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Editorial

$P2Y_{12}$ Inhibitor Monotherapy in Coronary Artery Disease: Translating Evidence Into Practice

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The optimal antithrombotic regimen following percutaneous coronary intervention (PCI) remains a central issue in the management of patients with coronary artery disease (CAD) [1–3]. Balancing the ischemic benefits of dual antiplatelet therapy (DAPT) with its inherent bleeding risks is a complex challenge, especially as PCI techniques and stent technologies continue to evolve [4–9]. Traditionally, DAPT—consisting of aspirin and a $P2Y_{12}$ inhibitor—has been recommended for 6–12 months post-PCI, followed by long-term aspirin monotherapy. However, over the past decade, there has been increased interest in the strategy of early aspirin withdrawal and continuation with $P2Y_{12}$ inhibitor monotherapy, an approach supported by a series of high-quality trials, which have been comprehensively reported in individual patient data (IPD) meta-analyses [5]. This editorial aims to review these pooled analyses, and highlight key messages for clinical practice.

1. $P2Y_{12}$ Inhibitor Monotherapy Versus Standard DAPT After PCI

The first landmark meta-analysis published by Valgimigli *et al.* [10] in 2021 on this topic pooled IPD from six randomized trials including 24,096 patients who underwent coronary revascularization, predominately with PCI. The study found that $P2Y_{12}$ inhibitor monotherapy after 1–3 months of DAPT was non-inferior to continued DAPT with respect to major adverse cardiovascular events (MACE), including all-cause death, myocardial infarction (MI), and stroke (hazard ratio [HR] 0.93, 95% CI 0.79–1.09; $p = 0.005$ for non-inferiority). $P2Y_{12}$ monotherapy significantly reduced major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5 bleeding) by nearly 50%. The results also showed a significant heterogeneity in the treatment effect for sex, indicating that $P2Y_{12}$ inhibitor monotherapy may lower the risk of MACE in females but not in males, driven by a reduction in cardiovascular mortality. The potential benefit on cardiovascular mortality observed in female patients warrants careful consideration and should be interpreted as hypothesis-generating due to the multiple subgroup analyses that were conducted and the absence of correction for multiplicity [10]. Of note, this mortality benefit did not appear to be related to sex-specific differences in bleeding reduction, as both the relative and absolute reductions in major bleeding were similar in males and females. Previously reported sex-related disparities in bleeding management may partly account for this observation, but further investigation is needed [10].

The results of this meta-analysis were further expanded through a secondary analysis stratified by PCI complexity [11]. Among 22,941 patients, 4685 (20.4%) met the criteria for complex PCI. $P2Y_{12}$ monotherapy maintained similar ischemic protection compared with DAPT in both complex and non-complex procedures (p for interaction = 0.77), with a consistent and significant 50% reduction in major bleeding across all strata (p for interaction = 0.92). These findings challenge the long-standing recommendation that complex PCI mandates prolonged DAPT and instead highlights the potential for simplifying antithrombotic strategies using $P2Y_{12}$ inhibitor monotherapy without compromising efficacy.

A subsequent study advanced the field by evaluating whether the efficacy of $P2Y_{12}$ inhibitor monotherapy depends on the type of $P2Y_{12}$ inhibitor used [12]. In over 25,000 patients, the risks and benefits of ticagrelor monotherapy or clopidogrel monotherapy compared with standard DAPT after PCI were reviewed. Ticagrelor monotherapy was non-inferior to DAPT for MACE (HR 0.89; 95% CI 0.74–1.06; p for noninferiority = 0.004) and superior in reducing major bleeding (HR 0.47; 95% CI 0.36–0.62; $p < 0.001$) and net adverse clinical events (NACE) (HR 0.74; 95% CI 0.64–0.86; $p < 0.001$). Clopidogrel monotherapy, however, failed to show noninferiority for MACE (HR 1.37; 95% CI 1.01–1.87; p for noninferiority >0.99), while demonstrating consistent benefit in terms of major bleeding reduction (HR 0.49; 95% CI 0.30–0.81; $p = 0.006$) compared with DAPT, ultimately resulting in a neutral effect on NACE (HR 1.00; 95% CI 0.78–1.28; $p = 0.99$). This evidence suggests that the treatment efficacy of $P2Y_{12}$ inhibitor monotherapy varies depending on the type of $P2Y_{12}$ inhibitor, underscoring the importance of the choice of medication and patient selection when considering clopidogrel as a monotherapy agent.

