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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

Prior Evidence: Prior research has raised questions about the impact of metformin on cardiovascular outcomes in type 2 diabetes mellitus (T2DM) patients. These studies highlighted the uncertainty surrounding metformin's effectiveness in reducing the risk of cardiovascular disease (CVD). Limitations of prior research included varying findings, potential bias, and heterogeneity in study populations.

Evidence added by this study: Our meta-analysis of 22 studies (involving 612,823 participants) found no significant impact of metformin on cardiovascular outcomes but noted a potential reduction in CVD-related mortality. Despite heterogeneity and sensitivity to one study, it suggests metformin's consideration for at-risk patients, emphasizing personalized decisions and vigilant monitoring, informing ongoing discourse and guiding future research on metformin's role in CVD risk management.

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).

Objective: This study aimed to combine data from observational studies and randomised controlled trials to determine the impact of metformin on cardiovascular outcomes in diabetic and non-diabetic population.

Methods: On February 24, 2023, a thorough article search was performed in PubMed, EBSCO, Scopus, Web of Science, and ProQuest using keywords and synonyms of Metformin and CVD, coupled with specific terms for different CVDs. Study quality was evaluated using the Cochrane risk of bias tool and Newcastle–Ottawa Scale. 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, for the meta-analysis. The overall pooled effect estimate for CVD outcome with metformin treatment was found to be a Risk Ratio (RR) of 0.88 (95% CI:0.76-1.03). The pooled effect estimate indicated a significant reduction in CVD-related mortality with metformin treatment, with an RR of 0.75 (95% CI: 0.60-0.93).

Conclusions: This study provides evidence that metformin treatment may not have a significant effect on composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE. However, we observed a potential reduction in CVD mortality with metformin use.

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), stroke and peripheral artery disease [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 observational studies and randomised controlled trials (RCTs) that have examined the impact of metformin 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 diet, lifestyle, 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 systematic review and 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. The results of this study have the potential to inform clinical decision-making and improve patient outcomes.

Methods

The systematic review process followed the PRISMA guidelines as documented in **Table S1**. The review protocol was also registered with PROSPERO and assigned 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 observational studies and clinical trials. 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 narrative reviews, protocols, unpublished reports, editorials, clinical case reports, abstracts, and commentaries. We also excluded studies that reported only cardiovascular risk factors without actual events. We considered only preprints and published articles in English, without any restrictions, based on the country or research environment. Further details regarding the eligibility 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 PubMed, EBSCO, Cochrane, Scopus, Web of Science, and ProQuest. Our search strategy utilised various 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 readings of all the studies that passed the primary screening were 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

Two investigators performed data extraction using Excel software from the included studies. The data extracted included specific information such as the name of the first author, the country where the study was conducted, the year of publication, the study's design, characteristics of the participants, average age, average HbA1c levels, metformin dosage, total sample size, and the type of CVD outcome.

In order to assess the methodological quality of the included studies, the Newcastle–Ottawa Scale (NOS) was used for observational studies, while the Cochrane's Risk of Bias 2 tool was employed for RCTs. Higher scores on NOS indicate better methodological quality and a lower risk of bias.

Data synthesis and statistical analysis

We utilised R Version 4.2.3, a software package provided by the R Foundation, to perform all statistical analyses. The inclusion criteria for the selected studies were based on reports of the presence or absence of CVD, a dichotomous variable, in the metformin (treatment) and control (non-treatment) groups, along with the total number of participants in each group. We computed a combined effect size using the risk ratio (RR) for CVD incidents that occurred in both groups using the Mantel-Haenszel (MH) model with random effects in order to get an effect size with a 95% confidence interval (CI) and corresponding p-values. We assessed heterogeneity across the studies using I^2 statistics and corresponding p-values, with heterogeneity classified as high (I^2 > 50%), medium (I^2 = 26-50%), and low (I^2 < 25%). We generated forest plots to provide a summary of the meta-analysis. Subgroup analyses were conducted to identify the source of heterogeneity. Meta-regression was performed to identify variables that affect the overall risk ratio, and bubble plots were used to illustrate the effect of these variables on the result. We conducted sensitivity analyses by removing one study at a time to assess the impact of individual studies on the pooled summary estimate. Outliers in the meta-analysis were determined using Baujat plots. We also used Doi and funnel plots with Egger's test to examine the potential of publication bias. We set the level of statistical significance for all analyses at p-values less than 0.05.

