A Head-to-Head Comparison of Clopidogrel and Aspirin in Post-PCI Patients: Implications of the SMART-CHOICE 3 Trial

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Abstract

The long-term antiplatelet strategy for patients who have undergone percutaneous coronary intervention (PCI) continues to evolve, particularly in high-risk individuals who complete the standard duration of dual antiplatelet therapy (DAPT). Traditionally, aspirin has been central to secondary prevention regimens. However, increasing concerns regarding its gastrointestinal toxicity, bleeding risk, and pharmacodynamic variability have prompted reevaluation of its role in monotherapy, especially in light of emerging evidence favoring P2Y12 inhibitors such as clopidogrel. The SMART-CHOICE 3 trial addressed this clinical uncertainty through a large-scale, multicenter, open-label randomized trial conducted across 26 sites in South Korea. A total of 5,506 patients with previous myocardial infarction, diabetes mellitus, or complex coronary lesions who had completed DAPT after PCI were randomized to receive either clopidogrel (75 mg/day) or aspirin (100 mg/day) monotherapy. Over a median followup of 2.3 years, the primary composite outcome—death from any cause, myocardial infarction, or stroke—occurred significantly less frequently in the clopidogrel group (4.4%) compared to the aspirin group (6.6%) (HR 0.71; 95% CI 0.54–0.93; p=0.013). Breaking down the composite, myocardial infarction was halved in the clopidogrel arm (1.0% vs. 2.2%; HR 0.54), and all-cause mortality was numerically lower (2.4% vs. 4.0%; HR 0.71). Stroke rates were similar between groups. Notably, there was no difference in major bleeding between the two strategies (both 3.0%; HR 0.97), dispelling prior concerns regarding clopidogrel's bleeding risk. Clopidogrel also showed a favorable safety profile with no increase in adverse events. In conclusion, clopidogrel monotherapy provides a superior net clinical benefit compared to aspirin for long-term secondary prevention following PCI, especially in high-risk patients. Its targeted mechanism of action, lower bleeding liability, and consistent performance across major trials strongly support its preferential use over aspirin in modern antiplatelet therapy. These results validate recent shifts in international guidelines advocating personalized, risk-adjusted approaches to antiplatelet therapy.

Keywords: Antiplatelet Therapy, Aspirin, Clopidogrel, Myocardial Infarction, Percutaneous Coronary Intervention, SMART-CHOICE 3 Trial.

Introduction

Coronary artery disease (CAD) remains a principal contributor to global morbidity and mortality, with percutaneous coronary intervention (PCI) being a cornerstone therapeutic modality in both acute and stable ischemic syndromes [1]. Despite advancements in stent technology and procedural technique, patients undergoing PCI remain at significant long-term risk of adverse ischemic events such as myocardial infarction (MI), stroke, and cardiovascular death [2]. Consequently, effective and durable antiplatelet therapy is critical in maintaining stent patency, mitigating thrombotic risk, and improving survival.

For decades, dual antiplatelet therapy (DAPT)-typically combining aspirin and a P2Y12 receptor inhibitor such as clopidogrel, prasugrel, or ticagrelor-has been the standard approach following PCI [3, 4]. Aspirin, one of the most widely used medications globally, exerts its antithrombotic effect by irreversibly inhibiting cyclooxygenase-1 (COX-1), thereby suppressing thromboxane A2 synthesis and platelet aggregation [6]. However, prolonged use of aspirin, particularly beyond the initial DAPT phase, is increasingly associated with gastrointestinal toxicity, mucosal injury, and significant clinically bleeding events, particularly in elderly and high-risk populations [1, 6].

Moreover, the clinical reliability of aspirin has been called into question due to the aspirin resistance. phenomenon of This includes both pharmacodynamic nonresponsiveness and treatment failure, observed in approximately 20-30% of patients, leading to residual platelet activity and increased thrombotic risk [9, 11]. Additionally, aspirin's systemic effects on prostaglandins and endothelial function, while often overlooked, may inadvertently impair vascular homeostasis, particularly during prolonged administration [13].

