Response to Reviewers

Reviewer 01:

1. Protocol registration (PROSPERO / similar platforms) The manuscript states that a protocol was drafted a priori, but no registration number or public link is provided. Please clarify whether the protocol was registered prospectively (e.g., in PROSPERO). If prospective registration was not performed, I strongly recommend retrospective registration and inclusion of the protocol link in the manuscript.

The review has been registered with PROSPERO (ID: PROSPERO 2026 CRD420261299344).

2. This would substantially strengthen the methodological credibility of the review. Databases searched (MEDLINE and PubMed) The Methods section reports MEDLINE and PubMed as separate databases. Since PubMed is the primary interface for MEDLINE, this distinction is unclear. Please clarify: Whether MEDLINE was searched via another platform (e.g., Ovid, EBSCO), and How this differed from the PubMed search. Clear specification of search platforms is essential for reproducibility. Search strategy availability The manuscript states that the full search strategy is available “on request.” Current best practices strongly encourage making complete search strategies publicly available, preferably: As supplementary material, or Within the main manuscript if supplementary files are not permitted by the journal. This change would substantially improve transparency and alignment with PRISMA standards. Study screening and selection process The screening process lacks information on the software or platform used (e.g., Rayyan, Covidence, EndNote, Excel, manual screening). Please explicitly state: Which software or tool was used, and Whether screening was conducted independently and in duplicate within that platform. PRISMA flow diagram – internal inconsistencies Several issues in the flow diagram require clarification: It would be helpful to report the number of records identified per database, rather than only aggregate totals, to enhance reproducibility. Although the Methods state that no language restrictions were applied, four studies were excluded for being in “other languages.” This appears contradictory. Please clarify: Which languages were excluded, and Whether a language restriction was effectively applied during full-text screening. There is

confusion regarding the number of full-text articles assessed and excluded (n = 64). If all 64 were excluded, it is unclear how four studies remained included. The numerical flow should be carefully revised for internal consistency.

The search was dine via MEDLINE via Pubmed Interface. The search strategy is added in the supplementary files. The screening tool used has been added in the manuscript and highlighted in yellow as The screening was done via citation manager i.e. Zotero. No language restrictions were applied. The discrepancies have been sorted out and highlighted in yellow as pointed out by the reviewer. A comprehensive table is added as suggested by the reviewer and has been highlighted in yellow.

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	7,119	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	3,056	3 months	12 months	Composite of major bleeding and major adverse cardiac and cerebrovascular events	Major bleeding (TIMI major), ischemic outcomes, contributed to NACE

		(East Asian cohort)					
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

3. Discussion – breadth of referenced literature While the Discussion is well written, it relies almost exclusively on the included trials. A discussion section can (and often should) incorporate relevant external literature that was not eligible for inclusion (e.g., observational studies, mechanistic studies, broader antiplatelet therapy literature) to better contextualize findings. I recommend reassessing whether additional references could strengthen interpretation and external validity. Table summarizing characteristics of included studies I could not identify a table providing a structured synthesis of the included trials (e.g., study design, population, sample size, clinical setting, DAPT duration, follow-up, primary outcomes). Such a table is essential for transparency and allows readers to quickly understand key similarities and differences among the included studies. I strongly

recommend including a comprehensive “Characteristics of included studies” table.

Discussion section to explicitly acknowledge the potential impact of clinical heterogeneity across included trials. Although statistical heterogeneity was low for most pooled outcomes, important clinical differences existed, including variation in DAPT run-in duration (ranging from <1 month to 3 months) and population characteristics, particularly the predominance of East Asian cohorts in TICO and partial Asian representation in T-PASS and ULTIMATE-DAPT.