Results

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.

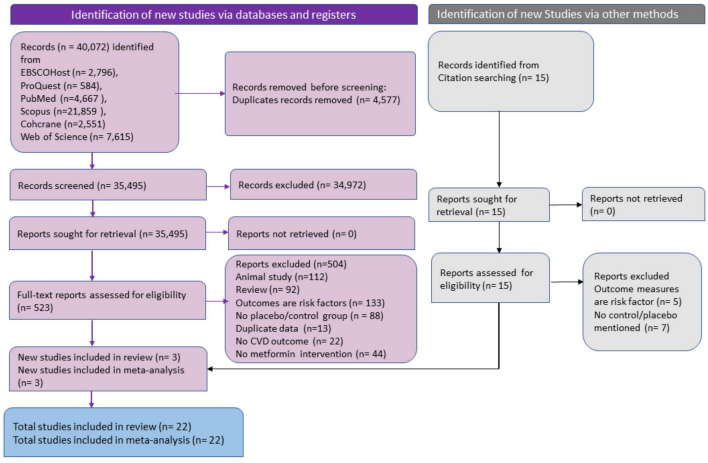

Figure 1. Prisma flow diagram presenting the screening process

Characteristics of included studies

The features of the 22 studies that satisfied the inclusion criteria are summarised in **Table 1**. There was a total of 612,823 individuals in these studies, with 423,673 being the metformin group and 128,903 being 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

As for the observational studies, four studies scored 8, 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 22 studies to investigate the effect of metformin treatment 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 be with an RR of 0.88 (95% CI: 0.76-1.03), p =0.100. The prediction interval was observed to be between 0.48-1.64. Significant heterogeneity was noted across the studies (I^2=98%). (**Figure 2**)

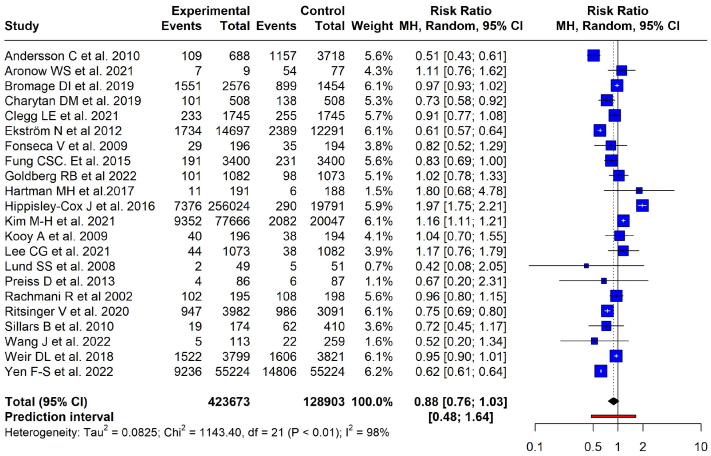

Figure 2. Forest plot depicting metformin's effect on composite CVD outcomes

Effect of metformin on CVD-related mortality

A total of nine studies reported CVD-related mortality outcomes. The pooled effect estimate indicated a significant reduction in CVD-related mortality with metformin treatment, with an RR of 0.75 (95% CI: 0.60-0.93), p= 0.014. The prediction interval ranged from 0.43 to 1.03. However, significant heterogeneity was observed across the studies, with an I^2 value of 78%. **(Figure 3)**

