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GLOBAL CARDIOLOGY
Global Cardiology 2026; **4**: 35-44
DOI: 10.4081/cardio.2026.99

REVIEW

Ischemic and bleeding outcomes by diabetes status in patients receiving ticagrelor monotherapy after percutaneous coronary intervention: an updated meta-analysis

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Abstract

Ticagrelor monotherapy after percutaneous coronary intervention (PCI) has been proposed to reduce bleeding risk while maintaining ischemic protection. The objective of this paper is to describe differences in ischemic and bleeding outcomes between patients with and without diabetes mellitus who were treated with ticagrelor monotherapy following PCI. A systematic review and meta-analysis were conducted using MEDLINE, Scopus, and Cochrane databases through 15th July 2025. Eligible studies included post hoc analyses of randomized trials comparing ticagrelor monotherapy outcomes between diabetic and non-diabetic patients. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model. Four trials were included with a total population of 18,596. Diabetic patients had significantly higher risk of major adverse cardiovascular events (RR 1.84, 95% CI 1.44-2.36; p<0.00001; I^2=37%), all-cause mortality (RR 2.46, 95% CI 1.95-3.10; p<0.00001; I^2=0%), cardiac death (RR 3.03, 95% CI 1.23-7.48; p=0.02; I^2=23%), stroke (RR 1.71, 95% CI 1.09-2.67; p=0.02; I^2=0%), clinically relevant bleeding (RR 1.35, 95% CI 1.15-1.58; p=0.0002; I^2=0%) and major bleeding (RR 1.81, 95% CI 1.40-2.34; p<0.00001; I^2=1%). Myocardial infarction and stent thrombosis did not differ significantly between groups. We can conclude that among patients treated with ticagrelor monotherapy after PCI, those with diabetes experienced higher ischemic and bleeding event rates than non-diabetic patients. These findings reflect diabetes-associated risk differences within a uniform antiplatelet regimen and should be interpreted as hypothesis-generating.

Key words: ticagrelor, diabetics, percutaneous coronary intervention, meta-analysis.

Received: 19 October 2025; Accepted: 10 March 2026.
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Introduction

Percutaneous coronary intervention (PCI) followed by dual antiplatelet therapy (DAPT) remains the cornerstone for preventing ischemic events such as stent thrombosis and myocardial infarction in patients with coronary artery disease.[1] However, prolonged use of DAPT is associated with an increased risk of bleeding complications, which can offset the benefits of ischemic protection.[2] Recent trials, including the TICO study, have explored shorter durations of DAPT followed by monotherapy with potent antiplatelet agents like ticagrelor, a potent P2Y12 receptor inhibitor, demonstrating potential to reduce bleeding risks without compromising ischemic safety.[3] Diabetes mellitus is a well-recognized risk factor for adverse cardiovascular events, associated with heightened platelet reactivity and a predisposition to thrombotic complications.[4] Conversely, diabetic patients often face a greater risk of bleeding, especially when subjected to prolonged antiplatelet regimens.[5]

Post hoc analyses of large, randomized trials have begun to shed light on the differential effects of ticagrelor monotherapy in diabetic *versus* non-diabetic populations, with some evidence suggesting that diabetic patients may derive comparable ischemic protection with reduced bleeding risk when transitioning to monotherapy after the initial period of DAPT.[6-8] However, these findings are exploratory and require cautious interpretation. Understanding these distinctions is critical for optimizing antiplatelet therapy tailored to diabetic status, balancing the risks of thrombotic and hemorrhagic events.

This meta-analysis aims to synthesize existing post hoc data from pertinent randomized trials to evaluate the outcomes of ticagrelor monotherapy in diabetic and non-diabetic patients post-PCI, thereby advancing personalized treatment strategies in this high-risk population.

Methods

Registration

We performed this systematic review and meta-analysis by following the guidelines set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[9] Since there was no patient data collected, we did not have to obtain approval from the Institutional Review Board.

Data sources and search strategy

Two reviewers (Muhammad Ahmed and Faiqa Iqbal) independently conducted a comprehensive literature search across multiple electronic databases, including PubMed/MEDLINE, Scopus, Embase, and the Cochrane Central Register of Controlled Trials, from database inception through 15th July 2025. The search strategy combined controlled vocabulary terms (*e.g.*, MeSH and Emtree) with free-text keywords related to diabetes mellitus, ticagrelor, P2Y12 inhibitors, antiplatelet therapy, monotherapy and de-escalation strategies, and percutaneous coronary intervention. No restrictions were applied based on publication status. The complete electronic search strategies for each database, including Boolean operators and applied limits, are provided in the Supplementary Materials (Supplementary Table S1).

