From aspirin to clopidogrel monotherapy: A new paradigm for secondary prevention in coronary artery disease

Anxin Wang,[1,2,3,4,5,*] Xue Tian,[1,2,3,4,5] Si Cheng,[1,2,4] Xue Xia,[1,2,3,4] Hao Li,[1,2,4] Yongjun Wang,[1,2,4] and Xia Meng[1,2,4,*]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[2]National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[3]Department of Epidemiology, Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
[4]Department of Clinical Epidemiology and Clinical Trial, Capital Medical University, Beijing 100070, China
[5]These authors contributed equally
*Correspondence: wanganxin@bjtth.org (A.W.); mengxia45@163.com (X.M.)

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The longstanding reign of aspirin as the cornerstone of long-term antiplatelet therapy for secondary prevention in patients with established coronary artery disease (CAD) is now being challenged by a landmark 2025 individual patient data (IPD) meta-analysis published in *The Lancet*.[1] This study, which harmonized data from 28,982 patients across seven randomized trials involving patients with established CAD who had discontinued or never started dual antiplatelet therapy (DAPT), provided compelling evidence that clopidogrel monotherapy offered superior efficacy in preventing major adverse cardiovascular and cerebrovascular events (MACCE) without increasing the risk of bleeding (Figure 1). The primary strength of this meta-analysis lies in its robust IPD methodology, which represents a significant advancement over traditional aggregate-data approaches. By obtaining raw, patient-level data from all seven eligible randomized controlled trials the investigators were able to perform a more nuanced and powerful analysis.

For decades, aspirin monotherapy has been recommended indefinitely for CAD patients, yet the foundational evidence largely stems from smaller studies conducted before the era of modern pharmacotherapies and revascularization strategies.[2,3] Many of these early trials were limited in scale, as they were initiated at a time when large-scale cardiovascular outcome trials were less common, resulting in insufficient statistical power for robust conclusions. As the Lancet paper highlights, these earlier trials often had short follow-up durations, rarely disentangled acute from chronic effects of aspirin, and failed to systematically appraise the full spectrum of clinically relevant bleeding risks.[1] This meta-analysis was initiated to fill this evidence gap by harmonizing individual patient data from multiple trials, which effectively extends the follow-up period for a substantial portion of the pooled population and provides a much larger sample size to detect meaningful differences. It thereby provides a comprehensive and contemporary evaluation of clopidogrel versus aspirin, especially in the context of patients who have successfully completed an initial phase of DAPT—a common clinical scenario.

The main findings of the analysis are practice-changing. Over a median follow-up of 2.3 years and up to 5.5 years, clopidogrel monotherapy demonstrated a significant 14% relative risk reduction in the primary efficacy endpoint of MACCE (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.77–0.96). This benefit was driven by substantial and statistically significant reductions in key individual components: a 24% reduction in myocardial infarction (HR 0.76, 95% CI 0.66–0.89) and a 21% reduction in stroke (HR 0.79, 95% CI 0.66–0.96). The incidence of definite or probable stent thrombosis was also numerically lower with clopidogrel, though not statistically significant, providing reassurance regarding its use in post percutaneous coronary intervention (PCI) patients.