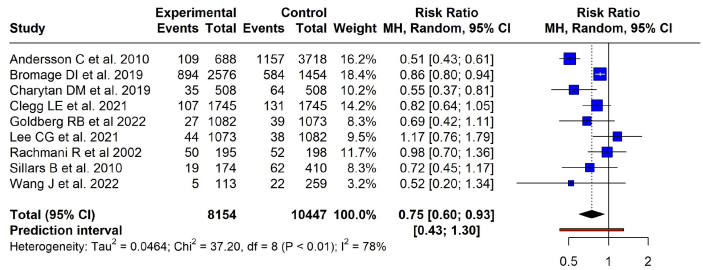

Figure 3. Forest plot depicting metformin's effect on CVD mortality

Effect of metformin on individual CVD outcomes

We conducted an analysis to determine the effect of metformin on individual CVD outcomes, including stroke, MI, HF, and MACE. The RR for stroke was 0.91 (95% CI: 0.71-1.61), with a p=0.37 and high heterogeneity (I^2=98%) and a prediction interval ranging from 0.5 to 1.64. For MI, the RR was 0.94 (95% CI: 0.80-1.10), with a p=0.34 and heterogeneity of I^2=53%, and a prediction interval ranging from 0.70 to 1.25. The RR for HF was 0.88 (95% CI: 0.61-1.28), with a p-value of 0.40 and high heterogeneity (I^2=96%) and a prediction interval ranging from 0.36 to 2.15. The RR for MACE was 0.96 (95% CI: 0.79-1.11), with a p = 0.60, high heterogeneity (I^2=94%), and a prediction interval ranging from 0.59 to 1.54. (**Figures S1-S4**)

Subgroup analysis

Given the significant heterogeneity observed across the studies, we conducted a subgroup analysis to explore the effect of metformin treatment on composite CVD outcomes based on different factors. These factors included the nature of the comparison group (diet/placebo/insulin/no-metformin), study design (RCT/observational study), and the presence of prior CVD/CKD in study participants. We found no significant difference in the RR estimates among any subgroups in our analysis. (**Table 2**)

Table 2. Subgroup analysis based on disease, study design, and comparator

Subgroup	RR	95%CI	I2	
Disease				P Subgroup=0.36
Prior CVD	0.84	0.67 - 1.06	98.2 %	
No prior CVD	0.87	0.68 - 1.11	96.9 %	
CKD	1.04	0.23 - 4.69	86.6 %	
Study design				P Subgroup= 0.638
RCT	0.91	0.78; 1.05	14.3%	
Observational	0.86	0.68; 1.07	98.9%	
Comparator				P Subgroup=0.513
Placebo	1.0141	0.844- 1.21	0.0%	
Diet	0.9195	0.06 - 13.7	46.9%	
Insulin	0.8211	0.31 - 2.14	99.1%%	
No-metformin	0.8745	0.74 - 1.02	99.0%	

Meta-regression

Meta-regression analyses were conducted to investigate the impact of several variables, including age, BMI, male percentage, follow-up duration, and HbA1c level, on composite CVD. However, none of these variables were found to be significantly associated with the outcome, as shown in **Table S6**.

Sensitivity analysis

We conducted various sensitivity and inferential analyses to detect the effects of individual studies on heterogeneity and effect estimates for both the composite CVD outcome and CVD-related mortality (**Figures S5-S8**). Leave-one-out sensitivity analyses, 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. However, the Baujat plot and leave-one-out sensitivity analyses revealed that the study by Andersson et al. contributed significantly to the heterogeneity of the CVD-related mortality outcome. After omitting the study by Andersson et al. and re-analysing the data, the heterogeneity was reduced to moderate (I^2=34%), and the effect estimate was increased to a RR of 0.81 (95% CI: 0.6788-0.9799), with a p-value of 0.0341. No significant effects were found for any individual study for 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 Doi plot with the LFK index is another statistical test that measures the association between study size and effect size, with a higher LFK index indicating a higher likelihood of publication bias. [35] The Doi plot displays the LFK index for each study, and a linear regression line is fitted to assess the presence and magnitude of publication bias.