Study selection and eligibility criteria

All search results were imported into EndNote X9 Reference Manager (Clarivate Analytics, Philadelphia, Pennsylvania) for duplicate removal. Following exclusion of duplicates, two reviewers (M.A. and F.I.) independently screened titles and abstracts to identify potentially eligible studies. Full-text articles were then retrieved for all records deemed relevant and independently assessed for eligibility based on predefined inclusion and exclusion criteria, including the presence of diabetic and non-diabetic subgroups, outcomes of interest, and methodological quality. Any disagreements at either screening stage were resolved by consensus, with arbitration by a third reviewer (Muhammad Talha Safdar) when necessary. Reasons for exclusion at the full-text review stage were documented and are summarized in the PRISMA flow diagram, which was carefully reviewed and corrected to ensure consistency and transparency of study counts at each stage of the selection process.

Studies were included in this meta-analysis if they met the criteria: i) studies with patients aged 18 years or above, ii) studies comparing ticagrelor monotherapy in diabetics *versus* non-diabetics, iii) studies that reported at least one of the following outcomes: major adverse cardiovascular events (MACE), all-cause mortality, cardiac mortality, myocardial infarction (MI), stroke, stent thrombosis, clinically relevant bleeding and major bleeding. Since MACE was reported differently for each study, we have summarized the components of MACE in each study in Supplementary Table S2. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type 3 or 5, whereas clinically relevant bleeding included BARC type 2, 3, or 5 events.

Studies were excluded from the meta-analysis if they met any of the following criteria: i) studies that did not involve ticagrelor monotherapy, including those using DAPT regimen or any antiplatelet agent other than ticagrelor; ii) studies that did not perform analysis between diabetic and non-diabetic patients; iii) studies that included patients younger than 18 years of age; iv) studies that did not report any of the predefined outcomes of interest, v) non-original research such as review articles, editorials, letters, commentaries, case reports, and conference abstracts without full-text data, and vi) non-human or preclinical studies.

Data extraction

Data were extracted independently by two reviewers using a pre-designed standardized extraction sheet. Any disagreement was resolved through discussion with a third reviewer (Muhammad Talha Safdar). Since this meta-analysis was of post-hoc studies, we could not extract the patient characteristic data and additional medications that patients had been using.[6-8,10] The sample sizes presented in the forest plots correspond to the number of diabetic and non-diabetic patients included in each outcome-specific subgroup analysis, as reported in the original trial publications or supplementary appendices. These denominators do not necessarily reflect the total randomized population of each trial, as subgroup sizes and reported outcomes varied across studies and endpoints due to post hoc analyses, differential follow-up, and outcome-specific reporting.

Outcomes of interest were extracted separately for diabetic and non-diabetic subgroups. The primary outcome was MACE, defined according to the composite endpoint reported in each individual trial. Prespecified secondary outcomes included all-cause mortality, cardiac mortality, myocardial infarction, definite or probable stent thrombosis, ischemic stroke, and bleeding events.

Definitions of MACE varied across the included studies. In the

GLOBAL LEADERS trial, MACE was defined as a composite of all-cause death, any stroke, or non-fatal new Q-wave myocardial infarction. The TICO trial defined MACE as cardiovascular death, myocardial infarction, or stroke, a definition also used in the TWILIGHT trial, which specified ischemic stroke. The ULTIMATE-DAPT trial employed a broader composite definition, including cardiac death, myocardial infarction, ischemic stroke, definite stent thrombosis, and clinically driven target vessel revascularization. Despite these differences, all MACE definitions incorporated core ischemic components, including death, myocardial infarction, and stroke, supporting the rationale for pooled analysis using trial-specific definitions.

Bleeding outcomes were consistently defined across all trials using the Bleeding Academic Research Consortium (BARC) criteria. Major bleeding was defined as BARC type 3 or 5, while clinically relevant bleeding included BARC type 2, 3, or 5 events. Bleeding endpoints were analyzed as reported in the original studies, without double counting overlapping components. Detailed outcome definitions for each trial are provided in Supplementary Table S2.

Quality assessment

The Cochrane Risk of Bias 2 (ROB 2) tool was utilized to assess the risk of bias across five domains: the randomization process, variations from intended interventions, missing outcome data, outcome assessment, and selection of the reported result.[11] Each study was identified as displaying a low risk of bias, moderate risk of bias, or a high risk of bias. Two reviewers performed assessments independently, and the disparities were resolved through the agreement of a third reviewer. Although the included studies were randomized controlled trials, the present meta-analysis evaluates post hoc subgroup comparisons between patients with and without diabetes. As diabetes status was not a randomized exposure, these comparisons represent non-randomized contrasts embedded within randomized trials and should be interpreted as observational in nature. Therefore, potential confounding due to baseline clinical and procedural differences cannot be fully excluded.

