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Effect of metformin on cardiovascular outcomes: a systematic review and meta-analysis of observational studies and RCTs

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Evidence in Context

• By 2045, 783 million people aged 20-79 are expected to have diabetes. • Metformin improves cardiovascular outcomes by enhancing lipid and glucose metabolism. • Studies show inconsistent results on metformin's cardiovascular impact. • Meta-analysis suggests metformin may reduce cardiovascular events and mortality. • Metformin use should be tailored to individual patients, requiring further research.

To view Article

Abstract

Background: Metformin is an oral medication most commonly prescribed to lower blood glucose levels. However, previous systematic reviews have cast doubt on its effectiveness in reducing the risk of cardiovascular disease (CVD), the costliest side effect of type 2 diabetes mellitus (T2DM). This study aimed to combine data from observational studies and randomized controlled trials to determine the impact of metformin on cardiovascular outcomes in diabetic and non-diabetic populations.

Methods: On February 24, 2023, an article search was conducted in multiple databases, including PubMed, Scopus, EBSCO, Web of Science, and ProQuest, utilizing keywords, synonyms, and specific terms for Metformin and various CVDs. Study quality was evaluated using the Cochrane risk of bias tool for trials and Newcastle–Ottawa Scale for observational studies. Statistical analysis of the data was conducted using R software. PROSPERO registration: CRD42023404151.

Results: A total of 40,087 studies were found through a literature search, of which 22 studies were identified as eligible, involving 612,823 participants. The overall pooled effect from RCTS estimate for CVD outcome with metformin treatment was found to be a Risk Ratio (RR) of 0.91 (95% CI:0.78-1.05). The pooled effect estimate indicated a reduction in CVD-related mortality with metformin treatment, with an RR of 0.57 (95% CI: 0.176-1.87), Observational studies also showed a reduction in CVD mortality with metformin treatment.

Conclusions: The present analysis provides evidence that metformin treatment not have a effect on composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE. Metformin may have potential reduction in CVD mortality.

Keywords: *cardiovascular diseases, diabetes mellitus, heart failure, metformin, myocardial infarction, stroke, angina pectoris, evidence synthesis, prevention, heart attack*

Introduction

Globally, approximately 537 million people between the ages of 20 and 79 have a persistent metabolic condition, type 2 diabetes mellitus (T2DM) which is linked to high morbidity and mortality. By 2030, 643 million individuals between the ages of 20 and 79 are expected to have diabetes; by 2045, 783 million is the projected increase. During this time, it's anticipated that there will be a 46% increase in the number of people with diabetes despite a 20% predicted increase in the world's population [1]. Cardiovascular diseases (CVDs) are significantly more likely to develop in people with T2DM than in people without the condition, and this increased risk is two–three times greater for those with T2DM. At least 50% of T2DM patients die as a consequence of the main CVDs linked to T2DM, including heart failure (HF), ischemic heart disease, coronary artery disease (CAD), peripheral artery disease and stroke [2].

It has been demonstrated that the oral hypoglycaemic medication metformin, which is frequently used to manage T2DM, positively impacts cardiovascular outcomes [3,4]. Metformin has been demonstrated to enhance cardiac energy state by enhancing cellular lipid and glucose metabolism via AMPK. By promoting AMPK and blocking alpha-dicarbonyl-mediated changes in apolipoprotein residues, metformin enhances high-density lipoprotein (HDL) dysfunction and diminishes low-density lipoprotein (LDL) alteration [5-7].