The results of our analysis for composite CVD outcome showed no evidence of publication bias according to the Egger test (p=0.21) and the funnel plot. However, an LFK index of 2.84 was observed (**Figure 4),** indicating the presence of possible publication bias. This suggests that there may be a tendency for smaller studies with larger effect sizes to be published, which can overestimate the treatment effect. On the other hand, for CVD mortality, the Egger test and the funnel plot did not indicate any evidence of publication bias (p=0.48). However, the Doi plot was asymmetrical with an LFK index of -2.41, which suggests a possible publication bias towards larger studies with smaller effect sizes. This can lead to an underestimation of the treatment effect (**Figure 4**).

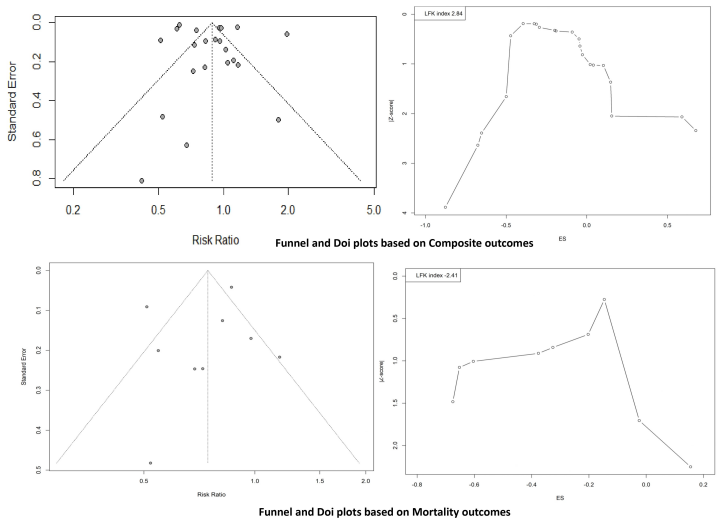

Figure 4. Doi and Funnel plots for detecting publication bias

Discussion

Through this systematic review and meta-analysis, we examined the impact of metformin medication on outcomes related to CVD. Our analysis found 22 suitable studies with a total of 612,823 participants, including both observational studies and RCTs. We did not observe a significant impact of metformin treatment on composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE. However, we did observe a reduction in CVD mortality with metformin use in the primary analysis. Despite high heterogeneity in the analysis, our subgroup analyses and meta-regression could not identify potential reasons behind the heterogeneity. However, sensitivity analyses showed that one study significantly affected the CVD mortality outcome estimate. Excluding this study reduced the beneficial impact of metformin on CVD mortality from a relative risk of 0.75 to 0.81 and decreased the high heterogeneity to a moderate level.

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, but they did not perform a separate analysis for each CVD outcome or subgroup analysis. 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 can 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 not significantly affect composite CVD outcomes or individual outcomes such as stroke, MI, HF, and MACE. However, our findings suggest a potential reduction in CVD mortality with metformin use, although this result should be interpreted with caution due to high heterogeneity in the analysis. 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).

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.

Supplementary Materials

Figure S1. Forest plot showing Metformin's effect on HF

Figure S2. Forest plot showing Metformin's effect on MACE

Figure S3. Forest plot showing the effect of Metformin on MI

Figure S4. Forest plot showing the effect of Metformin on stroke

Figure S5. Baujat plots of Composite CVD outcome and CVD Mortality

Figure S6. Influencer Analysis of Composite CVD Outcome and CVD Mortality

Figure S7. Leave-one-out analysis of Composite CVD outcome and CVD Mortality

Figure S8. Ghosh plots of Composite CVD outcome and CVD Mortality

Table S1. PRISMA Checklist

Table S2. Inclusion and Exclusion criteria

Table S3. The adjusted search terms as per searched electronic databases

Table S4. Newcastle-Ottawa Scale for assessing the quality of observational studies

Table S5. Cochrane's Risk of Bias tool for assessing quality of RCTs

Table S6. Meta-regression of the potential factors of heterogeneity

References

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119. *[Crossref][PubMed][Google Scholar]*

2. Ma C-X, Ma X-N, Guan C-H, Li Y-D, Mauricio D, Fu S-B. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalised management. Cardiovascular diabetology. 2022;21(1):74. *[Crossref][PubMed][Google Scholar]*

3. Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovascular Diabetology. 2019;18(1):1-16. *[Crossref][PubMed][Google Scholar]*

4. Goel S, Singh R, Singh V, et al. Metformin: Activation of 5′ AMP-activated protein kinase and its emerging potential beyond anti-hyperglycemic action. Frontiers in Genetics. 2022;13. *[Crossref][PubMed][Google Scholar]*

5. Lv Z, Guo Y. Metformin and its benefits for various diseases. Frontiers in endocrinology. 2020;11:191. *[Crossref][PubMed][Google Scholar]*

6. Kaur R, Singh V, Kumari P, Singh R, Chopra H, Emran TB. Novel insights on the role of VCAM-1 and ICAM-1: Potential biomarkers for cardiovascular diseases. Annals of Medicine and Surgery. 2022;84:104802. *[Crossref][PubMed][Google Scholar]*

7. Shabil M, Bushi G, Beig MA, Rais MA, Ahmed M, Padhi BK. Cardiovascular manifestation in Tuberculosis cases: a Systematic review and Meta-analysis. Current Problems in Cardiology. 2023:101666. *[Crossref][PubMed][Google Scholar]*

8. Lee CG, Heckman-Stoddard B, Dabelea D, et al. Effect of metformin and lifestyle interventions on mortality in the diabetes prevention program and diabetes prevention program outcomes study. Diabetes care. 2021;44(12):2775-2782. *[Crossref][PubMed][Google Scholar]*

9. Filion KB, Douros A, Azoulay L, Yin H, Yu OH, Suissa S. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: a population-based cohort study. British Journal of Clinical Pharmacology. 2019;85(10):2378-2389. *[Crossref][PubMed][Google Scholar]*

10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. New England journal of medicine. 2008;359(15):1577-1589. *[Crossref][PubMed][Google Scholar]*

11. Kim M-H, Oh HJ, Kwon SH, et al. Metformin use and cardiovascular outcomes in patients with diabetes and chronic kidney disease: a nationwide cohort study. Kidney Research and Clinical Practice. 2021;40(4):660. *[Crossref][PubMed][Google Scholar]*

12. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomised clinical trials. Diabetes, Obesity and Metabolism. 2011;13(3):221-228. *[Crossref][PubMed][Google Scholar]*

13. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia. 2017;60:1620-1629. *[Crossref][PubMed][Google Scholar]*

14. Xu Z, Zhang H, Wu C, Zheng Y, Jiang J. Effect of metformin on adverse outcomes in T2DM patients: Systemic review and meta-analysis of observational studies. Frontiers in Cardiovascular Medicine. 2022;9. *[Crossref][PubMed][Google Scholar]*

15. Aronow WS, Ahn C. Incidence of new coronary events in older persons with diabetes mellitus and prior myocardial infarction treated with sulfonylureas, insulin, metformin, and diet alone. American Journal of Cardiology. 2001;88(5):556-557. *[Crossref][PubMed][Google Scholar]*

16. Charytan DM, Solomon SD, Ivanovich P, et al. Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. Diabetes, Obesity and Metabolism. 2019;21(5):1199-1208. *[Crossref][PubMed][Google Scholar]*

17. Clegg LE, Jing Y, Penland RC, et al. Cardiovascular and renal safety of metformin in patients with diabetes and moderate or severe chronic kidney disease: Observations from the EXSCEL and SAVOR-TIMI 53 cardiovascular outcomes trials. Diabetes, Obesity and Metabolism. 2021;23(5):1101-1110. *[Crossref][PubMed][Google Scholar]*

18. Goldberg RB, Orchard TJ, Crandall JP, et al. Effects of long-term metformin and lifestyle interventions on cardiovascular events in the diabetes prevention program and its outcome study. Circulation. 2022;145(22):1632-1641. *[Crossref][PubMed][Google Scholar]*

