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Re-evaluating aspirin in the era of potent P2Y12 inhibitors: Ticagrelor monotherapy after percutaneous coronary intervention

Ticagrelor-based antiplatelet strategies in PCI

Abstract

BACKGROUND

High-risk patients undergoing percutaneous coronary intervention (PCI) need effective antiplatelet therapy to prevent thrombotic events, but prolonged dual antiplatelet therapy (DAPT) raises bleeding risk. Evidence suggests that early aspirin discontinuation with ticagrelor monotherapy may reduce bleeding without compromising ischaemic protection.

AIM

To assess the efficacy and safety of ticagrelor monotherapy *vs* continued DAPT in high-risk post-PCI patients through a systematic review and meta-analysis of randomized controlled trials (RCTs).

METHODS

MEDLINE/PubMed, Cochrane, Clinicaltrials.gov and trial registries were searched to August 2025 for RCTs evaluating ticagrelor monotherapy after ≤ 3 months of DAPT. Outcomes included clinically relevant bleeding (BARC 2/3/5), major bleeding (BARC 3/5 or TIMI major), major adverse cardiac events (MACE: Death, myocardial infarction, stroke), and net adverse clinical events (NACE). Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using random-effects models.

RESULTS

Four RCTs (TWILIGHT, TICO, T-PASS, ULTIMATE-DAPT; > 20,000 participants) were included. Ticagrelor monotherapy significantly reduced clinically relevant bleeding (HR 0.53, 95%CI 0.44–0.65; I^2 = 0%) and major bleeding (HR 0.45, 95%CI 0.28–0.71; I^2 = 34%) without excess MACE (HR 0.97, 95%CI 0.79–1.17; I^2 = 0%). NACE was also reduced (HR 0.53, 95%CI 0.44–0.65).

CONCLUSION

Ticagrelor monotherapy after abbreviated DAPT lowers bleeding without increasing ischaemic events, providing a favourable net clinical benefit in high-risk PCI patients and supporting guideline trends toward shorter DAPT.

Key Words: Ticagrelor; dual antiplatelet therapy; percutaneous coronary intervention; P2Y12 inhibitors; Aspirin

Core Tip: Ticagrelor monotherapy after short-term DAPT significantly reduces bleeding without increasing ischaemic risk in high-risk PCI patients. This meta-analysis of > 20,000 patients supports aspirin discontinuation after 1–3 months of DAPT. Findings reinforce evolving guidelines toward simplified, safer antiplatelet strategies post-PCI.

INTRODUCTION

Percutaneous coronary intervention (PCI) is the cornerstone of contemporary revascularization strategies for patients with acute coronary syndromes and high-risk chronic coronary syndromes. Despite improvements in stent design and procedural techniques, recurrent ischaemic complications, including stent thrombosis and myocardial infarction, remain major concerns. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor has long been the standard of care following PCI, with international guidelines recommending at least 12 months of therapy in high-risk cohorts. While this strategy provides robust protection against thrombotic events, it carries a significant trade-off in the form of bleeding, which is now recognized as an equally important determinant of morbidity, mortality, and quality of life in cardiovascular patients[1,2].

The challenge of optimizing DAPT duration is particularly acute in patients at increased risk of bleeding, such as the elderly, those with renal impairment, anaemia, or those requiring concomitant oral anticoagulation. For such populations, prolonged DAPT can confer limited incremental ischaemic benefit while exposing them to

disproportionately higher bleeding hazards. Several large observational studies and registry data have confirmed that bleeding events after PCI are independently associated with long-term mortality, re-hospitalization, and resource utilization, underscoring the need for individualized antiplatelet strategies[3,4].

Ticagrelor, a potent, reversible $P2Y_{12}$ inhibitor, offers more rapid and consistent platelet inhibition than clopidogrel and has demonstrated superiority in reducing ischaemic events in acute coronary syndromes. These pharmacodynamic properties make it an attractive candidate for monotherapy, raising the hypothesis that aspirin may be safely discontinued early after PCI while maintaining effective platelet inhibition with ticagrelor alone. This hypothesis was formally tested in a series of randomized controlled trials. The landmark TWILIGHT trial evaluated high-risk PCI patients and showed that discontinuation of aspirin after three months of DAPT significantly reduced Bleeding Academic Research Consortium (BARC) type 2–5 bleeding without increasing death, myocardial infarction, or stroke[5]. Similar results were observed in the TICO trial, which studied an East Asian acute coronary syndrome cohort, reporting reductions in both bleeding and a composite of ischaemic outcomes with ticagrelor monotherapy. More recently, the T-PASS trial extended these findings by assessing aspirin withdrawal after just one month of DAPT, while the ULTIMATE-DAPT trial provided robust double-blind evidence in an international population that early aspirin discontinuation led to lower bleeding and net adverse clinical events without compromising ischaemic protection[1,6].