Inconsistent results have been found in numerous randomised controlled trials (RCTs) and observational studies examining metformin's impact on cardiovascular outcomes in patients with T2DM [8-11]. Therefore, a thorough analysis of the existing data is required to ascertain how metformin affects cardiovascular outcomes in T2DM patients. Metformin's impact on cardiovascular events and mortality has previously been assessed through meta-analysis of randomised studies. This analysis excluded any general negative impact of metformin on cardiovascular risk, indicating a potential advantage compared to placebo or no therapy [12]. Another meta-analysis of randomised trials among persons with T2DM identified the impact of metformin compared to lifestyle, diet or placebo. However, the result remained unclear as to whether metformin reduced the likelihood of cardiovascular disease in people with type T2DM [13]. A latest meta-analysis of observational studies focused on assessing the impact of metformin on mortality and cardiovascular events among patients with T2DM found that it was not significantly associated with a lower risk of cardiovascular outcomes when contrasted with non-metformin therapy [14]. Thus, the previous meta-analyses were either more than five years old or included only the observational studies evaluating the impact of the metformin on cardiovascular disease outcomes. Hence, the index systematic review and meta-analysis seek to uncover the impact of metformin on cardiovascular health among populations with and without diabetes. By synthesising data from observational studies and randomised controlled trials, we aim to provide a more conclusive understanding of the association between metformin and cardiovascular events. This research could significantly influence clinical decisions and enhance patient care outcomes.

Methods

The systematic review process followed the PRISMA guidelines as documented in **Table S1**. the review protocol was registered with PROSPERO, bearing the registration number CRD42023404151.

Inclusion and exclusion criteria

This systematic review's goal was to look at any possible connections between metformin use and cardiovascular events by analysing both clinical trials and observational studies. The review adopted a broad inclusion criterion, including participants with or without diabetes or prior CVD, regardless of their gender or the dosage of metformin they used. However, studies that evaluated metformin in combination with other drugs were excluded, as were studies that compared metformin with other anti-diabetic drugs without a control group. Conversely, studies that compared metformin with diet, placebo, or insulin were included in the review. We applied a dual screening process to identify eligible studies to ensure methodological rigour. We excluded studies that did not meet specific criteria, such as protocols, narrative reviews, clinical case reports, abstracts, unpublished reports, editorials, and commentaries. We also excluded studies that reported only cardiovascular risk factors without actual events. We considered only published articles and preprints in English, without any restrictions, based on the country or research environment. Further details regarding the inclusion criteria are outlined in **Table S2**.

Search strategy and screening

In order to identify relevant studies, we conducted a comprehensive literature search on February 24, 2023, across multiple databases, including Web of Science, PubMed, EBSCO, Cochrane, Scopus, and ProQuest. Our search strategy utilised several keywords, such as “Metformin” OR “biguanide” OR “biguanides” AND “heart disease” OR “vascular diseases” OR “stroke” OR “cerebrovascular accident” OR “sudden death” OR “cardiac arrest” OR “cardiovascular disease” OR “coronary artery disease” OR “heart failure” OR “cardiovascular mortality” OR “coronary death” OR “CHD” OR “CVD” OR “cardiac death” OR “myocardial infarction” OR “angina” OR “CAD” OR cardiac* OR myocardial* OR “Aortic disease” OR “congestive heart failure” OR cardio* OR “ischemic heart disease” OR “atherosclerosis” OR “Heart muscle disease” OR “Deep vein thrombosis” OR “pulmonary embolism” OR “Pericardial disease” OR “Rheumatic heart disease” OR “MI” OR “CVA” OR “heart” OR “re-infarction” OR re-vascularisation OR “cardiac mortality” OR “cardiac death.” We limited our search to English-language publications and did not impose any restrictions on the publication year. Our search strategy was designed to capture all relevant studies that investigated the association between metformin use and cardiovascular events (**Table S3**).

After retrieving the search results, we transferred them to Mendeley and removed duplicate entries. Two researchers, M.S and MA, conducted the primary screening using Rayyan. They reviewed the titles and abstracts of each study to exclude irrelevant articles. Next, the full-text screening of all the articles that passed the first pass screening was done to confirm their eligibility for inclusion in the review. In order to ensure consistency and accuracy, the two researchers independently conducted the screening process. Any disagreements or discrepancies between the researchers were solved by consulting a third senior researcher who provided an independent assessment of the study’s eligibility.