4. Risk of bias assessment – tables and figures Although the Methods section states that the Cochrane Risk of Bias 2 (RoB 2) tool was used, I could not find: A table summarizing the risk of bias judgments for each domain and each included study; nor The standard RoB 2 visual outputs (e.g., traffic light plots and/or summary figures). For transparency and consistency with best practices, these materials should be presented either in the main manuscript or as supplementary files. Discussion of study quality and risk of bias The Discussion does not explicitly address the methodological quality of the included trials. Even when overall risk of bias is low or judged as “some concerns,” it is important to: Discuss how study design features (e.g., open-label vs double-blind designs) may have influenced outcomes; and Acknowledge how risk of bias assessments affect confidence in the pooled estimates.

The Risk of bias was planned and therefore mentioned in the manuscript protocol but the dataset couldn’t be retrieved. So, it has been sorted out in the manuscript as highlighted by the reviewer.

Thank you for such a detailed review of the manuscript.

Reviewer 02

1.The corresponding author is listed as “Abdul Mabood Basil” with an email and address in Afghanistan, while the author list includes “Abdul Basit” as the first author from Pakistan. Please clarify whether this is the same person or a different

individual, and ensure that author names and affiliations are consistent throughout the manuscript.

There are two different authors i.e. Abdul Basit and Abdul Mabood Basil as mentioned in the manuscript and highlighted in yellow.

2.For the T-PASS trial, the authors state that hazard ratios were “estimated from reported event counts.” The method used for this estimation should be explicitly described (e.g., using a Cox model approximation or other validated method). Without this, the validity of the pooled HR is uncertain. The description of which trials contributed to which outcomes is sometimes confusing (e.g., in the “Major bleeding” section, TICO and T-PASS are mentioned, but the footnote references ULTIMATE-DAPT). Please ensure consistency between text and footnotes.

In the T-PASS trial, hazard ratios were not directly reported for several outcomes. Therefore, we derived effect estimates using published cumulative event counts and total sample sizes in each treatment group. We thank the reviewer for this important observation. We have carefully revised the Results section and corresponding figure footnotes to ensure complete consistency between the text and referenced trials. Specifically, the “Major bleeding” subsection has been corrected and highlighted in yellow as depicted by the reviewer.

3.The authors state that sensitivity and subgroup analyses were not performed due to limited trial numbers, which is understandable. However, given the clinical diversity among trials (e.g., DAPT duration, population ethnicity), a brief discussion on the potential impact of these factors on the results would strengthen the discussion. The statement “I^2=0% in all outcomes except three-point MACE” appears inconsistent with the reported I^2=34% for major bleeding. Please verify and correct. 4.The discussion largely reiterates the results and does not sufficiently engage with potential mechanistic explanations for the findings (e.g., pharmacodynamic properties of ticagrelor, platelet reactivity profiles). The clinical implications section could be expanded to address practical scenarios (e.g., how to define “high bleeding risk,” management in patients on oral anticoagulation, cost considerations).

Discussion section to explicitly acknowledge the potential impact of clinical heterogeneity across included trials. Although statistical heterogeneity was low for most pooled outcomes, important clinical differences existed, including variation in DAPT run-in duration (ranging from <1 month to 3 months) and population characteristics, particularly the predominance of East Asian cohorts in TICO and partial Asian representation in T-PASS and ULTIMATE-DAPT. These factors may influence both bleeding risk profiles and pharmacodynamic response to antiplatelet therapy and could potentially affect the magnitude of treatment effect observed. We have now incorporated this consideration into the limitations. Regarding the heterogeneity statement, we have corrected the wording to improve clarity and consistency. The revised text now states that low statistical heterogeneity ($I^2 = 0\%$) was observed for clinically relevant bleeding and NACE, while moderate heterogeneity was present for major bleeding ($I^2 = 34\%$), and low statistical heterogeneity was observed for three-point MACE ($I^2 = 0\%$).

5.Several in-text citations are incorrectly formatted (e.g., “[3]” appears in the Methods section but references TWILIGHT, which is citation [1] in the reference list). Please ensure all citations match the numbered reference list accurately. Some references include hyperlinks, which are not appropriate for a formal manuscript. Replace with standard journal citations.

This correction aligns the narrative description with the reported meta-analytic results and forest plot outputs. Citations and references are corrected as suggested by the reviewer.