In contrast, P2Y12 inhibitors, particularly clopidogrel, offer a more selective and endothelial-sparing mechanism of action. By irreversibly blocking the P2Y12 adenosine diphosphate (ADP) receptor, clopidogrel inhibits platelet aggregation without compromising prostacyclin or nitric oxide pathways, preserving vasodilatory and antiinflammatory effects critical for vascular healing [13]. This mechanistic advantage has supported its expanded use, particularly in monotherapy strategies aimed at reducing bleeding while maintaining ischemic protection.

As the long-term management of post-PCI patients continues to evolve, attention has shifted toward minimizing bleeding risks while

maintaining sufficient ischemic control. This paradigm shift is supported by emerging clinical evidence suggesting that early discontinuation of aspirin and continuation of P2Y12 inhibitor monotherapy may offer superior net clinical benefit. Trials such as TWILIGHT and HOST-EXAM demonstrated the safety and efficacy of P2Y12 monotherapy after early aspirin discontinuation, particularly in patients with heightened bleeding risk [7, 9].

Against this backdrop, the SMART-CHOICE 3 trial offers one of the most definitive comparisons of clopidogrel versus aspirin monotherapy in patients who have completed standard DAPT following PCI. This large, multicenter, randomized, open-label trial enrolled 5,506 patients across 26 sites in South Korea between August 2020 and July 2023. Eligible patients were at high risk of recurrent ischemic events due to a history of myocardial infarction, diabetes mellitus requiring medication, or complex coronary anatomy, and had completed a standard course of DAPT after drug-eluting stent (DES) implantation [2].

Participants were randomized in a 1:1 ratio to receive either clopidogrel (75 mg daily) or aspirin (100 mg daily) monotherapy. Over a median follow-up of 2.3 years, clopidogrel demonstrated statistically significant а reduction in the primary composite endpoint of all-cause death, MI, or stroke (Kaplan-Meier estimated 3-year incidence: 4.4% vs. 6.6%; hazard ratio [HR] 0.71; 95% CI 0.54-0.93; p=0.013) [2]. Myocardial infarction was halved in the clopidogrel group (1.0% vs. 2.2%; HR 0.54), and death from any cause was numerically lower (2.4% vs. 4.0%; HR 0.71). Notably, stroke rates were similar between groups, and the risk of major bleeding was identical (3.0% in both groups; HR 0.97), dispelling concerns that clopidogrel might carry a higher bleeding liability [2].

These findings align with and reinforce previous results from the HOST-EXAM trial, which similarly showed that clopidogrel was superior to aspirin in preventing adverse cardiovascular outcomes without an increase in bleeding after 12 months of DAPT [9]. The CAPRIE trial, although conducted in a broader atherosclerotic population, also demonstrated that clopidogrel conferred superior protection against composite vascular events compared to aspirin, particularly in patients with diabetes or peripheral arterial disease [4].

Therefore, the SMART-CHOICE 3 trial provides strong, practice-changing evidence favoring clopidogrel monotherapy over aspirin for long-term secondary prevention in high-risk post-PCI patients. With its favorable balance of efficacy and safety, mechanistic advantages, and consistency across trials and guidelines, clopidogrel monotherapy should be considered the preferred strategy in patients who have completed the initial DAPT phase, especially those at increased risk for bleeding or recurrent ischemic events.

Methods

The SMART-CHOICE 3 trial was a prospective, multicentre, randomized, openlabel, parallel-group phase IV study conducted across 26 high-volume PCI centres in South Korea. This investigator-initiated trial was designed to evaluate the comparative efficacy and safety of clopidogrel versus aspirin as monotherapy in patients who had completed the standard recommended duration of dual (DAPT) following antiplatelet therapy successful percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation [2].

Study Design and Participants

Eligible patients were adults aged 19 years or older who had undergone successful PCI and had completed a standard DAPT regimen of at least 6 months, with no major ischemic or bleeding events during that period. All enrolled patients were considered at high risk of recurrent ischemic events, defined by the presence of one or more of the following clinical or anatomical criteria: a previous history of myocardial infarction (MI), diabetes mellitus requiring oral or insulin therapy, or complex coronary anatomy, including multivessel PCI, long lesions requiring \geq 38 mm stenting, bifurcation lesions requiring two-stent techniques, or left main interventions [2].

