LETTER

Effect of anti-diabetic drugs in primary prevention of cardiovascular disease in type 2 diabetes and prediabetes: A systematic review and meta-analysis of randomized trials

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Received: July 2, 2024; Accepted: September 27, 2024; Published Online: October 28, 2024; https://doi.org/10.59717/j.xinn-med.2024.100096

Citation: Zhang Y., Threapleton D., Shi H., et al., (2024). Effect of anti-diabetic drugs in primary prevention of cardiovascular disease in type 2 diabetes and prediabetes: A systematic review and meta-analysis of randomized trials. The Innovation Medicine **2(4)**: 100096.

Dear Editor,

An important adverse consequence of type 2 diabetes (hereafter diabetes) is cardiovascular disease (CVD) and thus an important goal of anti-diabetic drug treatment ought to prevent CVD. Although anti-diabetic drugs are shown effective in preventing CVD events in diabetic patients already with CVD, it is unclear whether the same benefit can extend to those free of CVD.[1] This systematic review of randomized controlled trials (RCTs) aims to address two questions in this regard: is non-insulin anti-diabetic drug treatment, overall, effective in reducing the risk of CVD in diabetic or pre-diabetic patients free of CVD, and are there any factors, particularly baseline CVD risk, which may affect or modify the size of this effectiveness if existent?

STUDY ELIGIBILITY, LITERATURE SEARCH, AND RISK OF BIAS ASSESSMENT

We conducted a systematic literature search up to 20 September 2022 in Medline, Embase, the Cochrane library, and trial registries. Eligible studies were RCTs that compared any non-insulin anti-diabetic drugs (single or in combination) with placebo or no treatment for a minimum of 24 weeks in people with diabetes and/or prediabetes and free of CVD at baseline. Detailed literature search strategy is shown at https://github.com/PelikanM400/XINN-medicine-2024-0099/blob/main/ST1.pdf. The primary outcome of interest was major cardiovascular events, a composite endpoint including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular deaths. Secondary outcomes included all-cause mortality, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and an extended composite cardiovascular endpoint including cardiovascular death, myocardial infarction, stroke, coronary heart disease, coronary artery disease, heart failure, unstable angina, and revascularization. The risk of bias was assessed by using the Cochrane's tool.

STATISTICAL ANALYSIS

The random-effects model was used to combine the treatment effectiveness expressed in the odds ratio (OR) across studies. We conducted predefined subgroup analyses according to baseline CVD risk, baseline glycated hemoglobin (HbA_{1c}), reduction in HbA_{1c} after treatment, diabetic status, type of anti-diabetic drugs, current anti-diabetic treatment at baseline, and duration of treatment to see if they affected the effectiveness. The one-year incidence of major cardiovascular events in the control group was used as a proxy measure of the baseline CVD risk. The incidence of the outcomes was all converted to a one-year rate. The quartile values of the baseline CVD risk ([0.00%~0.03%], (0.03%~0.93%], (0.93%~1.93%], (1.93%~11.01%]), median baseline HbA_{1c}, and median HbA_{1c} reduction were used as the cut-off points to divide studies into subgroups. The association of the treatment effectiveness expressed in the OR with the one-year baseline CVD risk was also demonstrated graphically using the bubble plot and further examined with random-effects meta-regression analyses to assess effect modifiers and to adjust for the effects of potential confounders, namely the subgroup analysis factors. Diabetes status was not included in the model as it was highly correlated with baseline HbA_{1c}.

FINDINGS

A total of 132 eligible RCTs were identified and all included in the analyses. Of these 132 trials, 122 were on people with diabetes, with a median intervention of 26 weeks ranging between 24 weeks and 558 weeks. The remaining 10 trials were on people with prediabetes, with a median intervention of 155 weeks ranging between 56 weeks and 207 weeks. The mean baseline HbA_{1c} level was 8.2% in the trials of diabetic patients and 5.6% in those on prediabetes, and the mean reduction in HbA_{1c} after treatment was 0.7% and 0.1% respectively in the two groups of trials. Major cardiovascular events, the primary outcome of this systematic review, were reported in 110 trials with 80623 participants, and the median one-year baseline CVD risk in these trials was 0.93% ranging from 0.00% to 11.01%. As for secondary outcomes, 68, 90, 83, and 129 trials reported data on all-cause deaths, myocardial infarction, stroke, and the extended composite cardiovascular events, respectively.