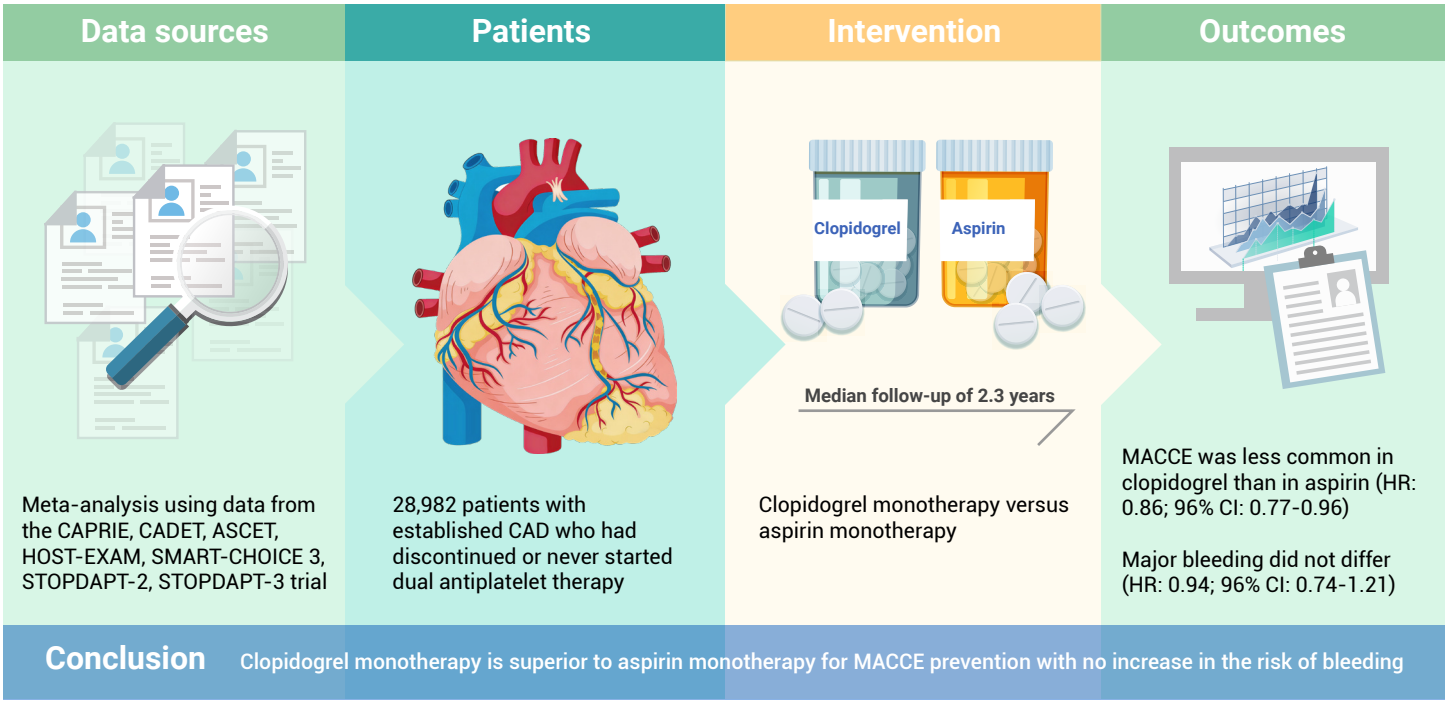

Figure 1. The overall summary of the clopidogrel monotherapy for the secondary prevention in coronary artery disease Abbreviations: CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular or cerebrovascular events

Crucially, this robust anti-ischemic benefit was achieved without an associated increase in the risk of major bleeding (HR 0.94, 95% CI 0.74–1.21). Furthermore, there were no significant differences in any bleeding, major gastrointestinal bleeding, or any gastrointestinal bleeding. The safety outcomes, particularly the comparable gastrointestinal bleeding rates in an era of widespread proton pump inhibitor use, shift the argument for clopidogrel firmly onto its superior efficacy, establishing an unambiguous net clinical benefit as evidenced by the significant reduction in the key secondary endpoint of net adverse clinical events.

A major historical barrier to the broader adoption of clopidogrel monotherapy has been the concern over interindividual variability in response, linked to *CYP2C19* loss-of-function alleles. This is a particularly relevant consideration in East Asian populations, where the prevalence of these alleles is nearly 60%.[4] This meta-analysis directly and powerfully addresses this concern. Despite the inability to perform a genetic sub-analysis due to data limitations, the investigators used the clinical components of the validated ABCD-GENE score. They demonstrated that the superior efficacy of clopidogrel over aspirin was remarkably consistent across all prespecified subgroups, including in patients with a high ABCD-GENE score (>10), indicating a presumed higher likelihood of poor clopidogrel responsiveness. This pivotal insight suggests that for long-term secondary prevention in the chronic, stable phase of CAD, the net clinical benefit of clopidogrel prevails regardless of an individual's predicted pharmacodynamic response. This potentially obviates the need for routine genetic testing or platelet function monitoring in this specific context, significantly simplifying its implementation in diverse populations and healthcare systems, including China. The authors hypothesize that the prognostic impact of *CYP2C19* genotype may be more pronounced in the acute phase of coronary syndromes, an effect that attenuates over the long term.