Data extraction and quality assessment

Data extraction from the selected studies was carried out by two researchers using Excel software. The extracted data encompassed detailed elements like the first author's name, the study's country of origin, publication year, study design, participant characteristics, average participant age, average HbA1c levels, metformin dosage, overall sample size, and the nature of CVD outcomes.

To evaluate the methodological quality of the studies, the Newcastle-Ottawa Scale (NOS) was applied for observational studies, and the Cochrane’s Risk of Bias 2 tool was utilized for randomized controlled trials (RCTs). On the NOS, higher scores signify superior methodological quality and a reduced risk of bias.

Data synthesis and statistical analysis

In our study, we employed R Version 4.2.3, for all statistical calculations. Our selection criteria for studies focused on the presence or absence of CVD, a binary variable, in groups receiving metformin (treatment group) versus those not receiving it (control group), along with the total participant count in each group. We calculated the pooled risk ratio (RR) for CVD occurrences in both groups using the Mantel-Haenszel (MH) method with a random-effects model to estimate a combined effect size. This approach provided us with a 95% confidence interval (CI) for the effect size and its associated p-values. We evaluated the variation between studies using I^2 statistics, classifying heterogeneity as high ($I^2 > 50\%$), moderate ($I^2 = 26\text{-}50\%$), or low ($I^2 < 25\%$), and analyzed this heterogeneity via its corresponding p-values. Forest plots were created to summarize the meta-analysis findings visually. To pinpoint the sources of heterogeneity, we conducted subgroup analyses. We also performed meta-regression to discover variables influencing the overall risk ratio, visually represented through bubble plots. To understand the influence of each study on the overall summary estimate, we carried out sensitivity analyses by sequentially excluding individual studies. Baujat plots helped in identifying outliers within the meta-analysis. To assess the likelihood of publication bias, we used Doi and funnel plots, complemented by Egger’s test. In all our analyses, p-values less than 0.05 were deemed to indicate statistical significance.

Result

Literature search

In order to locate pertinent papers, a literature search was done, as **Figure 1** outlines in detail. Initially, we identified 40,072 articles from EBSCOhost, ProQuest, PubMed, Scopus, Cochrane, and Web of Science, of which 4,577 were duplicates. After eliminating duplicates, the initial screening of 35,495 research (reading of titles and abstracts) resulted in 34,972 studies being disqualified, leaving 523 papers for subsequent screening or full-text reading. Five hundred and four articles were excluded, of which 112 were animal studies, 92 were reviews, 133 were risk factors for CVD, 88 were not placebo/control groups, 13 were duplicates, 22 were non-CVD outcomes, and 44 were without metformin intervention. Additionally, a citation search was performed, and 15 studies were found, of which seven were excluded due to no control group or only reported risk factor outcomes. Finally, 22 studies were eligible for inclusion in this meta-analysis.