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.4.1 (Cochrane Collaboration, UK). Dichotomous outcomes were summarized using risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Pooled estimates for both primary and secondary outcomes were calculated using a random-effects model, and results are presented as forest plots. Statistical heterogeneity was assessed using the I^2 statistic, with values <50% considered low, 50-75% moderate, and >75% indicative of high heterogeneity.[12] A p-value of less than 0.05 was considered statistically significant throughout the analysis. Given the absence of patient-level data, multivariable adjustment for baseline differences between diabetic and non-diabetic patients, including age, comorbidities, lesion complexity, and diabetes-related characteristics, was not possible. Considering variability in MACE definitions across trials, outcomes were extracted and pooled according to the trial-specific composite definitions reported in the original publications. The use of a random-effects model was intended to account for between-study heterogeneity arising from differences in endpoint composition, follow-up duration, and study design, while preserving internal validity within individual trials and allowing synthesis across studies sharing common core ischemic components. Although sensitivity analyses excluding broader composite endpoints were considered, the limited number of eligible trials precluded robust exclusion-based analyses; these further supports interpreting the results as hypothesis-generating. Formal assessment of small-study effects and publication bias using funnel plots or Egger's regression was considered but not performed, as these methods are underpowered and potentially misleading when fewer than 10 studies are included.

Pre-specified subgroup analyses based on duration of dual antiplatelet therapy (1 month *vs*. 3 months) were conducted using RStudio (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria) with the *meta* package. These analyses employed the same random-effects modeling approach to ensure methodological consistency with the primary analyses.

Results

Study selection and characteristics

Four randomized controlled trials were included, comprising a total of 18,596 patients, of whom 3598 were diabetics and 14,998 were non-diabetics. The studies included were GLOBAL LEADERS, TICO, TWILIGHT, and ULTIMATE-DAPT.[3,6,7,13] In the GLOBAL LEADERS trial, 3189 patients had diabetes and 10,513 were non-diabetic. In TWILIGHT, 1319 patients had diabetes and 2236 were non-diabetic. In TICO, 418 patients had diabetes and 1109 were non-diabetic. In ULTIMATE-DAPT, 540 patients had diabetes and 1160 were non-diabetic. Selection of articles has been summarized in the PRISMA chart in Supplementary Figure S1. Across these trials, patients with and without diabetes underwent ticagrelor monotherapy following an initial period of DAPT. The duration of the initial DAPT before switching to monotherapy varied: 1 month in GLOBAL LEADERS and ULTIMATE-DAPT, and 3 months in TICO and TWILIGHT. The follow-up periods ranged from 12 to 24 months. In all included trials, ticagrelor monotherapy was administered at a dose of 90 mg twice daily.

Primary outcome

Major adverse cardiovascular events

For the outcome of MACE, we included four studies, and the pooled effect was significantly higher in diabetics compared to non-diabetics with low heterogeneity (RR: 1.84, 95% CI: 1.44, 2.36; p<0.00001; I^2=37%) (Figure 1).

Secondary outcomes

All the results of the secondary outcomes are summarized in Table 1, and their corresponding forest plots are attached.

All-cause mortality

Three studies were included in the pooled analysis for all-cause mortality. The combined effect showed a significantly higher risk among diabetic patients (RR 2.46, 95% CI: 1.95-3.10; p<0.00001), with no heterogeneity (I^2=0%) (Figure 2).

Cardiac death

Two studies reported on cardiac death. The pooled estimate demonstrated a significantly elevated risk in diabetics (RR 3.03, 95% CI: 1.23-7.48; p=0.02), with low heterogeneity (I^2=23%) (Figure 3).

Myocardial infarction

Three studies contributed data for myocardial infarction. While diabetics had a higher risk, the association was not statistically significant (RR 1.52, 95% CI: 0.95-2.41; p=0.08). Heterogeneity was moderate (I^2=58%) (Figure 4).

Stroke

Three studies were included for stroke outcomes. The pooled analysis indicated a significantly increased risk in diabetics (RR 1.71, 95% CI: 1.09-2.67; p=0.02), with no heterogeneity (I^2=0%). (Figure 5).

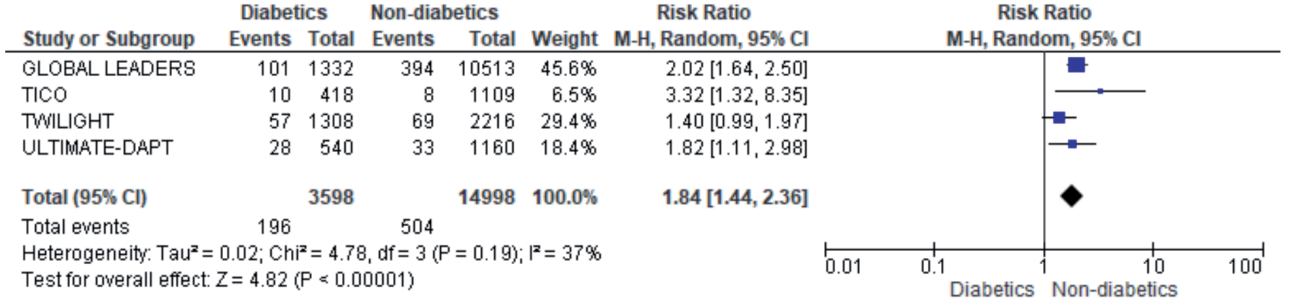

Figure 1. Forest plot of major adverse cardiovascular events.