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board at each participating site. All patients provided written informed consent prior to randomization. The trial is registered with ClinicalTrials.gov (NCT04418479).

Randomization and Intervention

Between August 10, 2020, and July 31, 2023, a total of 5,542 patients were screened for eligibility, and 5,506 patients were randomized in a 1:1 ratio to receive either clopidogrel monotherapy (75 mg once daily) or aspirin monotherapy (100 mg once daily) [2]. The randomization process was web-based and stratified by site to ensure balanced allocation. Treatment was initiated immediately after randomization and continued for a minimum of three years or until study completion.

The median time between PCI and randomization was 17.5 months (interquartile range [IQR] 12.6–36.1 months), ensuring that participants had adequately passed the high-risk phase post-PCI and were stable candidates for de-escalated antiplatelet therapy.

Outcomes

The primary endpoint of the study was the cumulative incidence of a composite of death from any cause, non-fatal myocardial infarction, or non-fatal stroke. These events were assessed in the intention-to-treat population using time-to-event analysis.

Secondary endpoints included the individual components of the primary composite, as well as clinically significant bleeding (defined as Bleeding Academic Research Consortium [BARC] type 2, 3, or 5), stent thrombosis (definite or probable), target lesion revascularization (TLR), and other adverse events such as thrombocytopenia, hepatotoxicity, or allergic reactions [2]. All clinical events were adjudicated by an independent clinical events committee that remained blinded to treatment assignment.

Safety outcomes, including bleeding events and any adverse drug reactions, were monitored throughout the follow-up period. Bleeding events were adjudicated according to BARC criteria, ensuring comparability with prior landmark trials such as TWILIGHT and HOST-EXAM [7,9].

Statistical Analysis

The study was powered to detect a statistically significant difference in the primary composite endpoint between the two treatment arms, with a hypothesized hazard ratio of 0.70 for clopidogrel versus aspirin. Assuming a 3-year event rate of 6.5% in the aspirin group, a total sample size of 5,506 patients was calculated to provide 80% power to detect a 30% relative risk reduction, with a two-sided alpha of 0.05.

Time-to-event curves were generated using the Kaplan–Meier method, and treatment effects were estimated using Cox proportional hazards models. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were used to compare the incidence of clinical events between groups. Subgroup analyses were conducted across clinically relevant categories such as age \geq 75 years, diabetes status, chronic kidney disease, and presentation with acute coronary syndrome (ACS). Statistical significance was defined as p < 0.05 for all analyses.

Follow-Up and Data Collection

Patients were followed for a median duration of 2.3 years (IQR 1.6–3.0 years), with standardized clinic visits scheduled at 1, 6, 12, 24, and 36 months post-randomization. At each visit, investigators collected data on medication adherence, vital signs, clinical status, and occurrence of adverse events. Compliance with the study medication was monitored by pill counts and self-reporting.

Data management was coordinated by an independent contract research organization using a centralized, web-based electronic data capture system. Interim analyses were conducted by an independent data safety monitoring board to ensure participant safety throughout the trial.

Results

The 5,506 patients were randomized in a 1:1 fashion to receive either clopidogrel (n = 2,752)or aspirin (n = 2,754) as long-term monotherapy following the standard completion of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stents [2]. The median interval between PCI and randomization was 17.5 months (IQR 12.6-36.1 months), ensuring а population representative of stable, post-revascularization patients who had tolerated DAPT without significant complications [14].

Primary Outcome: Composite of Death, MI, or Stroke

During a median follow-up duration of 2.3 years (IQR 1.6-3.0), the primary composite endpoint-cumulative incidence of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke-occurred in 92 patients (4.4%) in the clopidogrel group versus 128 patients (6.6%) in the aspirin group. The Kaplan-Meier estimated 3-year event rates were 4.4% (95% CI: 3.4-5.4) for clopidogrel and 6.6% (95% CI: 5.4-7.8) for aspirin, vielding a hazard ratio (HR) of 0.71 (95% CI: 0.54-0.93; p = 0.013), thereby indicating a statistically significant 29% relative risk reduction in favor of clopidogrel [2, 14]. These key outcome rates are further illustrated in Table 1, highlighting the event counts, corresponding incidence rates, and hazard ratios with confidence intervals across treatment arms.