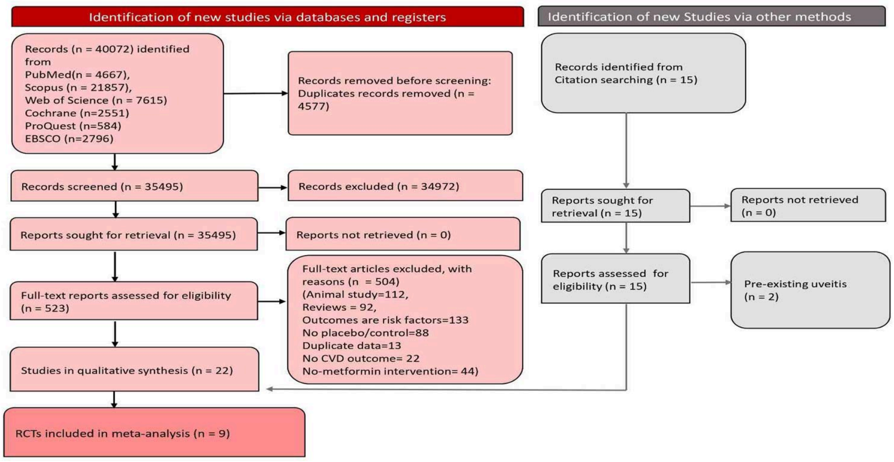

Figure 1. Prisma flow diagram presenting the screening process

Characteristics of included studies

The features of the 22 studies that satisfied the eligibility criteria are summarised in **Table 1**. There was a total of 612,823 individuals in these studies, with 423,673 beingthe metformin group and 128,903being a comparison group.The studies were performed in various countries, including the USA [8,15-19], the Netherlands [20-22], Denmark [23,24], the UK [25,26], Sweden [27,28], China [29,30], Korea [11], Israel [31], Taiwan [32], Australia [33], and England [34]. Of the 22 studies, 13 were observational, five were RCTs, and four were sub-analyses or post-hoc analyses of RCTs. Seven studies reported the dosage of metformin used, while nine reported CVD mortality. One study included non-diabetic participants, while another included type 1 diabetic subjects. Three studies included chronic kidney disease (CKD) patients, and seven studies included patients with prior CVD. The studies reported various outcomes, including MI, stroke, coronary heart disease (CHD), HF, or CAD, with some mentioning composite CVD outcomes or just CVD in general. Additionally, seven studies reported Major Adverse Cardiovascular Events (MACE).

Table 1. Characteristics of included studies

Author	Country, Year	Study design	Participants characteristics	Follow-up (years)	Age (mean/median)	Metformin population	Metformin CVD mortality	Type of Comparison	Control population	CVD events in control/placebo	Control mortality	Total population
Andersson C [23]	Denmark, 2010	Retrospective cohort	Prior HF and T2DM	9	69.5	688	109	Insulin	3,718	N/A	1157	1845
Aronow WS [15]	USA, 2021	Prospective observational	Older patients with Prior MI and T2DM	2.5	80	9	N/A	Diet	77	MI or CVD death=54	N/A	86

Bromage DI [25]	UK, 2019	Prospective cohort	Patients with T2DM and acute MI	N/A	71.3	2576	894	No-metformin	1454	Stroke=195, MI=433, HF=313, MACE=899	584	4030
Charytan DM [16]	USA, 2019	Subanalysis/Post hoc analysis of Trial	Individuals with diabetes and CKD	5	67	508	35	No-metformin	508	Composite CVD= 138	64	1016
Clegg LE [17]	USA, 2021	Subanalysis/Post hoc analysis of two trials: EXSCEL and SAVOR-TIMI 53	T2DM, CKD stages 3 to 4	Exscel =5, SAVOR-TIMI= 3	67	1745	107	No-metformin	1745	MACE=255, MI=127, Stroke=46	131	3490
Ekström N [27]	Sweden, 2012	Prospective cohort	Patients with T2DM	3.9	65.3	14697	N/A	Insulin	12291	2389	N/A	26988
Fonseca V [20]	Netherlands, 2009	Randomised placebo-controlled trial	Patients with T2DM	4.3	61	196	N/A	Placebo	194	Macrovascular= 35	N/A	390
Fung CSC [29]	China, 2015	Retrospective cohort	Patients with T2DM and without any CVD history	5	62	3400	N/A	No-metformin	3400	CHD=102, Stroke=86, HF=43	N/A	6800
Goldberg RB [18]	USA, 2022	Subanalysis/Post hoc analysis of Trial	T2DM, without previous CVD	21	N/A	1082	27	Placebo	1073	Major CVD events=98, Stroke= 28, MI=43	39	2155
Hartman MH [21]	Netherlands, 2017	Subanalysis/Post hoc analysis of Trial	STEMI diagnosed patients with previous MI and T2DM	2	58	191	N/A	Placebo	188	MACE=6, Stroke=1	N/A	379
Hippisley-Cox J [34]	England, 2016	Open cohort study	Patients with T2DM	5.9	64.5	256024	N/A	Insulin	19791	HF=220, All CVD=290	N/A	2,75,815
Kim M-H[11]	Korea, 2021	Retrospective observational	Patients with T2DM and CKD	5.3	66.3	77666		No-metformin	20047	MACCE=2082, CHD=1261, Stroke=821		97713
Kooy A [22]	Netherlands, 2009	Randomised, Placebo-controlled trial	Patients with T2DM	4.3	61.5	196	N/A	Placebo	194	MI= 25 HF=4	N/A	390