19. Weir DL, Abrahamowicz M, Beauchamp ME, Eurich DT. Acute vs cumulative benefits of metformin use in patients with type 2 diabetes and heart failure. Diabetes, Obesity and Metabolism. 2018;20(11):2653-2660. *[Crossref][PubMed][Google Scholar]*

20. Fonseca V. Adding metformin to insulin did not improve a composite of microvascular and macrovascular disease in type 2 diabetes. Annals of Internal Medicine. 2009;151(4):JC1-12. *[Crossref][PubMed][Google Scholar]*

21. Hartman MH, Prins JK, Schurer RA, et al. Two-year follow-up of 4 months metformin treatment vs. placebo in ST-elevation myocardial infarction: data from the GIPS-III RCT. Clinical Research in Cardiology. *2017;106:939-946 [Crossref][PubMed][Google Scholar]*

22. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Archives of internal medicine. 2009;169(6):616-625. *[Crossref][PubMed][Google Scholar]*

23. Andersson C, Olesen JB, Weeke P, et al. Metformin is Associated With a Low Mortality in Diabetes Patients With Heart Failure. Am Heart Assoc; 2009. . *[Crossref][PubMed][Google Scholar]*

24. Lund SS, Tarnow L, Astrup AS, et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomised study. PLoS One. *2008;3(10):e3363 [Crossref][PubMed][Google Scholar]*

25. Bromage DI, Godec TR, Pujades-Rodriguez M, et al. Metformin use and cardiovascular outcomes after acute myocardial infarction in patients with type 2 diabetes: a cohort study. Cardiovascular Diabetology. 2019;18(1):1-9. *[Crossref][PubMed][Google Scholar]*

26. Preiss D, Lloyd SM, Ford I, et al. Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. The lancet Diabetes & endocrinology. 2014;2(2):116-124. *[Crossref][PubMed][Google Scholar]*

27. Ekström N, Schiöler L, Svensson A-M, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ open. 2012;2(4):e001076. *[Crossref][PubMed][Google Scholar]*

28. Ritsinger V, Lagerqvist B, Lundman P, Hagström E, Norhammar A. Diabetes, metformin and glucose lowering therapies after myocardial infarction: Insights from the SWEDEHEART registry. Diabetes and Vascular Disease Research. 2020;17(6):1479164120973676. *[Crossref][PubMed][Google Scholar]*

29. Fung CSC, Wan EYF, Wong CKH, Jiao F, Chan AKC. Effect of metformin monotherapy on cardiovascular diseases and mortality: a retrospective cohort study on Chinese type 2 diabetes mellitus patients. Cardiovascular Diabetology. 2015;14(1):1-14. *[Crossref][PubMed][Google Scholar]*

30. Wang J, Lu Y, Min X, Yuan T, Wei J, Cai Z. The association between metformin treatment and outcomes in type 2 diabetes mellitus patients with heart failure with preserved ejection fraction: a retrospective study. Frontiers in Cardiovascular Medicine. 2021;8:648212. *[Crossref][PubMed][Google Scholar]*

31. Rachmani R, Slavachevski I, Levi Z, Zadok B-S, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. European Journal of Internal Medicine. 2002;13(7):428-433. *[Crossref][PubMed][Google Scholar]*

32. Yen F-S, Wei JC-C, Chiu L-T, Hsu C-C, Hwu C-M. Cardiovascular outcomes of metformin use in patients with type 2 diabetes and chronic obstructive pulmonary disease. Frontiers in Pharmacology. 2022;13. *[Crossref][PubMed][Google Scholar]*

33. Sillars B, Davis W, Hirsch I, Davis T. Sulphonylurea–metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. Diabetes, Obesity and Metabolism. 2010;12(9):757-765. *[Crossref][PubMed][Google Scholar]*

34. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. bmj. 2016;354. *[Crossref][PubMed][Google Scholar]*

35. Gandhi AP, Satapathy P, Rustagi S, Hermis AH, Sah R, Padhi BK. Comments on" Shigellosis in Southeast Asia: A systematic review and meta-analysis. Travel Medicine and Infectious Disease. 2023 25: 102593-102593. *[Crossref][PubMed][Google Scholar]*

