HOST-EXAM: Clopidogrel Monotherapy Non-Inferior to Aspirin at 10 Years

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For patients with stable coronary artery disease (CAD) following percutaneous coronary intervention (PCI) with drug-eluting stents (DES), the optimal long-term antiplatelet monotherapy strategy has been a subject of ongoing clinical debate. The 10-year follow-up data from the HOST-EXAM trial, presented at ACC.26, provides evidence that clopidogrel monotherapy is non-inferior to aspirin monotherapy for preventing thrombotic events and reducing bleeding risk in this population.

KEY TAKEAWAYS

- The Pivot: Long-term data now supports clopidogrel as a viable alternative to aspirin for monotherapy in stable CAD post-DES PCI.
- The Data: Clopidogrel monotherapy demonstrated a 26% lower risk of the primary composite endpoint compared to aspirin (HR 0.74, 95% CI 0.65-0.84, pThe Action: Clinicians should consider clopidogrel monotherapy as an effective and potentially safer long-term antiplatelet option for stable CAD patients after DES PCI.

Following PCI with DES, dual antiplatelet therapy (DAPT) is typically prescribed for a defined period, after which monotherapy is initiated. Aspirin has historically been the standard long-term monotherapy. However, concerns regarding its gastrointestinal bleeding risk and the potential for residual thrombotic events have prompted investigation into alternative strategies. The HOST-EXAM trial aimed to compare the long-term efficacy and safety of clopidogrel monotherapy versus aspirin monotherapy in patients with stable CAD who had undergone PCI with DES and completed 6-18 months of DAPT.1

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide. Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has revolutionized the management of CAD, significantly reducing restenosis rates compared to bare-metal stents. However, stent thrombosis, a rare but often fatal complication, and other atherothrombotic events necessitate ongoing antiplatelet therapy. DAPT, typically consisting of aspirin and a P2Y12 inhibitor, is crucial in the initial phase post-PCI to prevent these events. The optimal duration of DAPT and the choice of subsequent monotherapy have been subjects of extensive research and clinical debate, balancing the prevention of ischemic events against the risk of bleeding. Aspirin, by irreversibly inhibiting cyclooxygenase-1 (COX-1), reduces thromboxane A2 production, thereby inhibiting platelet aggregation. Clopidogrel, a thienopyridine, selectively and irreversibly inhibits the P2Y12 ADP receptor on platelets, preventing ADP-induced platelet activation and aggregation.

Both mechanisms are vital in preventing thrombotic events, but their safety profiles, particularly regarding bleeding, differ.

The Trial Design and Findings

The HOST-EXAM trial was a prospective, multicenter, randomized, open-label, non-inferiority trial that enrolled 5,436 patients from 37 centers in South Korea. Patients with stable CAD who had undergone successful PCI with DES and completed 6-18 months of DAPT without major adverse events were randomized 1:1 to receive either clopidogrel (75 mg once daily) or aspirin (100 mg once daily). The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or definite/probable stent thrombosis. The initial follow-up period was 24 months.1

Patient eligibility criteria included age 20 years or older, successful PCI with DES for stable CAD (including stable angina, silent ischemia, or prior myocardial infarction), and completion of 6 to 18 months of DAPT without experiencing major adverse cardiac or cerebrovascular events (MACCE) or major bleeding. Exclusion criteria included acute myocardial infarction within 30 days, cardiogenic shock, severe heart failure, significant valvular heart disease, severe renal or hepatic dysfunction, active bleeding, or a history of hemorrhagic stroke. The randomization process was performed using a web-based system, ensuring allocation concealment. Adherence to the assigned antiplatelet regimen was monitored through patient interviews and review of prescription records at follow-up visits. The trial's non-inferiority margin for the primary endpoint was a hazard ratio of 1.25, meaning clopidogrel would be considered non-inferior if its upper 95% confidence interval for the hazard ratio did not exceed 1.25 compared to aspirin. This design allowed for a robust comparison of the two monotherapy strategies.

The 10-year follow-up data, presented at ACC.26, extended the observation period significantly, providing robust long-term insights. At 10 years, clopidogrel monotherapy demonstrated a 26% lower risk of the primary composite endpoint compared to aspirin monotherapy (Hazard Ratio [HR] 0.74, 95% Confidence Interval [CI] 0.65-0.84, P2

Breaking down the composite endpoint, clopidogrel significantly reduced the risk of myocardial infarction (HR 0.70, 95% CI 0.56-0.88, P=.002) and stent thrombosis (HR 0.57, 95% CI 0.38-0.86, P=.007) compared to aspirin. There was no significant difference in the rates of all-cause death or stroke between the two groups.2

Regarding safety outcomes, clopidogrel monotherapy was associated with a 34% lower risk of major bleeding (HR 0.66, 95% CI 0.50-0.87, P=.003) and a 42% lower risk of gastrointestinal bleeding (HR 0.58, 95% CI 0.40-0.84, P=.004) compared to aspirin. This reduction in bleeding events contributed to the overall favorable safety profile of clopidogrel.2

The trial's strengths include its large sample size and extended follow-up duration, providing long-term evidence in a real-world setting. A limitation is that the study population was predominantly Asian, which may limit generalizability to other ethnic groups, given known differences in drug metabolism and genetic predispositions to bleeding or thrombotic events. Furthermore, the open-label design, while pragmatic, introduces potential for bias, though objective endpoints like death and myocardial infarction are less susceptible. The trial did not include other P2Y12 inhibitors, such as

ticagrelor or prasugrel, which are also used in CAD management. The generalizability of these findings to patients with acute coronary syndromes or those requiring longer DAPT durations also warrants further investigation. Future research could explore the cost-effectiveness of clopidogrel monotherapy in different healthcare systems and patient populations, as well as investigate the role of genetic testing for clopidogrel metabolism in guiding personalized antiplatelet strategies.1,2

CLINICAL IMPLICATIONS

The 10-year HOST-EXAM data provides compelling evidence that clopidogrel monotherapy is not merely an alternative to aspirin but may offer superior long-term outcomes in stable CAD patients post-DES PCI, particularly concerning thrombotic events and bleeding risk. This challenges the entrenched practice of defaulting to aspirin as the sole long-term antiplatelet agent. Clinicians should now seriously consider clopidogrel as a primary option for long-term monotherapy, especially in patients with a higher bleeding risk or those who have demonstrated good tolerance to clopidogrel during DAPT.

From an industry perspective, this extended follow-up could subtly shift market dynamics for antiplatelet agents. While clopidogrel is off-patent and inexpensive, its demonstrated long-term efficacy and safety profile might lead to increased prescribing, potentially impacting the market share of aspirin for this specific indication. Guideline bodies, such as the American College of Cardiology (ACC) and the European Society of Cardiology (ESC), will need to review these long-term data to update their recommendations, which currently often favor aspirin or offer clopidogrel as an alternative in specific scenarios.

For patients, this means a potential reduction in the dual burden of thrombotic events and bleeding complications, which are significant concerns in long-term antiplatelet therapy. The improved safety profile, particularly the reduction in gastrointestinal bleeding, could enhance patient adherence and quality of life. It underscores the importance of individualized patient assessment, moving beyond a one-size-fits-all approach to antiplatelet management in stable CAD.

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