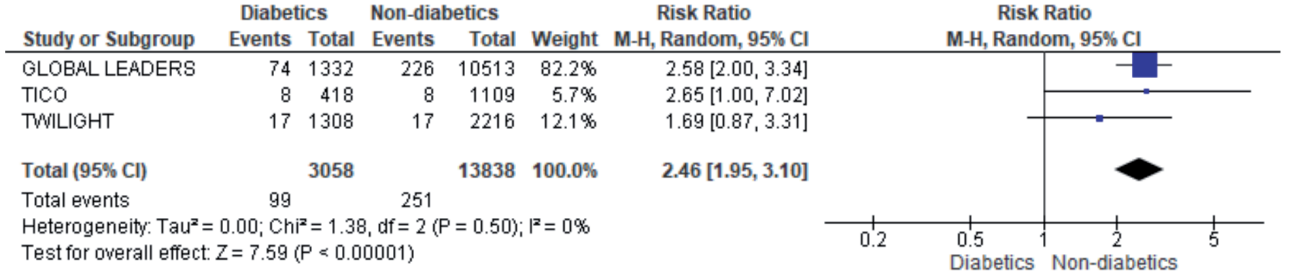

Figure 2. Forest plot of all-cause mortality.

Table 1. Secondary outcomes.

Outcome	Risk ratio (95%CI)	Heterogeneity, %	p	Figure
All-cause mortality	2.46 (1.95, 3.10)	0	<0.00001	2
Cardiac death	3.03 (1.23, 7.48)	23	0.02	3
Myocardial infarction	1.52 (0.95, 2.41)	58	0.08	4
Stroke	1.71 (1.09, 2.67)	0	0.02	5
Clinically relevant bleeding	1.35 (1.15, 1.58)	0	0.0002	6
Major bleeding	1.81 (1.40, 2.34)	1	<0.00001	7
Stent thrombosis	1.50 (0.81, 2.78)	22	0.20	8

Clinically relevant bleeding

Three studies reported on clinically relevant bleeding. Diabetic patients had a significantly higher risk (RR 1.35, 95% CI: 1.15-1.58; p=0.0002), with no heterogeneity (I^2=0%) (Figure 6).

Major bleeding

Three studies were included in the analysis of major bleeding. The pooled effect showed a significantly increased risk among diabetics (RR 1.81, 95% CI: 1.40-2.34; p<0.00001), with minimal heterogeneity (I^2=1%). (Figure 7).

Stent thrombosis

Three studies provided data on stent thrombosis. The pooled results showed no statistically significant difference between diabetics and non-diabetics (RR 1.50, 95% CI: 0.81-2.78; p=0.20), with low heterogeneity (I^2=22%) (Figure 8).

Quality assessment

The risk of bias for each included randomized controlled trial was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool.[11] Among the four studies, ULTIMATE-DAPT (2024) was judged to have a low risk of bias across all domains. GLOBAL LEADERS (2020), TWILIGHT-DM (2020), and TICO (2021) were considered to have some concerns, primarily due to post hoc or subgroup analyses of diabetic patients that were not part of the original trial design. All studies demonstrated low risk in randomization, adherence, outcome measurement, and data completeness. Findings are summarized below in Supplementary Table S3 and Supplementary Figures S2 and S3.

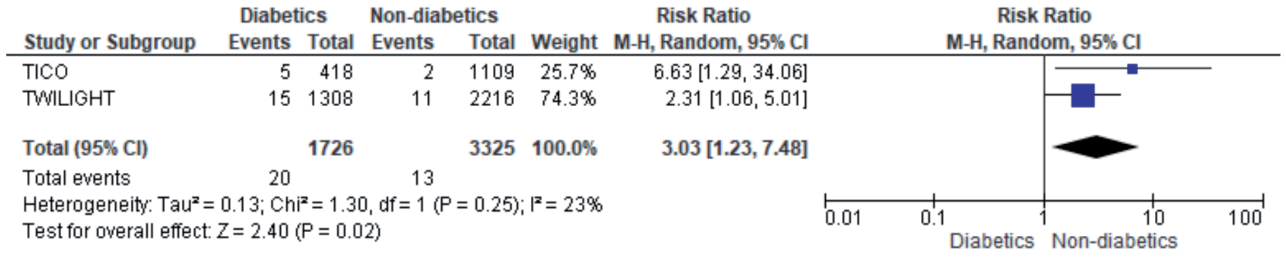

Figure 3. Forest plot of cardiac death.

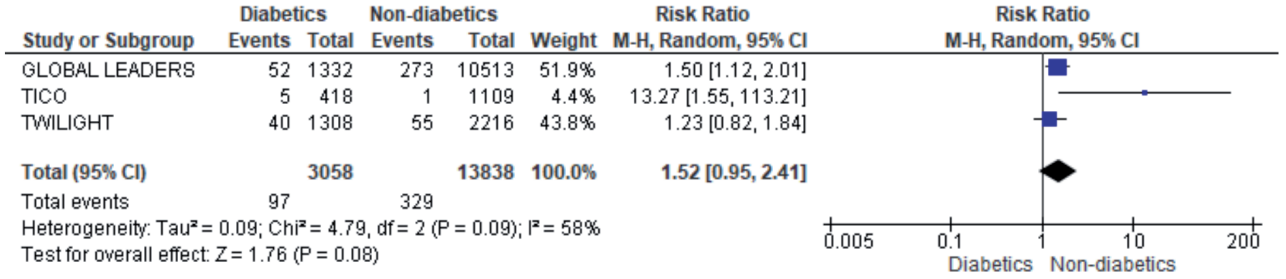

Figure 4. Forest plot of myocardial infarction.