Although these individual trials consistently suggest that ticagrelor monotherapy after a short course of DAPT is a safe and effective strategy, their differing designs, populations, and endpoints necessitate a comprehensive synthesis of evidence. Furthermore, uncertainties remain regarding generalizability across geographic regions, the optimal duration of the DAPT run-in phase, and the long-term trade-off between bleeding reduction and ischaemic safety. Previous analyses of $P2Y_{12}$ inhibitor monotherapy have often been dominated by clopidogrel trials and therefore may not

adequately reflect the efficacy and safety profile of ticagrelor, which is pharmacologically distinct[3,4,5].

Given the clinical importance of this question, we conducted a systematic review and meta-analysis of randomized controlled trials evaluating ticagrelor monotherapy following abbreviated DAPT in high-risk PCI patients. Our objective was to assess the impact of this strategy on bleeding, major adverse cardiovascular events, and net clinical benefit, thereby informing evidence-based optimization of antiplatelet therapy in this vulnerable population.

MATERIALS AND METHODS

Protocol

This systematic review was conducted in line with the PRISMA 2020 statement. A formal protocol describing the objectives, eligibility criteria, search strategy, outcomes and methods for data extraction and synthesis was drafted a priori. No amendments were made after the review commenced. The study was registered on PROSPERO (ID: CRD420261299344).

Eligibility criteria

Randomised controlled trials enrolling adults undergoing PCI were eligible if they compared ticagrelor monotherapy after ≤ 3 months of DAPT with continued DAPT (ticagrelor + aspirin). Trials enrolling acute coronary syndrome or stable coronary disease were included. Studies of other $P2Y_{12}$ inhibitors or switching to clopidogrel were excluded. Primary outcomes were clinically relevant bleeding (Bleeding Academic Research Consortium- BARC 2–5) and major bleeding (BARC 3–5 or TIMI major: Thrombolysis in Myocardial Infarction). Secondary outcomes were three-point major adverse cardiac events (MACE: Death, myocardial infarction or stroke) and net adverse clinical events (NACE), defined as a composite of bleeding and ischaemic outcomes.

Search strategy

We systematically searched databases *i.e.* MEDLINE/PubMed, Clinicaltrials.gov and trial registries from inception to 31 August 2025. Our search strategy combined free text and medical subject headings for the concepts of ticagrelor, monotherapy, dual antiplatelet therapy, aspirin and percutaneous coronary intervention, with filters for randomised controlled trials using MeSH Terms *i.e.* (ticagrelor AND (monotherapy OR aspirin discontinuation) AND randomized AND percutaneous coronary intervention); the full strategy is added as the supplementary file). No language restrictions were applied and no date limits were applied at the search stage. Additionally, we searched conference abstracts, trial protocols and reference lists of relevant articles and reviews to identify ongoing or unpublished studies. Two reviewers independently screened titles and abstracts, retrieved full texts for potentially eligible studies and determined final inclusion; discrepancies were resolved by consensus. We recorded numbers of records identified, screened, assessed for eligibility and excluded, and provide these in a PRISMA flow diagram. The screening was done *via* citation manager *i.e.* Zotero.

RESULTS

Four randomised controlled trials met the inclusion criteria and were included in qualitative and quantitative synthesis.

Study characteristics

Four trials met inclusion criteria. TWILIGHT randomised high-risk patients after 3 months of DAPT[1]. TICO randomised acute coronary syndrome patients after 3 months of DAPT[2]. T-PASS randomised acute coronary syndrome patients after a shorter DAPT duration (< 1 month). ULTIMATE-DAPT randomised acute coronary syndrome patients one month post-PCI[5]. All trials compared ticagrelor monotherapy (aspirin placebo) with ticagrelor plus aspirin for 12 months. Populations differed in ethnicity (Asian-only in TICO and majority Asian in T-PASS and ULTIMATE-DAPT),

run-in duration and bleeding definitions. Sample sizes ranged from 2,850 to 7,119 participants.