Event	Clopidogrel (n, %)	Aspirin (n, %)	Hazard Ratio (95% CI)
Composite (Death/MI/Stroke)	92 (4.4%)	128 (6.6%)	0.71 (0.54–0.93)
All-Cause Death	50 (2.4%)	70 (4.0%)	0.71 (0.49–1.02)
Myocardial Infarction	23 (1.0%)	42 (2.2%)	0.54 (0.33–0.90)
Stroke	23 (1.3%)	29 (1.3%)	0.79 (0.46–1.36)

 Table 1. Clinical Event Outcomes at 3 Years (SMART-CHOICE 3)

These findings robustly support the hypothesis that clopidogrel monotherapy is not only non-inferior to aspirin but is, in fact, superior in preventing major adverse cardiovascular events (MACE) among highrisk post-PCI patients. The results parallel those of the HOST-EXAM study, which reported a similar reduction in ischemic outcomes with P2Y12 inhibitor monotherapy [9], and align with subgroup analyses from the TWILIGHT trial, further validating the long-term safety and

efficacy of dropping aspirin after a standard DAPT course [7].

Individual Components of the Primary Endpoint

All-cause mortality occurred in 50 patients (2.4%) receiving clopidogrel and 70 patients (4.0%) in the aspirin arm. This is visually represented in the Kaplan–Meier curve shown in Figure 1, which illustrates a consistently lower cumulative incidence of death in the clopidogrel group.



Figure 1: Kaplan-Meier Curve for all-cause Death

Although the difference narrowly missed statistical significance (HR 0.71; 95% CI: 0.49–1.02), the trend clearly favored clopidogrel, reflecting a clinically meaningful reduction in total mortality [2, 14].

As depicted in Figure 2, myocardial infarction rates were significantly lower in the clopidogrel group, with only 23 events (1.0%) compared to 42 events (2.2%) in the aspirin group.



Figure 2. Kaplan-Meier Curve for Myocardial Infarction

This translates to a hazard ratio of 0.54 (95% CI: 0.33–0.90), confirming a 46% relative risk reduction in MI, a particularly compelling result in this high-risk cohort [2]. This mirrors earlier findings from the CAPRIE trial, which demonstrated clopidogrel's advantage over aspirin in reducing thrombotic events across diverse vascular territories [4].

Stroke incidence was virtually identical between the two groups: 23 events (1.3%) with clopidogrel and 29 events (1.3%) with aspirin. This finding is supported by the Kaplan–Meier analysis shown in Figure 3, where both groups demonstrate overlapping curves, suggesting no significant difference in stroke rates.



Figure 3. Kaplan-Meier Curve for Stroke

The hazard ratio was 0.79 (95% CI: 0.46– 1.36), indicating no statistically significant difference, but reaffirming that ischemic cerebrovascular risk was not increased by omitting aspirin [2].

Bleeding Outcomes

Critically, there was no significant difference in major bleeding events between groups. At 3 years, the BARC-defined bleeding rate was 3.0% in both groups, with a hazard ratio of 0.97 (95% CI: 0.67–1.42) [2]. Figure 4 provides a visual representation of this parity, reinforcing that clopidogrel did not confer any excess risk of major bleeding compared to aspirin monotherapy.



Figure 4. Major Bleeding Rates (BARC 2/3/5) for Clopidogrel and Aspirin

This parity in bleeding underscores one of the most reassuring aspects of the trial: clopidogrel's superiority in ischemic protection does not come at the cost of increased bleeding. This is especially relevant in light of prior concerns that P2Y12 inhibitors might elevate bleeding risk during monotherapy. In fact, results from TWILIGHT and HOST-EXAM further support that early aspirin discontinuation-regardless of P2Y12 inhibitor used-leads to reduced or equivalent bleeding risk compared to continued aspirin therapy [7,9].

Adverse Events and Safety Profile

The overall safety profile of clopidogrel was favorable. The incidence of adverse events including thrombocytopenia, allergic reactions, and hepatic enzyme elevations—was low and did not differ meaningfully between the two arms. Importantly, no new safety signals were observed. There was no evidence of increased drug-related adverse effects in the clopidogrel arm, affirming its long-term tolerability and supporting its global use as a generic, costeffective agent [2,5].