In 2024, a new meta-analysis focused on the clinical efficacy of ticagrelor monotherapy following short-term DAPT (from 2 weeks to 3 months) compared with standard DAPT after PCI, and whether the treatment effect differs between patients with and without acute coronary syndrome (ACS). In over 24,000 patients, ticagrelor monotherapy demonstrated non-inferior efficacy in terms of MACE (HR 0.91; 95% CI 0.78–1.07; $p = 0.0039$ for non-inferiority) and superior safety for BARC type 3 or 5 bleeding (HR 0.43; 95% CI 0.34–0.54; $p < 0.0001$) compared to 12-month DAPT [13]. The risk of all-cause death was also lower with ticagrelor monotherapy (HR 0.76; 95% CI 0.59–0.98; $p = 0.034$). The benefits of ticagrelor monotherapy were especially evident in ACS patients, and provided data supporting the early discontinuation of aspirin in this high-risk group, which has been traditionally managed with a 12-month course of DAPT.

2. $P2Y_{12}$ Inhibitor Monotherapy Versus Aspirin Monotherapy in Patients With CAD

Two additional IPD meta-analyses examined the comparative efficacy and safety of long-term antiplatelet monotherapy with a $P2Y_{12}$ inhibitor versus aspirin. In 2023, the PANTHER meta-analysis compared the two monotherapy strategies using data from seven randomized trials which included 24,325 patients with established CAD, irrespective of their initial treatment (e.g., PCI, coronary artery by-pass grafting, or medical therapy alone) [14]. In the $P2Y_{12}$ inhibitor monotherapy group, 7545 (62.0%) were assigned to clopidogrel and 4633 (38.0%) to ticagrelor. Over two years of follow-up, $P2Y_{12}$ inhibitor monotherapy was associated with a significant reduction in the composite endpoint of cardiovascular death, MI, or stroke (HR 0.88, 95% CI 0.79–0.97; $p = 0.012$) primarily due to a decreased incidence of MIs. Bleeding rates remained comparable between the two antiplatelet strategies. These findings were reinforced by an updated IPD meta-analysis published in 2025 in BMJ [15]. Compared to PANTHER [14], this analysis included newer trials and extended follow-up data from earlier studies, and exclusively focused on PCI patients who had completed DAPT [15]. In 16,117 patients from five trials with a median follow-up of over 3.5 years, $P2Y_{12}$ inhibitor monotherapy significantly reduced the primary efficacy outcome of cardiovascular death, MI, or stroke (HR 0.77; 95% CI 0.67–0.89; $p < 0.001$), without increasing the risk of major bleeding. The number needed to treat for MACE was 45.5, highlighting the clinical relevance of these results.

3. Future Perspectives and Conclusions

Collectively, this evidence provides a strong foundation for revisiting the role of aspirin in secondary prevention, particularly in the context of contemporary PCI. Recent clinical guidelines have begun to incorporate these data: the latest American guidelines for the management of ACS endorse ticagrelor monotherapy from 1 month (Class I, A) as an alternative to standard DAPT [3]; the latest European guidelines for the management of chronic coronary syndromes recommend clopidogrel monotherapy (Class I, A) as a safe and effective alternative to aspirin [2]. These updates mark a clear shift toward broader recognition and endorsement of $P2Y_{12}$ inhibitor monotherapy compared with previous guidelines. Although current guidelines do not identify a specific patient subgroup for preferential use of this strategy, available evidence suggests that females may experience increased benefit from $P2Y_{12}$ inhibitor monotherapy. Furthermore, in patients treated with early clopidogrel monotherapy after PCI, genetic or platelet function testing may help to identify poor responders, thereby optimizing antiplatelet efficacy through a more personalized approach.

In summary, $P2Y_{12}$ inhibitor monotherapy has emerged as a viable and often preferable alternative to prolonged DAPT or aspirin monotherapy across a broad spectrum of patients with CAD. This strategy challenges the historical dominance of aspirin in secondary prevention and represents a paradigm shift in antiplatelet therapy, increasingly aligned with contemporary evidence. While current data support early aspirin discontinuation after a short course of DAPT after ACS or PCI, several questions remain. For instance, the perioperative management of patients receiving $P2Y_{12}$ inhibitor monotherapy remains undefined, highlighting the need for standardized protocols to be established in future clinical guidelines.

Author Contributions

FG, VDS, AC, PC designed the research study. FG drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al*. 2023 ESC Guidelines for the management of acute

coronary syndromes. European Heart Journal. 2023; 44: 3720–3826. https://doi.org/10.1093/eurheartj/ehad191.