Treatment modality evaluated in the eligible trials included single drug therapy, combination therapy, and mixture of the two. Anti-diabetic drugs evaluated in eligible trials included dipeptidyl peptidase 4 (DPP4) inhibitors, metformin, thiazolidinediones, sodium glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists, alpha-glucosidase inhibitors, sulfonylureas and meglitinides. In 98 trials, some participants were already on anti-diabetic medications at baseline. The overall quality of eligible trials was judged as moderate. Details of the trial characteristics and risk of bias assessment results are shown at https://github.com/PelikanM400/XINNmedicine-2024-0099/blob/main/ST2-ST3.pdf.

Meta-analyses of the 110 trials with data on the primary outcome showed that anti-diabetic treatment could on average reduce the risk of major cardiovascular events by 18% (OR = 0.82, 95% CI: 0.70 to 0.97, P = 0.022, I^2 = 0%; median follow-up = 28 weeks ranging between 24 weeks and 558 weeks, Figure 1A). Anti-diabetic drugs also showed a similar and statistically significant protective effect on myocardial infarction, stroke and extended composite CVD events (P ≤ 0.046) but not all-cause mortality (P = 0.224) (Figure 1A).

However, further analyses on the primary outcome showed that the CVD reduction effect of anti-diabetic drugs was statistically significant only in trials with the highest baseline CVD risk group (i.e., ≥ 1.93%): OR = 0.53, 95% CI: 0.40 to 0.71 (Figure 1B). Given the group's median baseline one-year CVD risk of 2.71% and the OR of 0.53, the one-year number-needed-to-treat was estimated to be approximately 79. Taking the one-year baseline CVD risk as a continuous variable, the treatment effectiveness is found to increase continuously and almost linearly as the baseline CVD risk increases (P < 0.001, Figure 1C), implying the baseline risk of 1.93% is not an absolute threshold below which the drugs are certainly ineffective. When the potential confounding factors were controlled for, multivariate meta-regression analyses

A

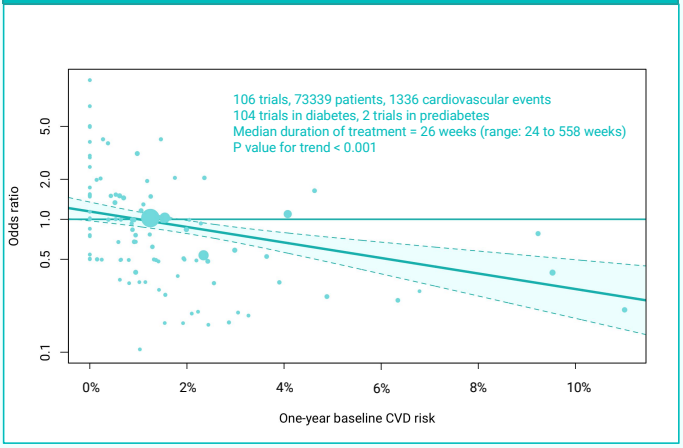
Combined effectiveness of anti-diabetic drugs in preventing major cardiovascular events and secondary outcomes

Outcome	No. of trials	No. of patients	No. of outcome events	Combined OR (95% CI)	P	I^2 (%)
Primary outcome						
Major cardiovascular events*	110	80623	1415	0.82 (0.70 to 0.97)	0.022	0
Secondary outcomes						
All-cause mortality	68	57885	784	0.91 (0.79 to 1.06)	0.224	0
Myocardial infarction	90	71060	684	0.81 (0.66 to 0.98)	0.032	0
Stroke	83	68822	457	0.80 (0.64 to 0.99)	0.046	0
Extended CVD events†	129	77894	1905	0.81 (0.71 to 0.91)	0.001	0

*Including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.
†Including cardiovascular death, myocardial infarction, stroke, coronary heart disease, coronary artery disease, heart failure, unstable angina, and revascularization.