Meta-analysis

Clinically relevant bleeding

Two trials (TWILIGHT and ULTIMATE-DAPT) reported BARC 2/3/5 bleeding. Both showed fewer clinically relevant bleeding events with ticagrelor monotherapy (4.0 % *vs* 7.1 % and 2.1 % *vs* 4.6 %). The pooled hazard ratio was 0.53 (95 % CI 0.44 to 0.65) low statistical heterogeneity (I^2 = 0%) was observed for clinically relevant bleeding. Figure 1 displays the forest plot.

Figure 1: Forest plot of comparison: 1 DAPT vs. SAPT, outcome: 1.1 clinically relevant bleeding (BARC 2/3/5).

Major bleeding

Two trials (TICO and T-PASS) reported severe bleeding. In TICO, TIMI major bleeding occurred in 1.7 % of monotherapy patients *vs* 3.0 % in the DAPT group (HR 0.56, 95 % CI 0.34–0.92). T-PASS reported similar reductions (0.6 % *vs* 1.7 %; HR 0.35). The pooled hazard ratio for major bleeding was 0.45 (95 % CI 0.28 to 0.71) moderate heterogeneity was present for major bleeding (I^2 = 34%). (Figure 2).

Figure 2: Forest plot of comparison: 1 DAPT vs. SAPT, outcome: 1.1 Major Bleeding

Three-point MACE

Three trials (TWILIGHT, T-PASS and ULTIMATE-DAPT) reported the composite of death, myocardial infarction or stroke*[3][8]*. Event rates were nearly identical: 3.9 % *vs* 3.9 % in TWILIGHT[1] and 3.6 % *vs* 3.7 % in ULTIMATE-DAPT[8]. The pooled hazard ratio was 0.97 (95 % CI 0.79 to 1.17) I^2 = 0% indicating no increase in ischaemic events as shown in Figure 03.

Figure 3: Forest plot of comparison: 1 DAPT vs. SAPT, outcome: 1.1 Three-point MACE

Net adverse clinical events

Two trials (TWILIGHT and ULTIMATE-DAPT) reported a composite of bleeding and ischaemic outcomes (definitions varied)*[2]. TWILIGHT followed TIMI definition.* ULTIMATE-DAPT's NACE combined any BARC 1–5 bleed with MACCE. All two favoured monotherapy. The pooled hazard ratio was **0.53 (95 % CI 0.44 to 0.65)** with $I^2 = 0$ % (Figure 4).

Figure 4: Forest plot of comparison: 1 DAPT vs. SAPT, outcome: 1.1 Net Adverse Clinical Events

Sensitivity and subgroup analyses

We didn't conduct sensitivity analyses as $I^2 = 0\%$ in all outcomes except three-point MACE where any two RCTs reported this variable. Subgroup analyses by region or run-in duration were not feasible because of limited trial numbers. The lack of heterogeneity across all analyses ($I^2 = 0$ % except Three-point MACE $I^2 = 34\%$) suggests consistent treatment effects despite design differences.

DISCUSSION

The findings of this systematic review and meta-analysis reinforce the evolving paradigm in antiplatelet therapy after PCI, particularly in high-risk patients where balancing thrombotic and bleeding events remains a persistent clinical challenge. Our pooled results show that ticagrelor monotherapy, following a short course of DAPT, significantly reduces clinically relevant and major bleeding compared with continued DAPT, without increasing the risk of ischaemic events. This is consistent across multiple randomized controlled trials, including TWILIGHT[1], TICO[2], T-PASS[3], and ULTIMATE-DAPT[4], which were individually powered to evaluate bleeding and safety endpoints in distinct high-risk subgroups.

Bleeding complications after PCI are not benign; they are strongly associated with increased mortality, rehospitalization, and impaired quality of life[5]. Prolonged DAPT, while historically justified to mitigate stent thrombosis, exposes patients to cumulative

bleeding hazards, especially in elderly populations, patients with chronic kidney disease, anemia, or concomitant use of oral anticoagulants. Our pooled hazard ratios indicate nearly a 50% relative reduction in both clinically relevant and severe bleeding events with ticagrelor monotherapy, a magnitude of benefit that surpasses many contemporary pharmacological interventions in cardiology. The absence of significant heterogeneity ($I^2 \approx 0\%$ in most outcomes) further underscores the reproducibility of this effect across diverse trial populations.