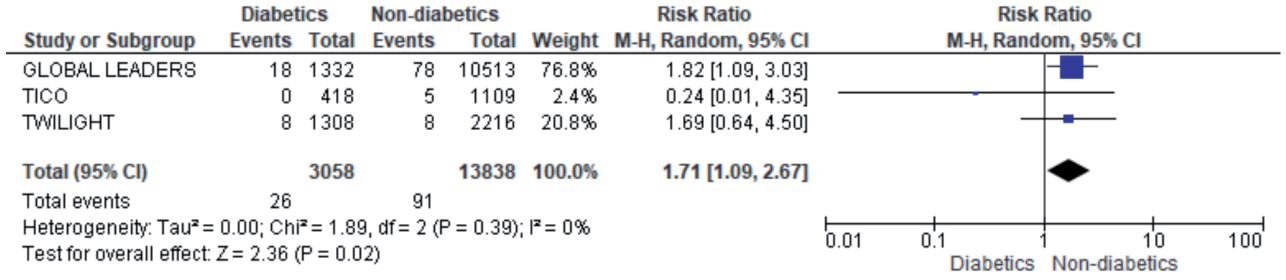

Figure 5. Forest plot of stroke.

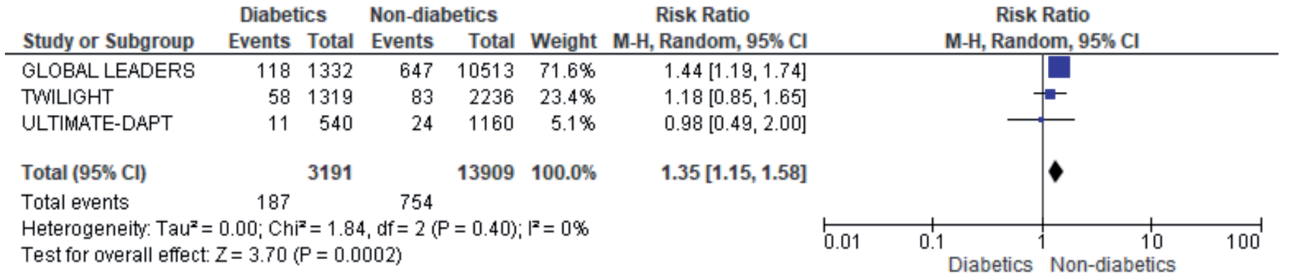

Figure 6. Forest plot of clinically relevant bleeding.

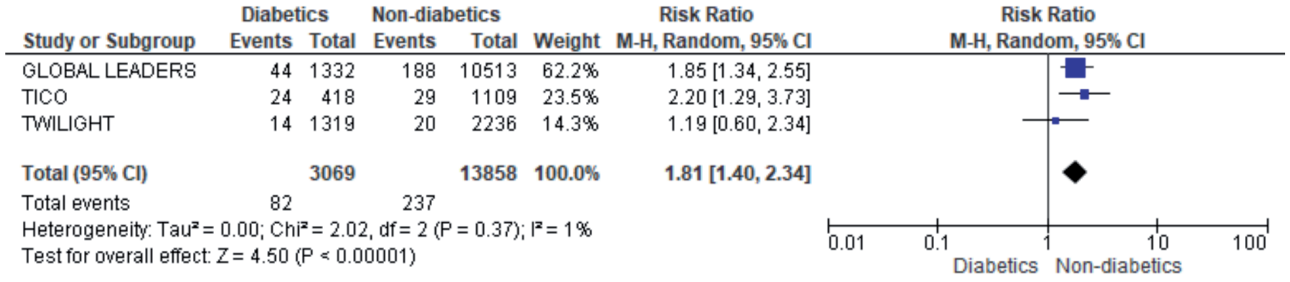

Figure 7. Forest plot of major bleeding.

