

Effect of Combination Therapy with SGLT2 Inhibitors and GLP-1 Receptor Agonists on Myocardial Infarction and Stroke in Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Supplementary Table S1. Summary of Findings for Primary Cardiovascular Outcomes

Supplementary Figure S1. Risk-of-bias assessment for non-randomized studies using the ROBINS-I tool, presented as a traffic-light plot.

Supplementary Figure S2. Summary of risk-of-bias judgments for non-randomized studies using the ROBINS-I tool.

Supplementary Figure S3. Risk-of-bias assessment for randomized controlled trial evidence using the RoB 2 tool, presented as a traffic-light plot.

Supplementary Figure S4. Summary of risk-of-bias judgments for randomized controlled trial evidence using the RoB 2 tool.

Supplementary Table S1. Summary of Findings for Primary Cardiovascular Outcomes

Outcome	No. of Studies (Comparisons)	Relative Effect (95% CI)	Certainty of Evidence (GRADE)	Plain-Language Interpretation
MI	8 studies (10 comparisons)	HR 0.79 (0.70 – 0.88)	⊕○○○ Very Low	Combination therapy may be associated with a lower risk of MI compared with monotherapy, but the evidence is very uncertain.
Stroke	8 studies (10 comparisons)	HR 0.85 (0.77 – 0.93)	⊕○○○ Very Low	Combination therapy may be associated with a lower risk of stroke compared with monotherapy, but the evidence is very uncertain.

HR: hazard ratio; **CI:** confidence interval; **MI:** myocardial infarction.

a. The evidence was initially rated as low certainty because the quantitative synthesis was predominantly informed by non-randomized observational comparisons.

b. Downgraded one level for serious inconsistency due to substantial heterogeneity for myocardial infarction ($I^2 = 72.8\%$) and moderate-to-substantial heterogeneity for stroke ($I^2 = 63.5\%$).

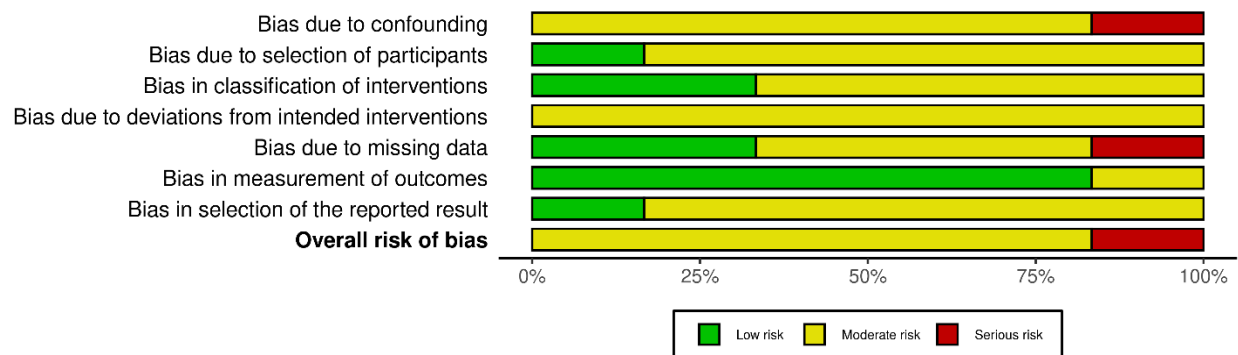
c. Not downgraded for imprecision; the pooled confidence intervals for both outcomes excluded the null effect.

d. Not downgraded for publication bias; Egger’s regression test was not statistically significant for myocardial infarction ($p = 0.179$) or stroke ($p = 0.266$). This assessment was interpreted cautiously due to the limited number of comparisons.

e. Absolute risks could not be calculated from the available aggregate hazard-ratio data.

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Chaiyakunapruk et al. (2025)								
	Clegg et al. (2019)								
	Liu et al. (2025)								
	Luo Z et al. (2023)								
	Riley et al. (2023)								
	Simms-Williams et al. (2024)								
		Domains: D1: Bias due to confounding. D2: Bias due to selection of participants. D3: Bias in classification of interventions. D4: Bias due to deviations from intended interventions. D5: Bias due to missing data. D6: Bias in measurement of outcomes. D7: Bias in selection of the reported result.							Judgement Serious Moderate Low

Supplementary Figure S1. Risk-of-bias assessment for non-randomized studies using the ROBINS-I tool, presented as a traffic-light plot.



Supplementary Figure S2. Summary of risk-of-bias judgments for non-randomized studies using the ROBINS-I tool.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Marx et al. (2025)						
	Mann et al. (2024)						

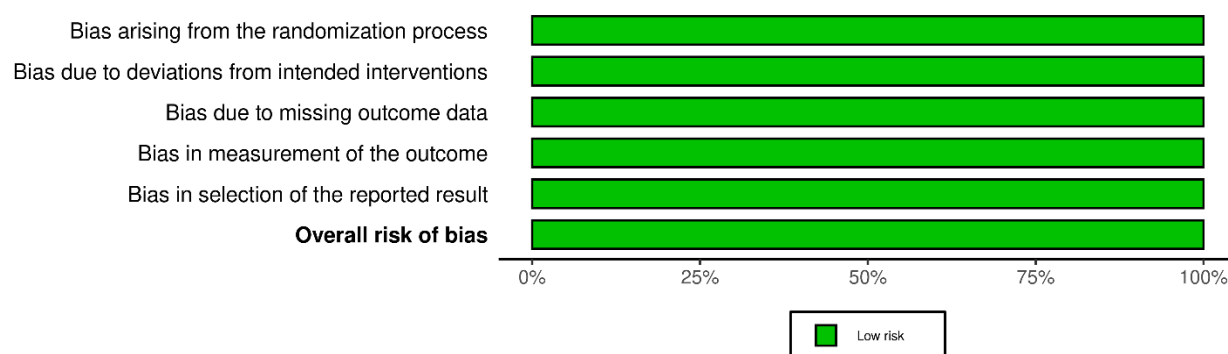
Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

 Low

Supplementary Figure S3. Risk-of-bias assessment for randomized controlled trial evidence using the RoB 2 tool, presented as a traffic-light plot.



Supplementary Figure S4. Summary of risk-of-bias judgments for randomized controlled trial evidence using the RoB 2 tool.