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Cite this as: *BMJ* 2025;389:r1089
http://doi.org/10.1136/bmj.r1089

Antiplatelet monotherapy after percutaneous coronary intervention

P2Y12 inhibitors preferred over aspirin

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Patients with coronary artery disease are often offered percutaneous coronary intervention (PCI) with drug eluting stents. International guidelines recommend dual antiplatelet therapy (DAPT) combining aspirin and P2Y12 inhibitors after PCI followed by lifelong aspirin monotherapy for secondary prevention of cardiovascular events.[1,2] These recommendations are based on pooled data from foundational randomised controlled trials that no longer represent contemporary practice.[3]

In a linked study, Giacoppo and colleagues (doi:10.1136/bmj-2024-082561) update the evidence base with their individual participant data meta-analysis of five randomised controlled trials: ASCET (ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial), CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), GLASSY (GLOBAL LEADERS Adjudication Sub-Study), HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy), and STOPDAPT-2 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 study).[4] Overall, 16 117 participants were included in this study comparing P2Y12 inhibitor monotherapy with aspirin after PCI and completion of DAPT. Compared with aspirin, P2Y12 inhibitor monotherapy reduced the composite primary efficacy endpoint of major adverse cardiac and cerebrovascular events (MACCE) by 23% at median follow-up of 3.7 years. This finding was driven by 31% and 33% reductions in myocardial infarction and stroke, respectively; no signal emerged for cardiovascular and all cause mortality. At first glance the primary safety endpoint of major bleeding appears similar, regardless of randomised allocation.

This meta-analysis reports novel and important findings.[4] More than 90% of included participants had undergone PCI in the past decade, making the results highly relevant to contemporary practice. Previously, the only study designed to directly compare the efficacy and safety of P2Y12 inhibitor monotherapy with aspirin post-PCI was HOST-EXAM.[5] By leveraging individual participant data, Giacoppo and colleagues[4] facilitated the inclusion of relevant data from additional trials that were not originally intended to answer these questions.[6-9] The reductions in myocardial infarction and stroke hold importance for patients and healthcare systems. In addition to increased risk of recurrent events[10,11] and mortality,[12,13] myocardial infarction and stroke are associated with psychological comorbidity and reduced functional status.[14,15] Consequently, these conditions are responsible for substantial healthcare expenditure and lost productivity.[16] Given the global burden of ischaemic heart disease,[13] reductions in myocardial infarction and stroke may translate to large population benefits.

Giacoppo and colleagues' result for major bleeding is challenging to interpret.[4] Reduced bleeding with P2Y12 inhibition in HOST-EXAM[5] is an outlier compared with the other included trials, which report effect estimates largely consistent with increased risk. The two studies contributing the largest weight to the meta-analysis, HOST-EXAM[5] and STOPDAPT-2,[6] demonstrate similar ischaemic reduction but non-overlapping bleeding risks with clopidogrel: 33% lower in HOST-EXAM but 46% higher in STOPDAPT-2. When inconsistency across trials in a meta-analysis generates considerable heterogeneity, the pooled result should be interpreted with caution until more randomised data accrue to better understand reasons underlying the divergence. Fortunately, SMART-CHOICE-3,[17] a recent Korean randomised controlled trial specifically designed to test clopidogrel versus aspirin monotherapy in participants (n=5506) at high risk for recurrent ischaemia post-PCI recently reported data consistent with Giacoppo and colleagues' meta-analysis[4]: reductions in MACCE with equivalent bleeding.[17] The ongoing Korean C-MODE (NCT05320926) trial testing clopidogrel monotherapy versus aspirin post-PCI in ~3700 participants will provide another piece of the puzzle. However, there remains a dearth of evidence from global regions other than East Asia, the eastern subregion of Asia that encompasses China (including Hong Kong and Macau), Japan, Mongolia, North Korea, Republic of Korea, and Taiwan. People from East Asia have distinct ischaemic and bleeding profiles, so further evidence is required as there is no guarantee these results generalise across populations.[18]

So, should these data influence clinicians and patients to switch from lifelong aspirin to P2Y12 inhibitor monotherapy after completion of DAPT post-PCI? Although now off-label, clopidogrel remains more expensive than aspirin, and comprehensive health economic evaluation is required to better understand cost effectiveness. Whether these findings apply equally to all P2Y12 inhibitors is also uncertain. While evidence supporting clopidogrel continues to accumulate, no trials have tested prasugrel, and only GLASSY[9] studied ticagrelor, although it did contribute ~42% of the randomised participants in Giacoppo and colleagues' study.[4] Future trials are required to replicate the GLASSY results and improve reliability, while prasugrel trials are needed to understand its role in secondary prevention monotherapy. These additional studies would help guide clinicians on using these more potent P2Y12 inhibitors, which have stronger antiplatelet effects than clopidogrel. In acute

coronary syndromes they have superior efficacy on ischaemic endpoints but increase bleeding,[19] limiting their prescription in patients at higher bleeding risk. A putative benefit with potent P2Y12 inhibitors is reduced variability in platelet response between individuals compared with clopidogrel,[20] although whether this translates to benefit on hard outcomes in this setting is untested.

Overall, Giacoppo and colleagues' study[4] supports preferential prescription of P2Y12 inhibitor monotherapy over aspirin owing to reductions in MACCE without increasing major bleeding in the medium term, further validated by results from the recent SMART-CHOICE-3 trial.[15] However, medium term efficacy does not necessarily extend lifelong, which is the duration we advise patients to continue these drugs. Whether the beneficial ischaemic and bleeding trade-off with antiplatelets remains durable over time is contentious, particularly in older adults, and randomised data are lacking beyond ~4 years.[21-23] In the current body of evidence, the appropriateness of existing recommendations for lifelong antiplatelet monotherapy remains an unanswered question. A large scale globally representative trial directly comparing different monotherapy strategies (including discontinuation) with extended follow-up would benefit our understanding of the long term effect of P2Y12 inhibitor monotherapy across the treatment class for secondary prevention after PCI.

Funding: RKR is supported by the Nuffield Department of Population Health, University of Oxford. RB is supported by the Rhodes Trust and Canadian Institutes of Health Research (FRN: 193224). MA is supported by a Medical Research Council Clinical Research Training Fellowship (MR/Z505146/1).

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare that there are no other relevant conflicts of interest.

Provenance and peer review: Commissioned; not externally peer reviewed.

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