[2] Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al*. 2024 ESC Guidelines for the management of chronic coronary syndromes. European Heart Journal. 2024; 45: 3415–3537. https://doi.org/10.1093/eurheartj/ehae177.

[3] Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, *et al*. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2025; 85: 2135–2237. https://doi.org/10.1016/j.jacc.2024.11.009.

[4] Gragnano F, van Klaveren D, Heg D, Räber L, Krucoff MW, Raposeiras-Roubín S, *et al*. Derivation and Validation of the PRECISE-HBR Score to Predict Bleeding After Percutaneous Coronary Intervention. Circulation. 2025; 151: 343–355. https://doi.org/10.1161/CIRCULATIONAHA.124.072009.

[5] Galli M, Gragnano F, Berteotti M, Marcucci R, Gargiulo G, Calabrò P, *et al*. Antithrombotic Therapy in High Bleeding Risk, Part I: Percutaneous Cardiac Interventions. JACC. Cardiovascular Interventions. 2024; 17: 2197–2215. https://doi.org/10.1016/j.jcin.2024.08.022.

[6] Montone RA, Rinaldi R, Niccoli G, Andò G, Gragnano F, Piccolo R, *et al*. Optimizing Management of Stable Angina: A Patient-Centered Approach Integrating Revascularization, Medical Therapy, and Lifestyle Interventions. Journal of the American College of Cardiology. 2024; 84: 744–760. https://doi.org/10.1016/j.jacc.2024.06.015.

[7] Galli M, Laudani C, Occhipinti G, Spagnolo M, Gragnano F, D'Amario D, *et al*. P2Y12 inhibitor monotherapy after short DAPT in acute coronary syndrome: a systematic review and meta-analysis. European Heart Journal. Cardiovascular Pharmacotherapy. 2024; 10: 588–598. https://doi.org/10.1093/ehjcvp/pvae057.

[8] Benenati S, Gragnano F, Scalamera R, De Sio V, Capolongo A, Cesaro A, *et al*. ICARUS score for predicting peri-procedural bleeding in patients undergoing percutaneous coronary intervention with cangrelor. International Journal of Cardiology. 2024; 417: 132568. https://doi.org/10.1016/j.ijcard.2024.132568.

[9] Gragnano F, Calabrò P, Valgimigli M. Is triple antithrombotic therapy, or rather its duration and composition, the true culprit for the excess of bleeding events observed in patients with atrial fibrillation undergoing coronary intervention? European Heart Journal. 2019; 40: 216–217. https://doi.org/10.1093/eurheartj/ehy675.

[10] Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y, *et al*. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. BMJ (Clinical Research Ed.). 2021; 373: n1332. https://doi.org/10.1136/bmj.n1332.

[11] Gragnano F, Mehran R, Branca M, Franzone A, Baber U, Jang Y, *et al*. $P2Y_{12}$ Inhibitor Monotherapy or Dual Antiplatelet Therapy After Complex Percutaneous Coronary Interventions. Journal of the American College of Cardiology. 2023; 81: 537–552. https://doi.org/10.1016/j.jacc.2022.11.041.

[12] Valgimigli M, Gragnano F, Branca M, Franzone A, da Costa BR, Baber U, *et al*. Ticagrelor or Clopidogrel Monotherapy vs Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: A Systematic Review and Patient-Level Meta-Analysis. JAMA Cardiology. 2024; 9: 437–448. https://doi.org/10.1001/jamacardio.2024.0133.

[13] Valgimigli M, Hong SJ, Gragnano F, Chalkou K, Franzone A, da Costa BR, *et al*. De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials. Lancet. 2024; 404: 937–948. https://doi.org/10.1016/S0140-6736(24)01616-7.

[14] Gragnano F, Cao D, Pirondini L, Franzone A, Kim HS, von Scheidt M, *et al*. $P2Y_{12}$ Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events. Journal of the American College of Cardiology. 2023; 82: 89–105. https://doi.org/10.1016/j.jacc.2023.04.051.

[15] Giacoppo D, Gragnano F, Watanabe H, Kimura T, Kang J, Park KW, *et al*. $P2Y_{12}$ inhibitor or aspirin after percutaneous coronary intervention: individual patient data meta-analysis of randomised clinical trials. BMJ (Clinical Research Ed.). 2025; 389: e082561. https://doi.org/10.1136/bmj-2024-082561.