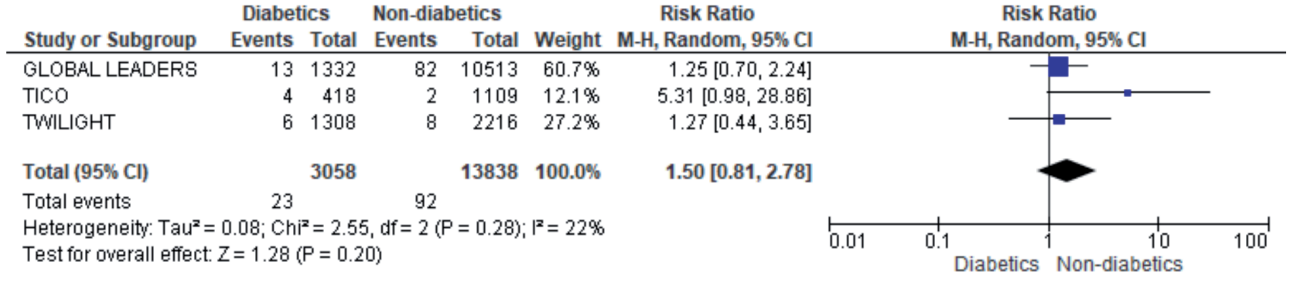

Figure 8. Forest plot of stent thrombosis.

Subgroup analysis

Subgroup analysis based on DAPT duration (1 month *vs* 3 months) was performed for MACE to evaluate whether shorter or longer DAPT regimens influenced the pooled effect estimates between diabetic and non-diabetic patients. In studies employing a 1-month DAPT regimen, the pooled RR for MACE was 1.99 [95% CI: 1.64-2.42; I^2=0%], demonstrating consistent findings across trials and indicating a higher incidence of MACE among diabetic patients compared with non-diabetics. Conversely, in studies with a 3-month DAPT regimen, the pooled RR was 1.93 [95% CI: 0.85-4.37; I^2=66.1%], reflecting moderate variability between studies. Overall, these results suggest that while shorter DAPT duration was associated with a higher event rate in diabetics, extending DAPT to 3 months did not significantly alter the relative risk of MACE between diabetic and non-diabetic patients receiving ticagrelor monotherapy (Supplementary Figure S4).

Discussion

Our findings reveal a consistently unfavorable risk profile for diabetic patients across both ischemic and bleeding endpoints. Diabetics on ticagrelor monotherapy had a significantly higher risk of MACE, all-cause mortality, cardiac death, stroke, clinically relevant bleeding, and major bleeding compared to non-diabetics. Although diabetic patients demonstrated a higher relative risk of myocardial infarction, the pooled estimate did not reach statistical significance. Stent thrombosis rates, however, did not differ significantly. Notably, heterogeneity was low to moderate across most outcomes, reinforcing the robustness of the pooled

estimates. This may illustrate the persistent pro-thrombotic state in diabetes that is not sufficiently mitigated by ticagrelor as a monotherapy, even after an initial DAPT course. In addition, the increased susceptibility to bleeding risk suggests that the overall clinical benefit of ticagrelor monotherapy in diabetic patients may differ from that observed in the general population. Our analysis demonstrated a significantly elevated risk of MACE in diabetic patients compared to non-diabetics. The findings highlight that the increased ischemic risk in diabetics persists even after the transition to monotherapy, suggesting no major improvement post the short DAPT course. The findings align with the pathophysiological links to multiple intersecting mechanisms driving the adverse cardiovascular events despite the potent P2Y12 inhibition.[5] Interestingly, while ticagrelor has demonstrated efficacy in reducing MACE in the general PCI population, our subgroup-specific analysis challenges the generalizability of such benefits to diabetic patients.[18] With the inclusion of 1700 patients, the recent ULTIMATE-DAPT trial, coupled with refined stratification methods, enhances the accuracy and robustness of estimating diabetes-specific ischemic risk.[7] Similarly, the TWILIGHT-DM sub-study reported no statistically significant difference in ischemic events between ticagrelor monotherapy and continued DAPT among diabetics; however, the absolute event rates remained somewhat elevated, reinforcing the inclination of ischemic risk in this subgroup.[6] While TICO included a diabetic cohort as a subgroup, the overall ischemic benefit observed with ticagrelor monotherapy was primarily driven by the general population, since no statistical interaction was specifically recorded for diabetes status.[3] These findings suggest that the pro-thrombotic milieu in diabetes, driven by elevated PAI-1 levels, increased thrombin generation, and the coagulation cascade, may diminish the ischemic protection offered by ticagrelor monotherapy.[5]