C

Association of the one-year baseline CVD risk with the effectiveness of anti-diabetic drugs in preventing major cardiovascular events



B

Univariate subgroup analysis to identify potential effect modifiers of the effectiveness of anti-diabetic drugs in preventing major cardiovascular events

Potential effect modifiers	No. of trials	No. of patients	No. of outcome events	Combined OR (95% CI)	I^2 (%)	P for between group difference
One-year baseline CVD risk						< 0.001
Lowest: [0.00%~0.03%]	28	15684	48	1.81 (1.01 to 3.26)	0	
Low: (0.03%~0.93%]	27	25122	200	1.02 (0.73 to 1.41)	0	
High: (0.93%~1.93%]	27	27930	780	1.00 (0.86 to 1.15)	0	
Highest: (1.93%~11.01%]	28	11887	387	0.53 (0.40 to 0.71)	0	
Diabetes or prediabetes						0.771
Diabetes	106	69592	1331	0.83 (0.70 to 0.97)	0	
Prediabetes	4	11031	84	0.70 (0.24 to 2.07)	69	
Baseline HbA1c						0.173
Low (baseline HbA1c < 8.1%)	38	23916	381	0.76 (0.57 to 1.01)	0	
High (baseline HbA1c ≥ 8.1%)	68	49423	955	0.95 (0.83 to 1.09)	0	
Reduction in HbA1c						0.023
Small (reduction < 0.6%)	46	37708	924	0.97 (0.85 to 1.12)	0	
Large (reduction ≥ 0.6%)	62	36217	414	0.72 (0.57 to 0.90)	0	
Type of anti-diabetic drugs						0.021
Incretin-based drugs*	64	35786	239	0.86 (0.66 to 1.12)	0	
Sodium/glucose cotransporter 2 inhibitor	26	24280	790	0.98 (0.85 to 1.14)	0	
Thiazolidinedione	4	8154	66	1.46 (0.88 to 2.41)	0	
Other drugs†	5	3366	254	0.62 (0.32 to 1.21)	60	
Combination of different drugs	11	9037	66	0.47 (0.27 to 0.81)	0	
Current anti-diabetic treatment at baseline						0.125
None	19	16095	263	0.66 (0.42 to 1.01)		
Non-insulin anti-diabetic treatments	55	39207	382	0.85 (0.67 to 1.07)		
Insulin	36	25321	770	1.01 (0.87 to 1.17)		
Duration of treatment						0.066
< 1 year	66	35841	184	0.64 (0.47 to 0.87)	0	
≥ 1 year	44	44782	1231	0.90 (0.74 to 1.10)	6	

Abbreviations: CVD, cardiovascular disease; HbA1c, hemoglobin A1c.
*Dipeptidyl peptidase-4 inhibitor and Glucagon-like peptide-1 receptor agonist.
†Other drugs include alpha glucosidase inhibitor, sulphonylureas, metformin, and meglitinides.

D

Multivariate meta-regression analyses to confirm, by adjusting for potential risk factors, the relation between the effectiveness of anti-diabetic drugs in preventing major cardiovascular events and baseline CVD risk (106 trials, 73339 patients, 1336 cardiovascular events)

Potential effect modifiers	Coefficients* (95% CI)	P
One-year baseline CVD risk	0.89 (0.83 to 0.95)	0.001
Baseline HbA1c		
Low (baseline HbA1c < 8.1%)	Reference	--
High (baseline HbA1c ≥ 8.1%)	0.82 (0.52 to 1.29)	0.386
Reduction in HbA1c		
Small (reduction < 0.6%)	Reference	--
Large (reduction ≥ 0.6%)	0.93 (0.62 to 1.41)	0.737
Type of anti-diabetic drugs		
Incretin-based drugs†	Reference	--
Sodium/glucose cotransporter 2 inhibitor	0.92 (0.58 to 1.45)	0.709
Thiazolidinedione	1.70 (0.38 to 7.66)	0.490
Other drugs‡	0.76 (0.43 to 1.35)	0.352
Combination of difference drugs§	0.85 (0.44 to 1.64)	0.625
Current anti-diabetic treatment at baseline		
None	Reference	--
Non-insulin anti-diabetic treatments	1.10 (0.64 to 1.88)	0.728
Insulin	1.40 (0.81 to 2.42)	0.234
Duration of treatment		
< 1 year	Reference	--
≥ 1 year	1.26 (0.82 to 1.91)	0.289

Abbreviations: CVD, cardiovascular disease; HbA1c, hemoglobin A1c.
*Difference in the value of OR for 1% increase in the baseline CVD risk or compared with the reference group.
†Dipeptidyl peptidase-4 inhibitor and Glucagon-like peptide-1 receptor agonist.
‡Other drugs excluding those above-mentioned, including Alpha glucosidase inhibitor, sulphonylureas, metformin, and meglitinides.
§Multiple drugs were used in the intervention group(s).