	Stroke=9											
Lee CG [8]	USA, 2021	Open Label RCT	Patients with T2DM Patients with T2DM	21	50.6	1073	44	Placebo	1,082	N/A	38	2155
Lund SS[24]	Denmark, 2008	Double blind RCT	Patients with T1DM	1	46.1	49	N/A	Placebo	51	5	N/A	100
Preiss D[26]	UK, 2013	Double blind, Placebo-controlled trial	Patients with coronary heart disease and without T2DM	1.5	63	86	N/A	Placebo	87	6	N/A	173
Rachmani R [31]	Israel, 2002	Prospective, randomised observational	Patients diagnosed with T2DM	4	64	195	50	No-metformin	198	MI=53, All cvd evens=108	52	383
Ritsinger V [28]	Sweden, 2020	Prospective observational	Patients with T2DM	3.4	68	3982	N/A	Insulin	3091	MACE=986	N/A	70270
Sillars B[33]	Australia, 2010	Retrospective cohort	Patients with T2DM	10.4	63	174	19	Diet	410	N/A	62	584
Wang J [30]	China, 2022	Retrospective cohort	Patients with T2DM who were hospitalized with Heart Failure with Preserved Ejection Fraction (HFpEF).	4	71	113	5	No-metformin	259	N/A	22	372
Weir DL [19]	USA, 2018	Retrospective observational	T2DM and incident HF	1.7	54	3799	N/A	No-metformin	3821	Ischemic heart disease= 1606, MI=267	N/A	7620
Yen F-S [32]	Taiwan, 2022	Retrospective cohort	T2DM, COPD with previous HF, CAD, Stroke	12.3	61.5	55224	N/A	No-metformin	55224	HF=2220, CAD=9728 Stroke=6702, Composited CVD= 14806	N/A	110448

As for the observational studies, four studies achieved a score of 8, while seven studies scored 7, and two studies scored 6 in the NOS (Table S4). Among the nine RCTs, seven were clear about the randomisation procedure. Seven studies reported concealment of allocation, and two were unclear. None of the RCTs had performance bias. In all the RCTs, outcome assessment was blinded, thereby omitting the chances of detection bias. No reporting or attrition bias was detected in any RCTs (Table S5). Overall, the quality of the included studies was high.

Effect of Metformin on composite CVD outcome

In this meta-analysis, we examined 9 RCTs to evaluate the effect of metformin therapy on CVD outcomes. Some of these studies reported composite CVD outcomes, while others reported individual CVDs. In order to enable a comprehensive comparison across all studies, we combined the individual CVDs and treated them as composite CVDs. The overall pooled effect estimate for CVD outcome with metformin treatment was found to have an RR of 0.91 (95% CI: 0.78-1.05), p =0.175. The prediction interval was observed to be between 0.72-1.13. Low heterogeneity was noted across the studies (I^2=14%). (**Figure 2**) This indicate that metformin may reduce the incidence of CVD outcomes, though it is not statistically significant, but clinically relevant.