The adverse cardiovascular prognosis associated with diabetes following PCI is well established across antiplatelet regimens, and the findings of this study should be interpreted within this broader context. The primary contribution of the present meta-analysis is therefore not to re-establish this association, but to provide an updated synthesis of ischemic and bleeding outcomes stratified by diabetes status specifically among patients receiving ticagrelor monotherapy, incorporating recently published randomized trial data and standardized bleeding definitions. Importantly, this analysis does not compare alternative antiplatelet strategies by diabetes status, nor does it evaluate the efficacy or safety of ticagrelor monotherapy relative to other regimens in diabetic patients. Rather, it describes outcome differences between diabetic and non-diabetic patients treated with the same ticagrelor monotherapy strategy. Accordingly, the observed differences are best interpreted as reflecting baseline risk heterogeneity and the established adverse cardiovascular and bleeding risk associated with diabetes, rather than a causal treatment effect attributable to ticagrelor monotherapy. In diabetic patients, the optimal antiplatelet regimen following PCI remains a persistent challenge for clinicians due to the interplay between thrombotic and bleeding events in the respective cohorts.[14,15] Disrupted mechanisms such as endothelial dysfunctionality, inflammatory signaling pathways, and platelet-associated hyperreactivity and dysregulation add to the burden of ischemic complications in diabetic populations, especially after PCI.[5] Among the patients undergoing PCI, ticagrelor monotherapy following a short course of DAPT has emerged as a potential strategy to reduce bleeding while maintaining ischemic protection.[16] However, the dilemma pertaining to the safety profile of the therapy remains under evaluation in the biologically distinct subgroup of diabetic patients. A prior meta-analysis, which synthesized data from three trials comparing ticagrelor monotherapy in diabetics *versus* non-diabetics, predated the most recent randomized evidence and included only a limited number of safety endpoints.[17] Since the publication of earlier meta-analyses and systematic reviews, the ULTIMATE-DAPT trial (2024) has provided an additional dataset that allows further evaluation of outcome differences by diabetes status while enabling more refined endpoint definitions.[7] In particular, the inclusion of ULTIMATE-DAPT permits stratification of bleeding outcomes into both major and clinically relevant categories using standardized BARC criteria. Accordingly, the present study adds incremental evidence by incorporating this recent trial and by offering a more granular assessment of bleeding risk among diabetic and non-diabetic patients undergoing early aspirin withdrawal and ticagrelor monotherapy, an aspect that was not consistently addressed in earlier syntheses.

Our subgroup analysis revealed a higher incidence of MACE among diabetic patients treated with ticagrelor monotherapy after a 1-month DAPT regimen, whereas extending DAPT to 3 months attenuated this risk without achieving statistical significance. These results suggest that very short DAPT may be insufficient to counter the heightened thrombotic tendency observed in diabetics, who exhibit enhanced platelet reactivity and endothelial dysfunction. Prior meta-analyses have similarly reported that abbreviated DAPT (<3 months) increases ischemic risk in diabetic patients, while 3-month regimens may offer a more balanced ischemic-bleeding profile.[19,20]

Diabetic patients on ticagrelor monotherapy also experienced a significantly higher risk of all-cause and cardiovascular mortality compared to the non-diabetic group. This disparity may stem from a combination of thrombotic risk and the chronic cardiometabolic burden in diabetes, including autonomic dysfunction, diabetic cardiomyopathy, and impaired microvascular repair mechanisms including complications such as cardiovascular autonomic neuropathy (CAN).[21] Notably, the TWILIGHT-DM sub-study reported a higher incidence of cardiac deaths in people with diabetes, without significant statistical difference, indicating continued risk despite the optimized antiplatelet therapy.[6] The subgroup analysis of the GLOBAL LEADERS trial revealed comparable results of increased all-cause mortality in the diabetic population.[13] These findings raise concern that the survival benefit of ticagrelor monotherapy in clinical settings may decline in diabetic patients due to the complex interplay of ischemic and metabolic dysfunction. While ticagrelor tends to offer potent platelet inhibition, its efficacy is not sufficient as a monotherapy to counteract the diffuse atherosclerotic lesions, plaque ruptures, and ultimately

vascular calcification along with cardiac autonomic dysregulation observed in diabetic individuals.[22]

Despite the antithrombotic profile of Ticagrelor, diabetic patients remained at significantly elevated risk for stent thrombosis, myocardial infarction, and stroke compared to non-diabetics in our study. This persistent vulnerability aligns with the TWILIGHT-DM and GLOBAL LEADERS sub-study, which reported quantitatively higher event rates of MI, stroke, and stent thrombosis in diabetics, though not statistically significant.[6,13] Similarly, subgroups in TICO illustrated numerical advantage in MI and stent thrombosis; it did not reveal an evident ischemic benefit in the diabetic patient, underscoring the limited effectiveness monotherapy has to offer.[3] The pro-atherogenic environment in diabetes, characterized by sustained hyperglycemia, oxidative stress, and chronic inflammation, contributes to the progressive plaque progression and instability, ultimately leading to thrombotic complications.[23] The accumulation of advanced glycation end-products (AGEs) further destabilizes plaques and impairs nitric oxide bioavailability, amplifying vascular risk.[24] Moreover, impaired endothelial repair and persistently increased platelet reactivity in patients with diabetes may contribute to delayed or incomplete vascular healing after PCI, thereby increasing susceptibility to thrombotic complications, including stent thrombosis, despite potent P2Y12 receptor inhibition.[25] In addition to heightened platelet turnover, this subgroup exhibits increased expression of GP IIb/IIIa receptors, potentially triggering platelet insensitivity and hence diminished responsiveness to ticagrelor.[26] The higher rates of ischemic and bleeding events observed in diabetic patients receiving ticagrelor monotherapy should be interpreted in the context of diabetes as a complex, high-risk clinical condition rather than as evidence of reduced safety of ticagrelor itself. Given the absence of a comparator antiplatelet strategy in the present analysis, it is not possible to disentangle the contribution of underlying diabetic pathophysiology from treatment-related effects. The prothrombotic, proinflammatory, and endothelial dysfunction characteristic of diabetes likely play a central role in the persistence of adverse events despite potent P2Y12 inhibition.