Figure 1. Effectiveness of anti-diabetic drugs in preventing major cardiovascular events and secondary outcomes (A) Combined overall effectiveness of anti-diabetic drugs in preventing major cardiovascular events and secondary outcomes. (B) Univariate subgroup analysis to identify potential effect modifiers of the effectiveness of anti-diabetic drugs in preventing major cardiovascular events. (C) Association of the one-year baseline CVD risk with the effectiveness of anti-diabetic drugs in preventing major cardiovascular events. (D) Multivariate meta-regression analyses to confirm, by adjusting for potential confounding factors, the relation between the effectiveness of anti-diabetic drugs in preventing major cardiovascular events and baseline CVD risk.

showed that the one-year baseline CVD risk was still an independent and the only independent determinant of the treatment effectiveness (P = 0.001, Figure 1D).

Surprisingly, drug-related reduction in HbA_{1c} and types of anti-diabetic

drugs were not statistically significantly related with the size of the effectiveness of anti-diabetic drugs in reducing the CVD after the potential confounders were adjusted for (Figure 1D) although they were so related in the univariate analyses (Figure 1B). Furthermore, baseline HbA_{1c} and background anti-diabetic treatment were not associated with the effectiveness in both univariate and multivariate analyses (Figure 1B & D). More detailed methods and results are available at https://github.com/PelikanM400/XINN-medicine-2024-0099/blob/main/Supp.pdf.

INTERPRETATIONS

Overall, compared with placebo, pharmacological glucose-lowering treatment can reduce 18% of the risk of major cardiovascular events in patients with diabetes or prediabetes. However, this benefit appears to exist only in patients with a high baseline CVD risk. This phenomenon is similar to what was previously found with dyslipidemia[2] and hypertension,[3] i.e., the effectiveness of drugs in preventing CVD events is mostly determined by the baseline CVD risk of those treated.

However, it was found surprisingly that neither baseline blood glucose nor its reduction due to treatment was associated with the effectiveness when the confounders were adjusted for in the meta-regression analyses. This observation is consistent with previous studies that failed to find a clear effect on clinically important outcomes with intensive glucose-lowering treatment[4,5] and that found baseline HbA_{1c} and baseline FPG were not associated with the effectiveness of metformin.[6] Putting all the evidence together, it seems to suggest that baseline blood glucose and treatment-induced reduction in it alone may not be sufficient to produce an effect on CVD risk. In theory, there is no doubt that the reduction in CVD risk is an effect of anti-diabetic drugs but this effect may rely on the co-presence of other CVD risk factors in high-risk people that may interact with or augment the glucose-reduction effect of anti-diabetic drugs. The finding that the CVD prevention benefit from anti-diabetic drug treatment is determined by the baseline CVD risk rather than baseline blood glucose and its reduction raises important questions about the diagnostic cutoff value of diabetes, patient priority setting for drug treatment, and blood glucose targets for anti-diabetic drug treatment. In fact, these questions have long been raised and substantively discussed for cholesterol-lowering drugs and anti-hypertensive drugs.[2,3] Given that diabetes-related macro-vascular events are more common and severe than severe micro-vascular adverse events,[7] the findings of our study have important implications for guidelines on the diagnosis and drug treatment of diabetes. Our results suggest that assessing CVD risk before deciding on anti-diabetic treatment could make the treatment more precise and cost-effective, thus maximizing the cardiovascular benefits for those receiving treatment. This approach underscores the importance of not only controlling blood glucose but also strategically using anti-diabetic drugs based on individualized CVD risk, thereby enhancing overall cardiovascular benefits.