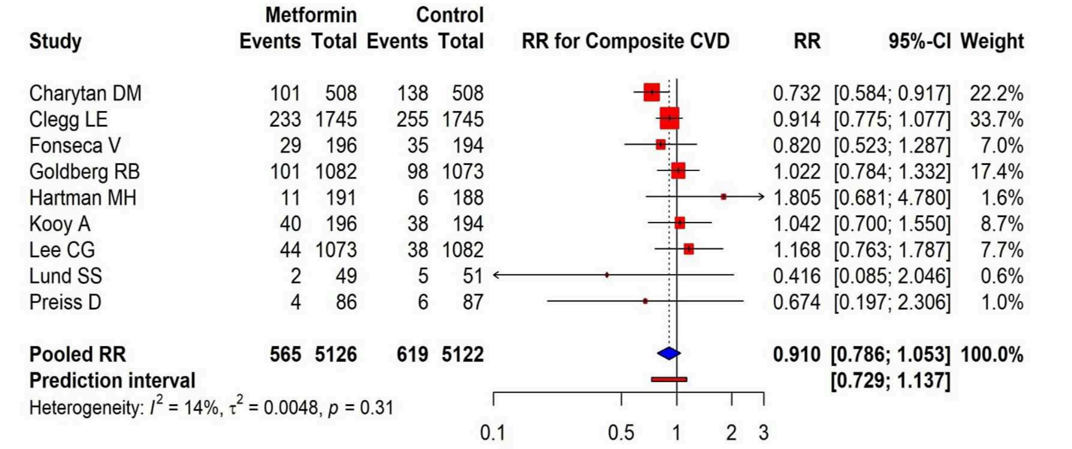

Figure 2. Forest plot depicting metformin's effect on composite CVD outcomes from RCTs

Effect of metformin on CVD-related mortality

A total of four RCTs reported CVD-related mortality outcomes. The pooled effect estimate indicated a reduction in CVD-related mortality with metformin treatment, with an RR of 0.57 (95% CI: 0.176-1.87), p= 0.23. However, significant heterogeneity was observed across the studies, with an I^2 value of 93%. **(Figure 3).** Observational studies has also shown metformin is associated with CVD mortality reduction [29,32,34].

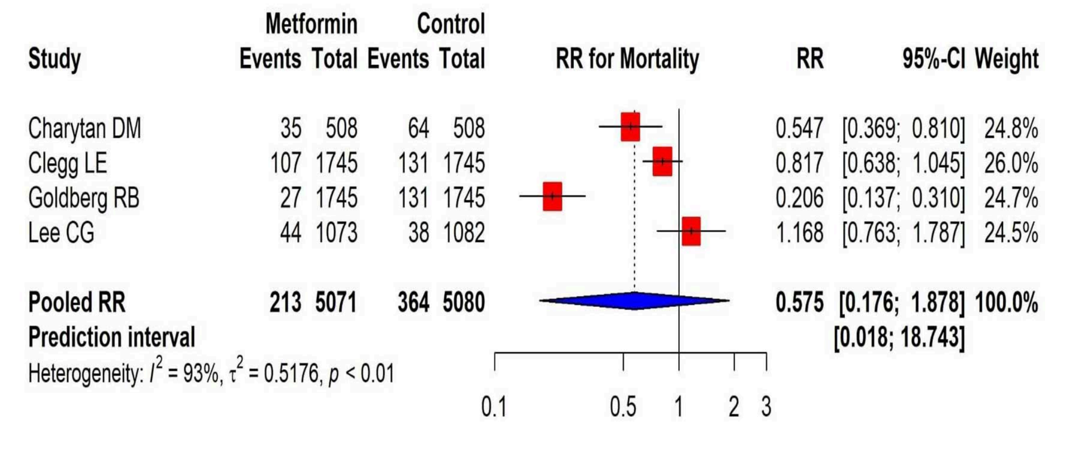

Figure 3. Forest plot depicting metformin's effect on CVD mortality from RCTs

Sensitivity analysis

We conducted various sensitivity to detect the effects of individual studies on heterogeneity and effect estimates for both the composite CVD outcome and CVD-related mortality (**Figures S1-S2**). Leave-one-out analysis, performed by omitting one study at a time, indicated that no individual study significantly affected the overall heterogeneity or effect size of the composite CVD outcome.

Publication Bias

The funnel plot is a visual display of effect estimates against their standard error, which can reveal

Publication bias by detecting a lack of smaller studies with non-significant results. The Egger test is a statistical assessment of the relationship between effect estimate and precision, with a significant result indicating potential publication bias. The results of our analysis for composite CVD outcome showed no evidence of publication bias according to the Egger test (p=0.88) and the funnel plot (Figure 4).

