Reviewer Response Form

Manuscript Title: Fractional Flow Reserve Guided Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Multivessel Coronary Artery Disease: A Systematic Review and Meta-Analysis

Corresponding Author: Asraf Hussain, MD

Response Date: July 7, 2025

Dear Editor and Reviewers,

We sincerely thank you for your thorough review and constructive feedback on our manuscript. We have carefully addressed each comment to improve the quality and clarity of the manuscript. Below, we outline how we have responded to each point raised, including actions already taken and additional revisions made to address the concern regarding the low number of included studies. For clarity, reviewer comments are summarized, followed by our responses.

General Comments

Reviewer Comment: The topic is relevant, but substantial revisions are needed. The manuscript appears to be organized or edited using AI, and the use of AI must be disclosed, including its purpose.

Response: We appreciate the recognition of the topic's relevance. To address the concern about AI use, we have added a statement in the manuscript's Methods section (Section 2) under a new subsection titled "Use of Artificial Intelligence." This statement clarifies that AI-based tools were used solely for language editing and formatting to enhance readability and ensure consistency, with all scientific content developed and verified by the authors. The specific AI tool and its role are disclosed to maintain transparency.

Abstract

Reviewer Comment: Remove acronyms and abbreviations from the abstract. Include methods of data analysis, key search terms, data quality assessment, tools for data quality and bias assessment, methods and models for data analysis, and statistical software used.

Response: As indicated, we have removed all acronyms and abbreviations from the abstract to improve clarity. We have revised the abstract to include details on the methods of data analysis (pooled risk ratios with the Mantel-Haenszel method), key search terms (e.g., "Fractional Flow

Reserve," "Percutaneous Coronary Intervention," "Coronary Artery Bypass," "Coronary Stenosis"), data quality assessment (using the GRADE approach), tools for bias assessment (Cochrane Risk of Bias 2 for RCTs), and statistical software (Review Manager 5.4). These additions ensure the abstract comprehensively covers the study's methodology while remaining concise.

Introduction

Reviewer Comment: The introduction is well-written but should highlight the gap and need for this work.

Response: We have revised the Introduction (Section 1, final paragraph) to explicitly highlight the research gap, emphasizing the conflicting results from prior randomized controlled trials (RCTs) and observational studies, variability in patient populations, and the need for an updated synthesis incorporating contemporary FFR-guided PCI and CABG practices. The necessity of this meta-analysis to provide robust evidence for clinical decision-making in multivessel coronary artery disease is now clearly articulated.

Methods

Reviewer Comment (Eligibility Criteria): Categorize eligibility criteria into inclusion (2.1.1) and exclusion criteria (2.1.2), and provide inclusion criteria based on PICOS principles. Clarify if articles were excluded based on risk of bias.

Response: As stated, we have reorganized Section 2.1 into subsections 2.1.1 (Inclusion Criteria) and 2.1.2 (Exclusion Criteria) for clarity. The inclusion criteria are now explicitly aligned with the PICOS framework, detailing Population (adults with multivessel coronary artery disease), Intervention (FFR-guided PCI with drug-eluting stents), Comparison (CABG, on-pump or off-pump), Outcomes (all-cause mortality, MACE, myocardial infarction, repeat revascularization, stroke), and Study Design (RCTs and observational cohort studies). We have also clarified in Section 2.3 that articles were not excluded based on risk of bias; instead, bias assessments were used to evaluate evidence quality, as detailed in the Risk of Bias and GRADE sections.

Reviewer Comment (Information Sources and Search Strategies): Provide one full search strategy (e.g., PubMed) and include others as a supplementary file. Describe how the strategy was constructed, including AND/OR/NOT principles.

Response: As noted, we have included the full PubMed search strategy in Section 2.2, explicitly detailing the use of MeSH terms and free-text keywords combined with Boolean operators (AND, OR). The strategy is presented as: ("Fractional Flow Reserve, Myocardial"[Mesh] OR "Myocardial Fractional Flow Reserve") AND ("Percutaneous Coronary Intervention"[Mesh] OR synonyms) AND ("Coronary Artery Bypass"[Mesh] OR synonyms) AND ("Coronary Stenosis"[Mesh] OR synonyms). We clarify that the NOT operator was not used to avoid excluding relevant studies. Search strategies for Embase, ScienceDirect, and ClinicalTrials.gov are provided in a supplementary file (Supplementary File 1) to maintain transparency and reproducibility.

Reviewer Comment (Data Extraction): Add the form with findings as a supplementary file, if applicable.

Response: We have included the standardized Google Sheets data extraction form as a supplementary file (Supplementary File 2). This form outlines the extracted data fields (e.g., study characteristics, participant demographics, outcomes) and includes a sample of extracted data for transparency, as described in Section 2.4.

Reviewer Comment (Risk of Bias Assessment): Explain how bias was assessed for RCTs and observational cohort studies, noting that different study designs may require different tools. Provide criteria lists or include as a supplementary file.

Response: As indicated, we have expanded Section 2.5 to clearly explain the bias assessment process. For RCTs, we used the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five domains (randomization, intervention deviations, missing outcome data, outcome measurement, result selection). Although observational cohort studies were eligible, none were included; however, we clarify that the Newcastle-Ottawa Scale (NOS) would have been used for such studies, assessing selection, comparability, and outcome domains. The criteria for both tools are provided in a supplementary file (Supplementary File 3) to ensure transparency. We emphasize that different tools were selected to address the unique biases inherent in each study design.

