the more potent available antiplatelet therapies, such as prasugrel and ticagrelor for PCI and ACS, and other agents (e.g., rivaroxaban) are awaiting

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approval for ACS. Nevertheless, even if one considers these new antiplatelet therapies superior to clopidogrel as DAPT and even DDAT, a serious issue for many of our patients is the cost of these newer, nongeneric, therapies. Many of our patients currently require 10 or more prescription medications, especially in the elderly population who are prone to increased coronary artery disease, ACS/MI, and who frequently require PCI; many of the agents used to treat these diseases are currently nongeneric. Considering cost restraints, TAPT with aspirin, clopidogrel, and cilostazol appears to be a viable alternative to DAPT and even DDAT. Clearly, this therapy should be compared with DAPT with the newer agents, as opposed to just clopidogrel, and the efficacy of TAPT should be studied with aspirin and cilostazol added to the newer therapies to determine if further clinical efficacy can be enhanced without producing nondesirable increases in bleeding complications.

As to whether cilostazol has a current place as a viable antiplatelet agent and “does it even matter?” the answer is a resounding “maybe.” Further studies with cilostazol that are adequately powered are needed to better determine its viability as an adjunctive antiplatelet therapy in the current management of ACS and PCI.

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