Diabetic patients were found to be particularly vulnerable to bleeding complications even with ticagrelor monotherapy, as demonstrated across multiple trials included in our analysis. The GLOBAL LEADERS, TWILIGHT, and ULTIMATE trials consistently observed higher rates of clinically relevant bleeding in diabetic subgroups, while major bleeding was more frequent in diabetics in GLOBAL LEADERS, TWILIGHT, and TICO as compared to the non-diabetics.[3,6,7,13] While ticagrelor monotherapy was administered to spare the bleeding risks by replacing it with the DAPT course, the benefit does not appear pronounced in the diabetic population. The observation aligns with the previous meta-analysis, indicating differential vascular responses to the ticagrelor monotherapy across the patient groups.[17] Besides platelet hyperreactivity, diabetes is known to induce widespread hemostatic imbalance, characterized by alterations in coagulation and fibrinolytic pathways. Diabetic state disrupts the levels of fibrinogen, PAI-1, and thrombin-antithrombin complexes, elevating prothrombotic tendencies coupled with hypo-fibrinolysis, producing thrombi instability and hence adding to the bleeding risk.[27]

Limitations

This meta-analysis has several important limitations. Only four randomized trials were available, with the GLOBAL LEADERS trial contributing approximately half of the pooled population and therefore exerting substantial statistical weight, as expected in inverse-variance weighted random-effects models. Although the direction of effect in GLOBAL LEADERS was consistent with other trials and heterogeneity across most outcomes was low to moderate, the limited number of studies and unequal sample sizes restrict generalizability and render the findings hypothesis-generating rather than definitive. In addition, the included analyses were largely based on post hoc subgroups not specifically designed to compare outcomes between diabetic and non-diabetic patients, limiting statistical robustness.

Methodological heterogeneity across trials, including differences in patient selection, follow-up duration, clinical settings, DAPT duration (1-3 months), and MACE definitions, may have influenced pooled estimates. Shorter DAPT may provide insufficient ischemic protection, particularly in diabetic patients, whereas longer durations may increase bleeding risk, underscoring the need for standardized endpoints and harmonized protocols in future studies. Key clinical variables such as diabetes type, disease duration, glycemic control, and antidiabetic therapies were not uniformly reported, precluding adjustment for important confounders. Finally, the small number of studies for certain outcomes limits assessment of publication bias, and although several associations were statistically significant, effect sizes were modest (all pooled relative risks <3). These findings should therefore be interpreted as descriptive and hypothesis-generating rather than indicative of clinically decisive effects, particularly as absolute risk differences were not assessed.

Strengths and clinical implications

This meta-analysis provides the most up-to-date synthesis of ischemic and bleeding outcomes in diabetic and non-diabetic patients treated with ticagrelor monotherapy after PCI. All included trials used standardized bleeding definitions (BARC), and subgroup data were obtained directly from trial reports or supplements, minimizing selective reporting bias. Although diabetic sample sizes were limited in some studies, the analysis identifies clinically relevant outcome heterogeneity by diabetes status.

Clinically, these findings should be interpreted as descriptive rather than prescriptive. The higher ischemic and bleeding risks observed in diabetic patients likely reflect the complex, high-risk pathophysiology of diabetes rather than reduced efficacy of ticagrelor. As no alternative antiplatelet strategies were compared, treatment selection cannot be inferred; instead, the results highlight diabetes as a key modifier of residual risk within a uniform antiplatelet regimen and emphasize the need for individualized risk assessment and future randomized trials

to define the optimal antiplatelet strategy in diabetic patients after PCI.

Conclusions

In conclusion, this meta-analysis demonstrates that diabetic patients receiving ticagrelor monotherapy after PCI experience modestly higher rates of ischemic and bleeding events compared with non-diabetic patients. Given the meta-analytic design, reliance on post hoc subgroup analyses, and the absence of a randomized comparator, these findings should be interpreted as descriptive and hypothesis-generating rather than as a basis for clinical recommendations. Overall, the results underscore diabetes as an important modifier of residual risk within antiplatelet therapy strategies and highlight the need for future randomized trials specifically designed to compare antiplatelet approaches in diabetic patients following PCI.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Online supplementary material:
Supplementary Table S1. Search string used in each database.
Supplementary Table S2. Definition of MACE used in each included study,
Supplementary Table S3. Summary of risk of bias assessment for included randomized controlled trials.
Supplementary Figure S1. PRISMA flowchart.
Supplementary Figure S2. Risk of bias graph summarizing the proportion of studies rated as low risk, some concerns, or high risk across domains.
Supplementary Figure S3. Risk of bias summary for individual studies.
Supplementary Figure S4. Subgroup analysis of major adverse cardiovascular events (MACE) based on DAPT duration (1-month vs. *3-month).*