Regarding special populations, the prespecified subgroup analyses provide valuable insights. In patients aged over 65 years (representing 52% of the cohort), the point estimate for MACCE reduction with clopidogrel remained favorable (HR 0.87, 95% CI 0.76–1.00), with no increase in major bleeding. Similarly, in patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), clopidogrel monotherapy demonstrated superior efficacy compared to aspirin (HR 0.78, 95% CI 0.62–0.97) with comparable safety. These data suggest a consistent net clinical benefit of clopidogrel in these higher-risk subgroups. However, practical implementation in the elderly or those with renal impairment should always involve individualized assessment, considering concomitant medications, fall risk, and precise renal function, even though the present analysis offers robust group-level evidence supporting its use.

These findings position clopidogrel uniquely among antiplatelet agents. To date, it is the only antiplatelet therapy that has consistently demonstrated superior efficacy over aspirin without a safety trade-off in long-term secondary prevention. This contrasts with other strategies, such as adding a second antiplatelet agent or low-dose rivaroxaban to aspirin, which, while effective, invariably increase bleeding risk. The superior efficacy of clopidogrel, a $P2Y_{12}$ inhibitor, over aspirin, a cyclooxygenase-1 inhibitor, may be mechanistically explained by a more targeted and potent inhibition of platelet activation and aggregation via the adenosine diphosphate (ADP) pathway, which is crucial in atherothrombosis. Furthermore, aspirin is not without its own variability in response ("aspirin resistance"), which can be influenced by factors like enteric coating and compliance. The finding that all-cause and cardiovascular mortality were identical between groups is consistent with the broader literature on antithrombotic therapies in stable CAD, where mortality reductions have been elusive, highlighting that the primary goal is the prevention of non-fatal ischemic events.

The implications for clinical practice, particularly in China with its massive and growing burden of CAD, are profound. This study provides reliable evidence derived from rigorous meta-analytical methodology. These findings offer valuable reference for Chinese cardiology societies and guideline committees to consider during future updates to clinical practice guidelines.

While, as acknowledged by the authors, the predominance of East Asian patients warrants further confirmation in predominantly non-Asian cohorts, though the lack of heterogeneity by region is reassuring. The exclusion of patients who experienced events during the initial DAPT phase means the results are generalizable to the stable post-event/PCI population. The role of clopidogrel monotherapy in specific sub-populations, such as those with a high genetic risk score or those requiring chronic oral anticoagulation, requires further dedicated study. Finally, none of the included trials compared clopidogrel against other $P2Y_{12}$ inhibitors like ticagrelor for long-term monotherapy, leaving that question open for future research.

An important dimension not addressed by the clinical data alone is the pharmacoeconomic evaluation of clopidogrel monotherapy, particularly within the Chinese healthcare system. While clopidogrel is now generic and widely included in China's national reimbursement drug list, its daily cost remains higher than that of aspirin. A formal cost-effectiveness analysis from the perspective of the Chinese healthcare system is warranted. Preliminary modeled analyses suggest that the significant reduction in non-fatal ischemic events (myocardial infarction and stroke) with clopidogrel could lead to an acceptable incremental cost-effectiveness ratio, especially for patients at high risk of recurrent events, by avoiding the substantial long-term costs associated with these complications. Future research should integrate real-world Chinese data on drug costs, medical resource utilization, and long-term outcomes to perform a robust economic evaluation. Such studies will be indispensable for informing optimal resource allocation, guiding updates to national essential medicine lists, and ultimately supporting the implementation of this evidence-based therapeutic shift in clinical practice across diverse regions in China.

In conclusion, this IPD meta-analysis unequivocally heralds a paradigm shift in the long-term management strategy for CAD among patients who have transitioned to monotherapy after an uneventful period of dual antiplatelet therapy. It provides strong evidence to demonstrate that, in this chronic, stable-phase population, clopidogrel monotherapy represents a superior long-term antiplatelet strategy compared to the decades-long entrenched standard of care, aspirin. Embracing this evidence represents a timely opportunity to optimize antiplatelet strategies, effectively prevent event recurrence, and significantly improve prognosis for these patients with established CAD.

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AUTHOR CONTRIBUTIONS

Anxin Wang and Xue Tian contributed to the contributed to the conception and manuscript drafting; Si Cheng, Xue Xia, Hao Li, Yongjun Wang, and Xia Meng contributed to critical revisions of the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.