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META-ANALYSIS

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

Abdul Basit, Muhammad Hamza Aslam, Muhammad Moneeb Anwar, Muhammad Ahmad Sarwar, Ammara Akram, Qamar Ismail, Abdullah Iftikhar, Majeed Haq

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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 ischemic 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 (Bleeding Academic

Research Consortium 2/3/5), major bleeding (Bleeding Academic Research Consortium 3/5 or thrombolysis in myocardial infarction major), major adverse cardiac events (death, myocardial infarction, stroke), and net adverse clinical events. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using random-effects models.

RESULTS

Four RCTs (TWILIGHT, TICO, T-PASS, ULTIMATE-DAPT; > 20000 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 major adverse cardiac events (HR = 0.97, 95%CI: 0.79-1.17; I^2 = 0%). Net adverse clinical event was also reduced (HR = 0.53, 95%CI: 0.44-0.65).

CONCLUSION

Ticagrelor monotherapy after abbreviated DAPT lowers bleeding without increasing ischemic events, providing a favorable 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 dual antiplatelet therapy significantly reduces bleeding without increasing ischemic risk in high-risk percutaneous coronary intervention patients. This meta-analysis of > 20000 patients supports aspirin discontinuation after 1-3 months of dual antiplatelet therapy. Findings reinforce evolving guidelines toward simplified, safer antiplatelet strategies post-percutaneous coronary intervention.

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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 ischemic complications, including stent thrombosis and myocardial infarction, remain major concerns. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 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, anemia, or those requiring concomitant oral anticoagulation. For such populations, prolonged DAPT can confer limited incremental ischemic 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 P2Y12 inhibitor, offers more rapid and consistent platelet inhibition than clopidogrel and has demonstrated superiority in reducing ischemic 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 (RCTs). 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 ischemic 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 (NACEs) without compromising ischemic 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 ischemic safety. Previous analyses of P2Y12 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[3-5].

Given the clinical importance of this question, we conducted a systematic review and meta-analysis of RCTs 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 Preferred Reporting Items for Systematic reviews and Meta-Analyses 2009 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 International Prospective Register of Systematic Reviews (No. CRD420261299344).

Eligibility criteria

RCTs 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 P2Y12 inhibitors or switching to clopidogrel were excluded. Primary outcomes were clinically relevant bleeding (BARC 2-5) and major bleeding (BARC 3-5) or thrombolysis in myocardial infarction (TIMI) major. Secondary outcomes were three-point major adverse cardiac events (MACE; Death, myocardial infarction or stroke) and NACE, defined as a composite of bleeding and ischemic 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, DAPT, aspirin and PCI, with filters for RCTs using Medical Subject Headings terms *i.e.* ["ticagrelor" AND ("monotherapy" OR "aspirin discontinuation") AND "randomized" AND "percutaneous coronary intervention"]; the full strategy is added as the Supplementary material. 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 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram. The screening was done *via* citation manager *i.e.* Zotero.

RESULTS

Four RCTs met the inclusion criteria and were included in qualitative and quantitative synthesis.

Study characteristics

Four trials met inclusion criteria. TWILIGHT randomized high-risk patients after 3 months of DAPT[1]. TICO randomized acute coronary syndrome patients after 3 months of DAPT[2]. T-PASS randomized acute coronary syndrome patients after a shorter DAPT duration (< 1 month). ULTIMATE-DAPT randomized 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), runin duration and bleeding definitions. Sample sizes ranged from 2850 to 7119 participants (Table 1).

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 (HR) was 0.53 [95% confidence interval (CI): 0.44-0.65] low statistical heterogeneity (I^2 = 0%) was observed for clinically relevant bleeding. Figure 1A displays the forest plot.

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 HR for major bleeding was 0.45 (95%CI: 0.28-0.71) moderate heterogeneity was present for major bleeding (I^2 = 34%; Figure 1B).

Three-point MACE: Three trials (TWILIGHT, T-PASS and ULTIMATE-DAPT) reported the composite of death, myocardial infarction or stroke[3,7]. Event rates were nearly identical: 3.9% *vs* 3.9% in TWILIGHT[1] and 3.6% *vs* 3.7% in ULTIMATE-DAPT[7]. The pooled HR was 0.97 (95%CI: 0.79-1.17; I^2 = 0%) indicating no increase in ischemic events as shown in Figure 1C.

Table 1 Characteristics of the studies included in the meta-analysis

Trial	Study design	Population/clinical setting	Sample size	DAPT run-in duration before randomization	Follow-up duration	Trial primary outcome	Outcomes used in this meta-analysis
TWILIGHT	Randomized, double-blind, placebo-controlled	High-risk patients undergoing PCI	7119	3 months	12 months	Clinically relevant bleeding (BARC 2-5) and ischemic composite (death, MI, stroke)	Clinically relevant bleeding (BARC 2/3/5), MACE (death, MI, stroke), NACE
TICO	Randomized, open-label with blinded endpoint adjudication	Acute coronary syndrome patients undergoing PCI (East Asian cohort)	3056	3 months	12 months	Composite of major bleeding and major adverse cardiac and cerebrovascular events	Major bleeding (TIMI major), ischemic outcomes, contributed to NACE
T-PASS	Randomized, open-label	Acute coronary syndrome patients undergoing PCI	As reported in trial publication	< 1 month	12 months	Composite of ischemic and bleeding events at 1 year	Major bleeding, MACE (approximated from reported event counts)
ULTIMATE-DAPT	Randomized, double-blind, placebo-controlled	Acute coronary syndrome patients undergoing PCI	As reported in trial publication	1 month	12 months	Clinically relevant bleeding with ischemic safety outcomes	Clinically relevant bleeding (BARC 2/3/5), major bleeding (BARC 3/5), MACE, NACE

PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy; BARC: Bleeding Academic Research Consortium; MI: Myocardial infarction; MACE: Major adverse cardiac event; NACE: Net adverse clinical event; TIMI: Thrombolysis in myocardial infarction.