Equally important, the neutral effect on three-point major adverse cardiovascular events (death, myocardial infarction, or stroke) confirms that aspirin discontinuation does not compromise ischaemic protection. This addresses a long-standing concern in clinical practice, given aspirin's central role as the cornerstone of antiplatelet therapy for decades. The consistency between TWILIGHT[1], T-PASS[3], and ULTIMATE-DAPT[4] is particularly reassuring, as these studies enrolled both chronic coronary syndrome and acute coronary syndrome patients, utilized varying run-in durations (one to three months), and were conducted across different ethnic populations. The robustness of the pooled estimate (HR ~0.97) suggests that ticagrelor monotherapy maintains sufficient platelet inhibition to prevent ischaemic recurrences while minimizing bleeding risks.

The reduction in net adverse clinical events (NACE), integrating both bleeding and ischaemic outcomes, further strengthens the argument for aspirin withdrawal after a short DAPT period. NACE represents a clinically meaningful endpoint reflecting real-world trade-offs faced by clinicians and patients. The consistency of benefit across TWILIGHT and ULTIMATE-DAPT[1,4] in our analysis indicates that ticagrelor monotherapy provides not only a safer bleeding profile but also a superior overall clinical net benefit. These findings align with current European Society of Cardiology recommendations, which increasingly support shorter DAPT durations in high-risk subsets[6].

Our results are concordant with evidence from platelet function studies, which demonstrate that ticagrelor provides more potent and consistent P2Y12 inhibition than clopidogrel, and that aspirin withdrawal does not necessarily translate into excess

thrombotic events[7]. Data from the PEGASUS-TIMI 54[8] and THEMIS[9] programs highlighted both the anti-ischaemic efficacy and bleeding hazards of ticagrelor, underscoring the importance of tailoring therapy to individual risk profiles. Moreover, meta-analyses of P2Y12 inhibitor monotherapy strategies—although often dominated by clopidogrel—support the safety of aspirin discontinuation and show reduced bleeding without a rise in ischaemic events[10].

Limitations:

Nonetheless, several limitations must be acknowledged. First, the included trials generally excluded patients with very high bleeding risk who might have experienced even greater benefit, as well as those unable to tolerate the initial DAPT run-in, limiting generalizability. Second, the lack of detailed subgroup analyses by clinical presentation, geographic region, or stent type prevents exploration of possible heterogeneity across important subgroups. While our analysis demonstrated minimal statistical heterogeneity, clinical diversity remains considerable. Third, long-term outcomes beyond 12 months remain unknown, and whether the bleeding benefits persist without late trade-offs in ischaemic protection requires further study. Most included trials were industry-sponsored, which may introduce bias, although double-blind design in TWILIGHT and ULTIMATE-DAPT mitigates this concern. Although statistical heterogeneity was low, clinically meaningful differences existed among included trials, including variation in DAPT run-in duration and population ethnicity. These factors may influence bleeding risk and antiplatelet response and could affect the generalizability of pooled estimates. Therefore, results should be interpreted cautiously across diverse clinical settings.

From a clinical standpoint, these findings should inform individualized patient management. In high-risk post-PCI patients, particularly those with heightened bleeding risk, discontinuation of aspirin after one to three months of DAPT and continuation with ticagrelor monotherapy appears to provide an optimal balance of safety and efficacy. This approach may be especially relevant in Asian populations,

where bleeding risk is inherently higher and was demonstrated convincingly in TICO and T-PASS[2,3]. Conversely, in patients with very high ischaemic risk (*e.g.*, prior stent thrombosis, diffuse multivessel disease, or concomitant oral anticoagulation), more tailored approaches may still be required

CONCLUSION

This meta-analysis demonstrates that ticagrelor monotherapy following abbreviated DAPT significantly reduces bleeding complications while preserving ischaemic protection, resulting in a favourable net clinical benefit. These results support the strategy of early aspirin discontinuation in high-risk PCI patients and align with the trajectory of contemporary guideline recommendations. Future research should clarify long-term outcomes, cost-effectiveness, and optimal patient selection to maximize benefit.

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