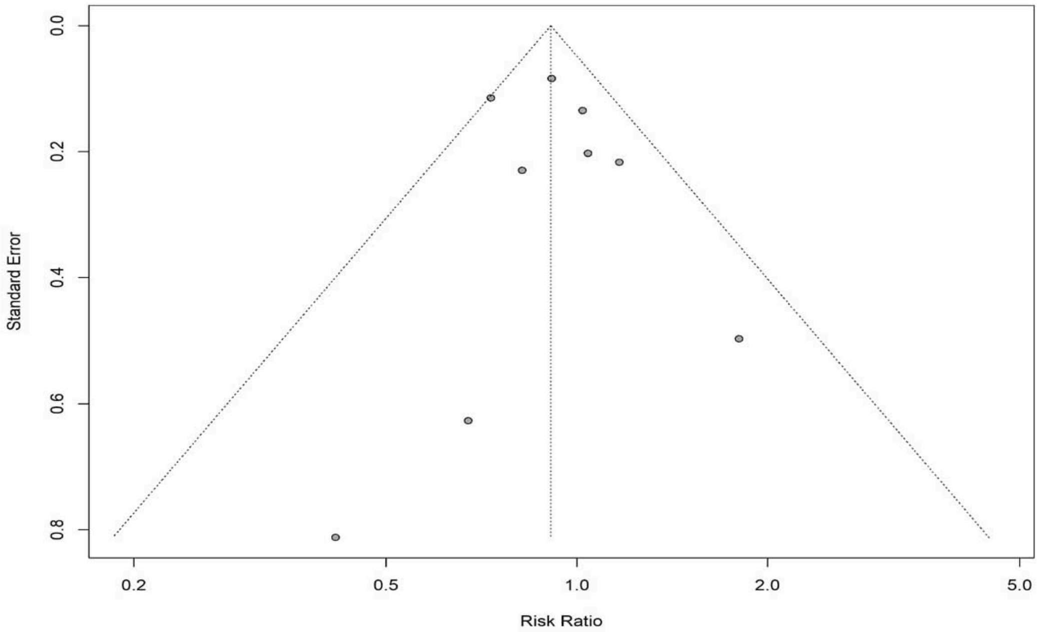

Figure 4. Funnel plots for detecting publication bias

Discussion

Through this systematic review and meta-analysis, we examined the impact of metformin medication on outcomes related to CVD. We did observe a significant impact of metformin treatment on composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE by looking evidence from RCTs and observational studies. Although our meta-analysis of RCTs are not statistically significant, they showed reduction of CVD related outcomes. We did observe a reduction in CVD mortality with metformin use in the observational studies.

Our study's findings align with previous meta-analyses, such as *Griffin et al.* [13], which only analysed RCTs. Another meta-analysis compared the effects of metformin on CVD events with other anti-diabetic drugs. However, they did not report any beneficial effects of metformin's in reducing CVD events [12]. On the contrary, they found a higher risk of CVD events with combination therapy of metformin and sulfonylurea. They concluded that metformin reduces the risk of cardiovascular disease when compared to no medication or a placebo, likely due to improved blood glucose control. However, this effect disappears when compared to other glucose-lowering treatments. Notably, no beneficial effects of metformin on cardiovascular events have been found in non-diabetic individuals. Similarly, a recent systematic review observed that using metformin as monotherapy in patients with T2DM can lower the risk of stroke, according to low to moderate-level evidence from RCTs [36]. However, this preventive effect is not observed in patients who are taking a combination of metformin with other hypoglycemic agents. A meta-analysis performed on observational studies found that metformin reduced the incidence of CVD. Additionally, a study by *Zhang K et al.* reported that, in individuals with coronary artery disease, metformin can lower cardiovascular mortality, death from all causes, and cardiovascular incidents [37]. However, in patients with myocardial infarction and coronary artery disease without T2DM, it was discovered that metformin had no discernible impact on the frequency of cardiovascular events. It is interesting to note that the study also revealed that metformin reduces the frequency of cardiovascular events more effectively than sulfonylureas.