Net adverse clinical events: Two trials (TWILIGHT and ULTIMATE-DAPT) reported a composite of bleeding and ischemic outcomes (definitions varied)[2]. TWILIGHT followed TIMI definition. ULTIMATE-DAPT's NACE combined any BARC 1-5 bleed with MACCE. All two favored monotherapy. The pooled HR was 0.53 (95%CI: 0.44-0.65) with I^2 = 0% (Figure 1D).

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 runin 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 ischemic events. This is consistent across multiple RCTs, 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 HRs 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 approximately of 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 ischemic 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 approximately of 0.97) suggests that ticagrelor monotherapy maintains sufficient platelet inhibition to prevent ischemic recurrences while minimizing bleeding risks.

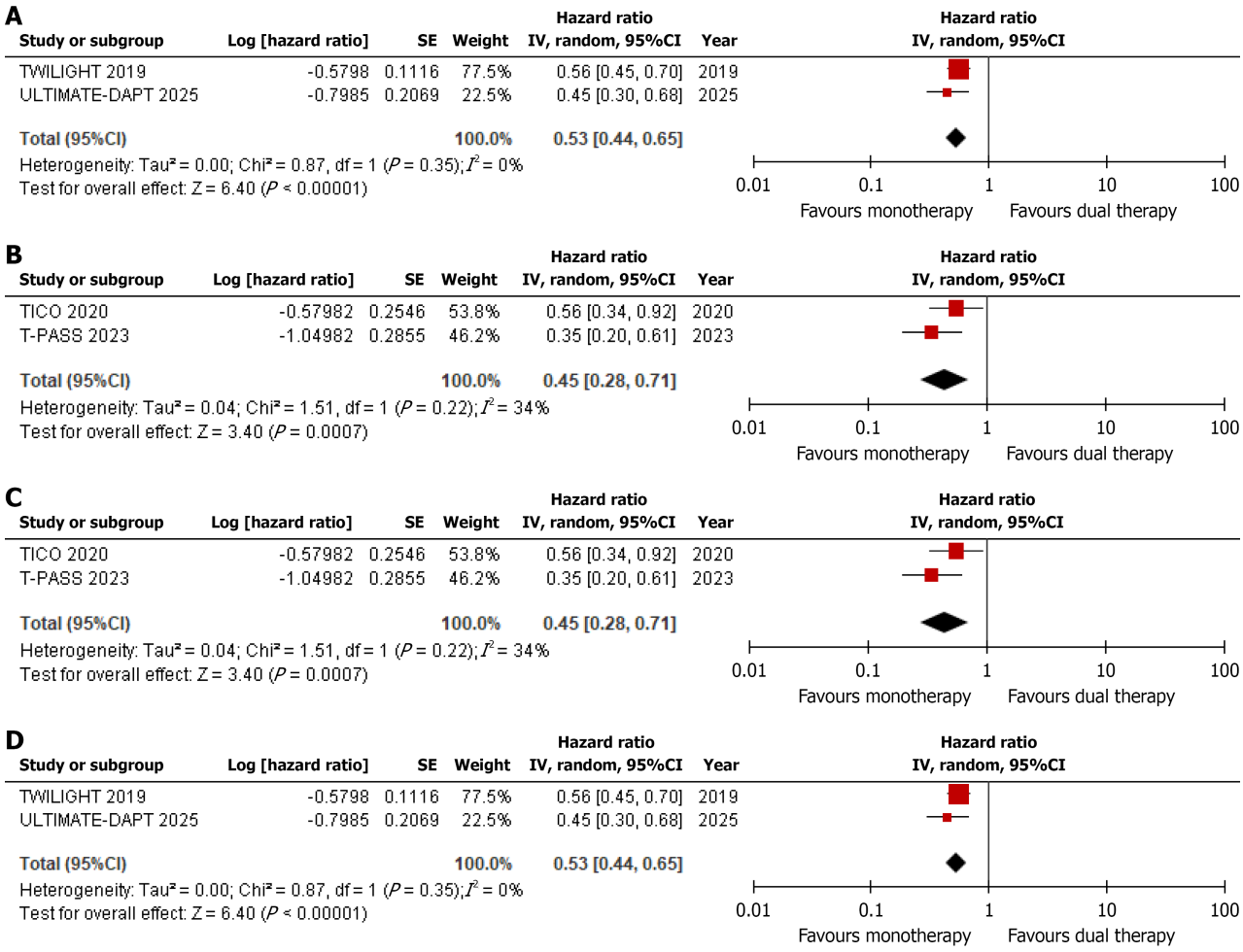

Figure 1 Forest plot of comparison. A: Dual antiplatelet therapy (DAPT) *vs* single antiplatelet therapy (SAPT), outcome: Clinically relevant bleeding (Bleeding Academic Research Consortium 2/3/5); B: DAPT *vs* SAPT, outcome: Major bleeding; C: DAPT *vs* SAPT, outcome: Three-point major adverse cardiac event; D: DAPT *vs* SAPT, outcome: Net adverse clinical events. CI: Confidence interval.

The reduction in NACEs, integrating both bleeding and ischemic 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[8]. Data from the PEGASUS-TIMI 54[7] and THEMIS[9] programs highlighted both the anti-ischemic 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 ischemic events [10].

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 ischemic 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 ischemic 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 ischemic protection, resulting in a favorable 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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