Results

Reviewer Comment (Study Selection): Include the list of databases with the number of articles retrieved (e.g., PubMed, N=601) and the types of included study designs with their respective numbers. Place the figure citation after the paragraph. The number of included articles is low; reconsider other articles and databases for representativeness and strength of evidence.

Response: As stated, we have revised Section 3.1 to include the list of databases and the number of articles retrieved: PubMed (N=118), Embase (N=23), ScienceDirect (N=389), and ClinicalTrials.gov (N=2). We also specify that all included studies were RCTs (N=3), with no observational cohort studies meeting the inclusion criteria. The PRISMA flowchart citation (Figure 1) has been moved to the end of the paragraph for clarity.

Regarding the concern about the low number of included studies (N=3), we acknowledge the reviewer's point about representativeness and evidence strength. However, our comprehensive search strategy, which spanned multiple databases and grey literature, was designed to identify all relevant studies adhering to our strict PICOS criteria. These criteria prioritized RCTs comparing FFR-guided PCI with contemporary drug-eluting stents versus CABG in patients with multivessel coronary artery disease, with a minimum 3-year follow-up. After thorough screening, only three RCTs met these stringent requirements, reflecting the specificity of our research question and the limited number of high-quality, long-term RCTs in this field. To address the reviewer's suggestion, we re-evaluated our search by extending it to additional databases (e.g., Scopus and Web of Science) and relaxing certain criteria (e.g., including shorter follow-up periods or observational studies). However, no additional studies met our core PICOS criteria, as most studies either lacked FFR guidance, focused on single-vessel disease, or had inadequate follow-up. We have added a statement in Section 3.1 explaining this re-evaluation and justifying the inclusion of only three studies, emphasizing that their high methodological quality (low to moderate risk of bias) and low heterogeneity (I^2 = 0–25%) support the reliability of our findings, despite the limited number. We also discuss this limitation in the Discussion (Section 4, Strengths and Limitations) to provide context and call for future large-scale RCTs to enhance evidence strength.

Reviewer Comment (Clinical Outcomes): Remove the sub-heading for Section 3.4, incorporate it into a paragraph, and cite the table.

Response: As noted, we have removed the sub-heading for Section 3.4 and integrated the clinical outcomes into a single paragraph, summarizing the findings for all-cause mortality, MACE, myocardial infarction, repeat revascularization, and stroke. The forest plots are now cited as Figure 2 at the end of the paragraph, and baseline characteristics are cited as Table 1, ensuring a streamlined presentation.

Discussion

Reviewer Comment: The discussion is well-written but does not address key strategies to prevent future related problems. There is no conclusion section. Include strengths and limitations.

Response: As indicated, we have revised the Discussion (Section 4) to include specific strategies for preventing future adverse events, such as hybrid revascularization, advanced stent technologies (e.g., bioresorbable scaffolds), optimized medical therapy (e.g., dual antiplatelet therapy, statins), patient selection using risk stratification tools (e.g., SYNTAX score), and structured long-term follow-up. These strategies are supported by references to enhance their evidence base. We have also added a distinct Conclusion subsection (Section 4.1) summarizing the key findings, reinforcing CABG's superiority for complex disease, and outlining future research directions. The Strengths and Limitations subsection (Section 4.2) has been expanded to highlight the study's strengths (e.g., use of RCTs, low heterogeneity) and limitations (e.g., small number of studies, incomplete baseline data), providing a balanced assessment.

Tables and Figures

Reviewer Comment: Provide a title at the bottom for figures and at the top for tables. Indicate reasons for exclusion in Figure 1. Ensure table and figure titles are full and standard.

Response: We have revised the tables and figures to meet the journal's standards. Table 1 now has a full title at the top: "Baseline Characteristics and Demographics of Included Studies Comparing FFR-Guided PCI and CABG in Multivessel Coronary Artery Disease." Figure 1 (PRISMA flowchart) and Figure 2 (forest plots) have titles placed at the bottom, e.g., "Figure 1: PRISMA Flowchart of Study Selection Process" and "Figure 2: Forest Plots of Clinical Outcomes for FFR-Guided PCI versus CABG." In Figure 1, we have added specific reasons for exclusion at each stage (e.g., "N=376 excluded: irrelevant topic, single-vessel disease, no FFR guidance") to improve transparency. All titles have been standardized to be descriptive and consistent with journal guidelines.

Additional Revisions

To enhance the manuscript's overall quality, we have:

- Added a list of abbreviations and acronyms as a new section (Section 5) before the References, ensuring all terms (e.g., CAD, PCI, CABG, FFR, MACE) are defined.
- Ensured all figure and table citations are correctly placed after the relevant text.
- Conducted a thorough proofreading to improve clarity and consistency, addressing any minor formatting issues.

We believe these revisions comprehensively address the reviewer's comments and significantly strengthen the manuscript. We are grateful for the opportunity to revise and resubmit and look forward to your feedback.

Sincerely,
Asraf Hussain, MD
On behalf of all authors