36. Paridari P, Jabermoradi S, Gholamzadeh R, et al. Can metformin use reduce the risk of stroke in diabetic patients? A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2023;17(2):102721. *[Crossref][PubMed][Google Scholar]*

37. Zhang K, Yang W, Dai H, Deng Z. Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: Results from meta-analysis. Diabetes Research and Clinical Practice. 2020;160:108001. *[Crossref][PubMed][Google Scholar]*

38. Schernthaner G, Brand K, Bailey CJ. Metformin and the heart: update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure. Metabolism. 2022 1;130:155160. *[Crossref][PubMed][Google Scholar]*

39. Abbasi F, Chu JW, McLaughlin T, Lamendola C, Leary ET, Reaven GM. Effect of metformin treatment on multiple cardiovascular disease risk factors in patients with type 2 diabetes mellitus. Metabolism. 2004 Feb 1;53(2):159-64. *[Crossref][PubMed][Google Scholar]*

Table 1. Characteristics of included studies

Author	Country, Year	Study design	Participants characteristics	Follow-up (years)	Age (mean/ median)	Male (%)	BMI	HbA1c (%)	Metformin dose	Metformin population	CVD events in Metformin	Metformin CVD mortality	Type of Comparison	Control population	CVD events in control/ placebo	Control mortality	Total population	Type of CVD
Anderson C [23]	Denmark, 2010	Retrospective cohort	Prior HF and T2DM	9	69.5	N/A	N/A	N/A	N/A	688	N/A	109	Insulin	3,718	N/A	1157	1845	CVD death
Aronow WS [15]	USA, 2021	Prospective observational	Older patients with Prior MI and T2DM	2.5	80	37.21	N/A	N/A	N/A	9	MI or CVD death=7	N/A	Diet	77	MI or CVD death=54	N/A	86	MI or CVD death
Bromage DI [25]	UK, 2019	Prospective cohort	Patients with T2DM and acute MI	N/A	71.3	60	23	N/A	N/A	2576	Stroke=294, MI=807, HF=589, MACE=1551	894	No-metformin	1454	Stroke=195, MI=433, HF=313, MACE=899	584	4030	HF, MI, Stroke, CVD death, MACE
Charytan DM [16]	USA, 2019	Subanalysis/Post hoc analysis of Trial	Individuals with diabetes and CKD	5	67	35.83	31.5	6.8	N/A	508	Composite CVD= 101	35	No-metformin	508	Composite CVD= 138	64	1016	Composite CVD events, CVD death
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	62	31.69	7.97	N/A	1745	MACE=233 MI=104 Stroke=49	107	No-metformin	1745	MACE=255, MI=127, Stroke=46	131	3490	MACE, MI, Stroke
Ekström N [27]	Sweden, 2012	Prospective cohort	Patients with T2DM	3.9	65.3	57	29.5	7.3	1100 mg	14697	1734	N/A	Insulin	12291	2389	N/A	26988	Total CVD events
Fonseca V [20]	Netherlands, 2009	Randomised placebo-controlled trial	Patients with T2DM	4.3	61	45	N/A	7.5	850 mg 1–3 times daily	196	Macrovascular= 29	N/A	Placebo	194	Macrovascular= 35	N/A	390	MI, heart failure, acute coronary syndrome, peripheral arterial disease, sudden death
Fung CSC [29]	China, 2015	Retrospective cohort	Patients with T2DM and without any CVD history	5	62	40.69	25.56	6.57	N/A	3400	CHD=81, Stroke=76, HF=34	N/A	no-metformin	3400	CHD=102, Stroke=86, HF=43	N/A	6800	CHD, stroke, HF
Goldberg RB [18]	USA, 2022	Subanalysis/Post hoc analysis of Trial	T2DM, without previous CVD	21	N/A	N/A	34	N/A	850 mg twice daily	1082	Major CVD events=101, Stroke= 16, MI=46	27	Placebo	1073	Major CVD events=98, Stroke= 28, MI=43	39	2155	Major adverse cardiovascular events, MI, Stroke, CVD death
Hartman MH [21]	Netherlands, 2017	Subanalysis/Post hoc analysis of Trial	STEMI diagnosed patients with previous MI and T2DM	2	58	78	N/A	N/A	500 mg twice daily	191	MACE=11, Stroke=1	N/A	Placebo	188	MACE=6, Stroke=1	N/A	379	MACE, Stroke
Hippisley-Cox J [34]	England, 2016	Open cohort study	Patients with T2DM	5.9	64.5	57.35	30.2	7.8	N/A	256024	HF=3334, All CVD=7376	N/A	Insulin	19791	HF=220, All CVD=290	N/A	2,75,815	HF
Kim M-H [11]	Korea, 2021	Retrospective observational	Patients with T2DM and CKD	5.3	66.3	64.7	25.2	N/A	N/A	77666	CHD=4983, Stroke=4369, MACCE=9352		No-metformin	20047	MACCE=2082, CHD=1261, Stroke=821		97713	CHD, stroke, MACCE
Kooy A [22]	Netherlands, 2009	Randomised, placebo-controlled trial	Patients with T2DM	4.3	61.5	45.64	30	7.9	850 mg 1-3 times daily	196	MI= 28 HF=3 Stroke=9	N/A	Placebo	194	MI= 25 HF=4 Stroke=9	N/A	390	MI, HF, Stroke
Lee CG [8]	USA, 2021	Open Label RCT	Patients with T2DM Patients with T2DM	21	50.6	48.4	34	5.9	850 mg twice daily	1073	N/A	44	Placebo	1,082	N/A	38	2155	CVD mortality
Lund SS [24]	Denmark, 2008	Double blind RCT	Patients with T1DM	1	46.1	64	26.2	9.62	N/A	49	2	N/A	Placebo	51	5	N/A	100	MACE