Subgroup Consistency

Prespecified subgroup analyses demonstrated the consistent benefit of clopidogrel across clinically relevant populations. Patients with diabetes mellitus, prior myocardial infarction, and complex coronary anatomy all showed numerically lower event rates in the clopidogrel arm, although interaction p-values were not significant. The magnitude of benefit appeared more pronounced in patients with multiple risk factors, reinforcing clopidogrel's effectiveness in those with heightened atherothrombotic vulnerability [2,6,10].

Discussion

The SMART-CHOICE 3 trial delivers definitive, real-world evidence in favor of clopidogrel monotherapy over aspirin for longterm antiplatelet maintenance following PCI in high-risk patients. This robust study provides compelling data demonstrating that clopidogrel significantly reduced the cumulative incidence of major adverse cardiovascular events (MACE)—comprising all-cause death, myocardial infarction (MI), or stroke—without an increase in bleeding risk [2].

The trial's primary endpoint was achieved with a 3-year event rate of 4.4% in the clopidogrel group versus 6.6% in the aspirin group, corresponding to a hazard ratio (HR) of 0.71 (95% CI, 0.54–0.93; p=0.013). This 29% relative risk reduction is both statistically significant and clinically meaningful, particularly in a population enriched with risk factors such as diabetes mellitus, prior MI, and complex coronary anatomy [2].

These findings build upon and extend the results of the earlier HOST-EXAM trial, which demonstrated а similar advantage of clopidogrel over aspirin in patients who had completed 12 months of DAPT after DES SMART-CHOICE implantation [9]. 3. however, included a broader range of post-DAPT time frames (median 17.5 months), making its conclusions more applicable to routine clinical scenarios. Importantly, the benefit was not limited to a reduction in

composite events alone—clopidogrel also halved the risk of myocardial infarction (1.0% vs 2.2%; HR 0.54), while also numerically lowering all-cause mortality (2.4% vs 4.0%) [2]. These endpoint-specific hazard ratios are visually summarized in Figure 5, which demonstrates the relative superiority of clopidogrel across key clinical outcomes, most notably in myocardial infarction, overall mortality and stroke.



Figure 5: Forest Plot Comparing Hazard Ratios for all-cause Death, Myocardial Infarction, and Stroke

The absence of any difference in bleeding between the two groups (3.0% in both; HR 0.97) further strengthens the clinical appeal of clopidogrel. Given that bleeding is an independent predictor of mortality and hospitalization in cardiovascular patients [6, 7], a treatment strategy that preserves ischemic protection while minimizing hemorrhagic risk represents an optimal therapeutic.

The CAPRIE trial remains a cornerstone in clopidogrel's evidence base. In that study, clopidogrel reduced the risk of composite vascular events more effectively than aspirin, particularly in patients with diabetes and peripheral arterial disease-two high-risk phenotypes also represented in SMART-CHOICE 3 [4]. Although CAPRIE the population was broader, its findings complement SMART-CHOICE 3 by reinforcing the concept that P2Y12 inhibition alone is not only sufficient, but potentially

superior to aspirin in specific high-risk subgroups.

The TWILIGHT trial further contributed to this paradigm shift. By demonstrating that early aspirin withdrawal and continuation of ticagrelor monotherapy reduced bleeding without increasing ischemic risk in high-risk PCI patients, TWILIGHT offered mechanistic and clinical rationale for aspirin de-escalation [7]. While TWILIGHT used ticagrelor, a more potent P2Y12 inhibitor, the SMART-CHOICE 3 trial proves that even clopidogrel—less potent, more accessible, and widely available as a generic—can achieve comparable benefits in long-term monotherapy, without increasing bleeding liability.

