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EDITORIAL COMMENT

Challenging the "Divinity" of Aspirin Monotherapy for Secondary Prevention of Cardiovascular Disease*

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Long after percutaneous coronary intervention (PCI), the optimal antiplatelet monotherapy for secondary prevention of cardiovascular events is ambiguous.[1] The HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis- EXtended Antiplatelet Monotherapy) study was performed in South Korea and recruited 5,530 individuals who received dual antiplatelet treatment (DAPT) for 6 to 18 months after PCI using drug-eluting stenting without clinical complications.[1] Individuals were randomly assigned to take either clopidogrel 75 mg (n = 2,710) or aspirin 100 mg (n = 2,728) once every day for a period of 24 months.[1] The mean duration between PCI and randomization was 382 days (IQR: 357-422 days).[1] The main endpoint was a composite of all-cause mortality, nonfatal myocardial infarction, stroke, rehospitalization for acute coronary syndrome, and Bleeding Academic Research Consortium (BARC) bleeding of type 3 or higher.[1] The main outcome occurred in 152 (5.7%) of the clopidogrel group and in 207 (7.7%) of the aspirin group (HR: 0.73; 95% CI: 0.59-0.90; $P = 0.0035$).[1] The beneficial effect of clopidogrel monotherapy was found in thrombotic (3.7% vs 5.5%; $P = 0.003$) and bleeding endpoints (2.3% vs 3.3%; $P = 0.036$), and the findings were similar between subgroups, such as baseline $P2Y_{12}$ inhibitor and time from index PCI (<365 days vs ≥365 days).[1]

This current large-scale randomized study assessed the long-term efficacy of 2 categories of antiplatelet monotherapy after PCI.[1] The analysis essentially corroborated the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) trial findings.[2] Approximately 20,000 individuals with coronary, cerebrovascular, and peripheral artery disorders were included in the CAPRIE study, which also demonstrated that clopidogrel was more efficacious than aspirin at preventing adverse cardiac outcomes.[2] HOST-EXAM, however, focuses on a current PCI-treated cohort managed with drug-eluting stenting.[1] Because clopidogrel is more costly than aspirin, evidence on the cost-effectiveness of lifelong clopidogrel and aspirin use following PCI is of vital concern, considering the economic demands on health institutions in various nations.[1]

In this issue of *JACC: Asia*, Koo et al[3] report on their cost-effectiveness analysis of the HOST-EXAM study in 3 health care systems (Korea, the United States, and the United Kingdom). These investigators found that the positive impact of clopidogrel monotherapy in the composite clinical results did not translate into a rise in quality-adjusted life-years.[3] Cardiac mortality was numerically greater in the clopidogrel group than in the aspirin group.[3] With clopidogrel monotherapy, health care expenses climbed in Korea but were reduced in the United Kingdom and the United States.[3] These discrepancies were mostly attributable to disparities in health care systems, costs associated with unfavorable clinical outcomes, and medication pricing.[3] Under the assumption of no variability in cardiac death, the scenario-based assessment revealed that clopidogrel monotherapy was not cost-effective in Korea. However, it may be the dominant therapeutic approach in the United Kingdom and the United States.[3]

The open label approach includes a risk of bias in event monitoring and ascertainment; thus, all

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outcomes were assessed by a group that was blinded to the participants' identities.[1,3] Although the research population was East Asian, phenotypic and genetic analysis for clopidogrel was not conducted.[4] The East Asian population has been found to have increased clopidogrel resistance rates.[4] Despite this finding, several investigations have demonstrated a decreased incidence of thrombotic events in this population, a phenomenon known as the East Asian paradox.[5] This study's generalizability is limited by the clinical impact of clopidogrel resistance in East Asians, an impact that may include decreased bleeding events.[3] Given that maintenance antiplatelet medication could be clinically regarded as "indefinite," the 2-year follow-up period could be insufficient for reaching a conclusive result.

Contemporary practice recommendations suggest DAPT to avert early issues following PCI, maintained by antiplatelet monotherapy throughout the long-term maintenance period for secondary prevention.[6] Aspirin is commonly considered to fulfill this role. Nevertheless, this well-executed study has the ability to transform patient care as it exists now.[1] The generalizability and cost-effectiveness of clopidogrel remain questionable.[3] However, the HOST-EXAM extended study will extend the mean follow-up to 10 years to investigate long-term maintenance monotherapy with clopidogrel thoroughly.[3]

The preliminary findings of the HOST-EXAM extended study show that clopidogrel monotherapy is superior to aspirin monotherapy as a long-term management medication in individuals who have fulfilled the requisite length of DAPT following PCI.[7] Benefits were observed in thrombotic and hemorrhagic episodes.[7] The superiority of clopidogrel over aspirin was maintained during a mean of 5.8 years of extended follow-up.[7] Clopidogrel was also associated with decreased bleeding, but myocardial infarction and stent thrombosis were comparable.[7] The increased compliance with clopidogrel monotherapy bolsters the effectiveness of clopidogrel as a lifetime antiplatelet drug throughout the long-term management phase following PCI.[7] Inadequate drug adherence appears to be another risk factor for adverse outcomes.

In recent years, there have been several intriguing DAPT studies.[8-10] Studies such as TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) have demonstrated that individuals after PCI could maintain ticagrelor monotherapy and discontinue aspirin after 3 months without a decrease in ischemic events or an increase in bleeding episodes.[8] Additionally, STOPDAPT-2 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study) indicated that individuals undergoing PCI for stable coronary artery disease and acute coronary syndromes could maintain clopidogrel monotherapy after 1 month.[9] In the present trial by Koo et al,[3] clopidogrel was associated with a statistically increased all-cause death rate; consequently, long-term follow-up is crucial.[9] In the DAPT (Dual Antiplatelet Therapy) study, individuals receiving extended-duration DAPT 12 months after PCI had a comparable indication for increased mortality, particularly noncardiac death.[10] In contrast to the DAPT study,[10] however, the incidence of bleeding was reduced in the present study by Koo et al.[3]

An optimal antiplatelet agent hinges on a meticulous equilibrium among ischemic and hemorrhagic risks; the choice of antiplatelets must be predicated on particular therapeutic goals with regard to evolving patient risk factors and the length of therapy.[11] Asian individuals may be more susceptible to CYP2C19 loss of function variants, enhanced platelet reactivity, and bleeding than their Western counterparts.[12,13] Bleeding risk scores, tailored antiplatelet medication on the basis of genetics, and platelet function are among the potential beneficial approaches attainable to Asian people.[12,13]

Clopidogrel monotherapy can be the most cost-effective therapeutic option in countries where the cost discrepancy between the 2 medications is modest or the expense of treating unfavorable cardiac outcomes is considerable.[3] Updated clinical practice recommendations may advocate clopidogrel as a viable alternative to aspirin for secondary prevention of heart disease and as the medication of preference for certain patient categories, such as patients at greater risk for gastrointestinal and cerebral bleeding.[12] We believe that more pragmatic studies are necessary to answer this critical subject, with a larger sample size of a more representative PCI group with a diverse genetic profile, specific efficacy and safety hard endpoints, longer follow-up, and pharmacogenetic and pharmacodynamic substudies to elucidate the primary drivers of medication response and their association with clinical outcomes.

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