Preiss D [26]	UK, 2013	Double blind, Placebo-controlled trial	Patients with coronary heart disease and without T2DM	1.5	63	76.88	N/A	5.68	850 mg twice daily	86	4	N/A	Placebo	87	6	N/A	173	Non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, unstable angina, or cardiovascular death.
Rachmani R [31]	Israel, 2002	Prospective, randomised observational	Patients diagnosed with T2DM	4	64	53.52	28.7	8.6	N/A	195	MI=51, All cvd events=102	50	No-metformin	198	MI=53, All cvd evens=108	52	383	MI, Total CVD events
Ritsinger V [28]	Sweden, 2020	Prospective observational	Patients with T2DM	3.4	68	70	N/A	N/A	N/A	3982	MACE=947	N/A	Insulin	3091	MACE=986	N/A	70270	MI, Heart failure, stroke
Sillars B [33]	Australia, 2010	Retrospective cohort	Patients with T2DM	10.4	63	49	31.4	7.6	N/A	174	N/A	19	Diet	410	N/A	62	584	CVD mortality
Wang J [30]	China, 2022	Retrospective cohort	T2DM patients with Heart failure with preserved ejection fraction (HFpEF) hospitalised	4	71	42	25.26	7.2	N/A	113	N/A	5	No-metformin	259	N/A	22	372	CVD mortality
Weir DL [19]	USA, 2018	Retrospective observational	T2DM and incident HF	1.7	54	58	N/A	7.5	N/A	3799	Ischemic heart disease= 1522, MI=208	N/A	No-metformin	3821	Ischemic heart disease= 1606, MI=267	N/A	7620	Ischemic heart disease, MI
Yen F-S [32]	Taiwan, 2022	Retrospective cohort	T2DM, COPD with previous HF, CAD, Stroke	12.3	61.5	47.5	N/A	N/A	N/A	55224	HF= 1368, CAD=5251, Stroke=4614, Composited CVD=9236	N/A	No-metformin	55224	HF=2220, CAD=9728 Stroke=6702, Composited CVD= 14806	N/A	110448	Stroke, CAD, heart failure, Composite CVD