Based on the available evidence, whether metformin may reduce CVD events in patients with T2DM remains uncertain. Some studies have suggested a reduction in CVD events with metformin, but this effect may be limited to certain subgroups of patients or when compared to no treatment or placebo. Combination therapy with other hypoglycemic agents, such as sulfonylureas, may also negate the beneficial effects of metformin on CVD outcomes. Therefore, clinicians should carefully consider individual patient characteristics and risk factors when prescribing metformin as a first-line therapy for T2DM. Patients taking metformin should be under close surveillance for potential adverse effects and lack of efficacy in reducing CVD events. It is important to note that further research is needed to fully understand metformin's effects on CVD outcomes and identify which patient subgroups may benefit most from its use.

Metformin largely lowers blood sugar levels by lowering hepatic glucose synthesis and enhancing peripheral tissues' sensitivity to insulin. Although metformin has been shown in several investigations to reduce the mortality rate from CVD, the precise mechanisms behind this connection are yet unknown. It is likely that the glucose-lowering effect of metformin indirectly leads to better outcomes in the cardiovascular system by reducing the risk of atherosclerosis and subsequent CVD events such as stroke and myocardial infarction. However, metformin's effect on CVD outcomes may vary depending on factors such as patient population, treatment duration, and other combination therapy medications. Clinicians should carefully consider the individual patient's characteristics and clinical situation before deciding to prescribe metformin as a preventative measure for CVD [38]. Additionally, it is essential to monitor patients on metformin therapy for any adverse effects and adjust the treatment plan accordingly. While some studies have recommended that the beneficial impact of metformin on CVD outcomes may be due to its glucose-lowering effect, others have found additional mechanisms of action that contribute to its cardiovascular benefits [19-25,39]. However, further research is needed to understand these mechanisms fully. In summary, metformin may be a beneficial therapeutic choice for T2DM patients who are at risk of mortality from CVD, but its usage should be tailored to the patient's needs and other risk factors. In order to evaluate the efficiency of the medication and any adverse effects, patients should also undergo routine monitoring. Further studies should evaluate the possible long-term impact of metformin usage on the outcomes of CVD. With more information, we can optimise metformin therapy for patients with T2DM and reduce their risk of cardiovascular events.

Our study had several strengths, including the ability to perform subgroup analysis, the inclusion of both RCTs and observational studies, and a large number of studies in our analysis, which increased the robustness of our findings. However, we acknowledge some limitations, such as only including studies published in English, which may have led to language bias. We were also unable to address the heterogeneity in composite CVD outcomes across studies, which may have affected our results. Additionally, our study was limited by the potential publication bias.

Conclusion

In conclusion, our study provides evidence that metformin treatment may reduce composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE. Our findings suggest a potential reduction in CVD mortality with metformin use. In order to validate this possible benefit and clarify the underlying mechanisms of metformin's impact on CVD outcomes, further research is required. Despite these limitations, our study provides a comprehensive analysis of the current evidence on metformin and CVD outcomes, which can assist in improving clinical judgment and enabling future research in this domain.

Supporting information

None

Ethical Considerations

None

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Author contribution statement

Muhammed Shabil1: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). **Ganesh Bushi**: conceptualization, Software (lead); writing – review and editing (equal). **Aarti Yadav**: Methodology (lead); writing – review and editing (equal). **Mohammed Ahmed**: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Jugal Kishore**: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Sarath Lekamwasam**: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Ashish Joshi**: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal).
All authors attest they meet the ICMJE criteria for authorship and gave final approvalforsubmission.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Jugal Kishore and Ashish Joshi are authors of this paper. Therefore, the peer review process was managed by alternative members of the Editorial Board and the authors had no involvement in the decision-making process.

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