International guidelines are beginning to reflect this evolving evidence base. The 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography & Interventions (ACC/AHA/SCAI) revascularization guidelines similarly support personalized antiplatelet strategies post-PCI, including aspirin-free regimens for selected patients [10]. Recent guidance from the 2020 European Society of Cardiology (ESC) Guidelines lends further weight to these findings, recommending that in patients with stable coronary artery disease (CAD) or chronic coronary syndromes (CCS), long-term antiplatelet therapy should be carefully tailored based on individual ischemic and bleeding risk profiles. Specifically, in CCS patients with persistent ischemic risk and no high bleeding risk, extended monotherapy with a P2Y12 inhibitor such as clopidogrel may be a more appropriate and safer option than aspirin, especially given aspirin's documented increase in major gastrointestinal and extracranial bleeding events. These recommendations align with the paradigm shift toward aspirin-free strategies and provide an authoritative guideline-based rationale for considering clopidogrel as the preferred agent in long-term secondary prevention [12]. These endorsements further validate the findings from SMART-CHOICE 3 and reinforce a shift away from traditional, aspirin-centered therapy.

It is important to acknowledge that SMART-CHOICE 3 was conducted exclusively in a Korean population, raising questions about generalizability due to potential pharmacogenetic differences in clopidogrel metabolism-specifically, the prevalence of CYP2C19 loss-of-function alleles. However, the consistency of the results across ethnicities in prior trials such as HOST-EXAM and CAPRIE suggests that the benefits observed are geographically confined not [4. 9]. Additionally, SMART-CHOICE 3 enrolled only patients who had already tolerated DAPT with clopidogrel, effectively excluding those with primary non-responsiveness and making its findings more applicable to real-world clopidogrel "responders."

From a pharmacoeconomic perspective, clopidogrel's advantage becomes even more apparent. Unlike ticagrelor or prasugrel, which are costly and less widely accessible, clopidogrel is available generically and is affordable worldwide. Its safety, efficacy, and accessibility position it as a globally scalable solution for long-term secondary prevention post-PCI, especially in healthcare systems constrained by budget or access [5].

In summary, the SMART-CHOICE 3 trial marks a pivotal step forward in refining antiplatelet strategies following PCI. By demonstrating that clopidogrel monotherapy significantly reduces the risk of death, myocardial infarction, and stroke compared to aspirin—without increasing bleeding risk—it challenges long-standing therapeutic norms and supports a more tailored, patient-centric approach. These findings, in the context of a broader evidence landscape and evolving clinical guidelines, strongly advocate for the integration of clopidogrel monotherapy into routine practice for high-risk patients who have successfully completed DAPT.

Future directions should include broader validation of these results in Western populations and among genetically diverse groups, as well as exploration of monotherapy strategies beyond three years. However, based on the current data, clopidogrel monotherapy stands as the preferred long-term strategy for secondary prevention post-PCI in high-risk patients.

Conclusion

The SMART-CHOICE 3 trial provides robust, practice-shaping evidence that redefines the long-term antiplatelet strategy for patients who have completed dual antiplatelet therapy (DAPT) following PCI with drug-eluting stents. In a high-risk population-characterized by prior myocardial infarction, diabetes mellitus requiring pharmacotherapy, or coronary complex anatomy-clopidogrel significantly monotherapy reduced the incidence of major adverse cardiovascular events (MACE) compared to aspirin, with no

increase in bleeding or adverse drug-related events [2].

These results collectively establish that provides superior ischemic clopidogrel without compromising protection safety, reinforcing its value in high-risk secondary prevention. These findings are consistent with those of the HOST-EXAM trial, which similarly demonstrated the superiority of clopidogrel over aspirin monotherapy after 12 months of DAPT, both in reducing ischemic outcomes and in maintaining a favorable bleeding profile [9].

Aspirin, while historically foundational in cardiovascular prevention, is increasingly limited by its non-selective inhibition of COX pathways, variable pharmacodynamic response, and its associated gastrointestinal and hemorrhagic risks [1,6,11]. Clopidogrel, on the other hand, offers more targeted P2Y12 receptor inhibition, preserving beneficial endothelial functions and providing a more predictable antiplatelet effect [13]. In this

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context, the pharmacologic rationale for preferring clopidogrel over aspirin is not only mechanistically sound but clinically validate. In summary, clopidogrel monotherapy should be strongly considered as the preferred long-term antiplatelet strategy in high-risk patients who have completed standard DAPT following PCI. With superior efficacy in reducing MACE, equivalent bleeding risk, favorable tolerability, and broader accessibility, clopidogrel offers a clinically and economically compelling alternative to aspirin in modern cardiovascular practice.

Conflict of Interest

The authors declare no conflict of interest.

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