Having said that, we have to point out that the findings of this study are mostly based on RCTs with a median follow-up of 26 weeks although there are three trials with treatment and follow-up over 3 years and one over 10 years.[8] The results may differ if the treatment and follow-up is extended to 26 weeks or longer. Second, in these trials CVD and death events were mostly considered as adverse events which might affected the accuracy and completeness of data collected on them. Third, the sample size of most included trials is relatively small and many had zero event in one or both comparison groups, making the estimates of the baseline risk and OR likely to be inaccurate and imprecise. Additionally, the lack of significant associations between glucose measures and treatment benefits, as well as the absence of differences in effectiveness among different drugs, might be a result of the small sample size and short follow-up period. For the same reasons, we were unable to stratify the analysis by drug type to assess whether the relationship between treatment effectiveness and baseline CVD risk differs among the various anti-diabetic drugs. As a result, our pooled findings may not fully reflect potential variations in this relationship across different drug types; further studies are warranted to investigate this. Fourth, the average reduction in HbA_{1c} of 0.7% in diabetes and 0.1% in prediabetes observed in this study may be too small to produce a clear effect in all patient groups.

CONCLUSION

We found that the benefit of anti-diabetic drugs in primary prevention of CVD is positively associated with patients' CVD risk (although it might exist only in high-risk patients), but does not appear to be related to baseline blood glucose level and its reduction due to drug treatment. These findings provide important new evidence for defining the diagnostic cutoff value of diabetes, patient priority setting for drug treatment, and blood glucose targets for anti-diabetic drug treatment, in addition to these drugs' effects on notably micro-vascular complications. Given the importance of these issues and the problems of this study, large studies with long duration of treatment are needed to reconfirm the findings of this study.

REFERENCES

1. American Diabetes Association Professional Practice Committee. (2024). 9. Pharmacologic approaches to glycemic treatment: Standards of care in diabetes-2024. Diabetes Care **47**: S158-S178. DOI: 10.2337/dc24-S009.
2. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova, B., Emberson, J., et al. (2012). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. Lancet **380**: 581–590. DOI: 10.1016/S0140-6736(12)60367-5.
3. Blood Pressure Lowering Treatment Trialists' Collaboration, Ying, A., Arima, H., et al. (2015). Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: A meta-analysis of randomised trials. Lancet **385**: 867–874. DOI: 10.1016/S0140-6736(14)61171-5.
4. Boussageon, R., Bejan-Angoulvant, T., Saadatian-Elahi, M., et al. (2011). Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. BMJ **343**: d4169. DOI: 10.1136/bmj.d4169.
5. Rodriguez-Gutierrez, R., Gonzalez-Gonzalez, J.G., Zuñiga-Hernandez, J.A., et al. (2019). Benefits and harms of intensive glycemic control in patients with type 2 diabetes. BMJ **367**: l5887. DOI: 10.1136/bmj.l5887.
6. Lamanna, C., Monami, M., Marchionni, N., et al. (2011). Effect of metformin on cardiovascular events and mortality: A meta-analysis of randomized clinical trials. Diabetes Obes. Metab. **13**: 221–228. DOI: 10.1111/j.1463-1326.2010.01349.x.
7. Zhu, Y.-Y., Yang, Z.-Y., Li, P., et al. (2020). Comparing the incidence of major cardiovascular events and severe microvascular complications in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. World Journal of Meta-Analysis **8**: 400–410. DOI: 10.13105/wjma.v8.i5.400.
8. UK Prospective Diabetes Study (UKPDS) Group. (1998). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet **352**: 854–865. DOI: 10.1016/S0140-6736(98)07037-8.

FUNDING AND ACKNOWLEDGMENTS

This work was partly supported by the Shenzhen Science and Technology Program (grant No. KQTD20190929172835662) and the Strategic Priority Research Program of Chinese Academy of Sciences (grant No. XDB38040200). The sponsors have no role in study design, data collection, data analysis, and results interpretation.

AUTHOR CONTRIBUTIONS

J.T. and Z.Y. conceived and oversaw the research project; literature searching was conducted by Y.Z. and D.T.; article screening was conducted by Y.Z., D.T., H.S., J.Y., M.D., and Y.Y.; data extraction were conducted by Y.Z. and H.S.; the statistical analyses were conducted by Y.Z.; Y.Z. prepared tables and figures for the manuscript; findings were interpreted by J.T., Z.Y., Y.Z., and D.T.; J.T., Z.Y., Y.Z., and D.T. wrote the manuscript and all authors have contributed to the final preparation of the manuscript and provided critical comments. J.T. and Z.Y. are the guarantors for this manuscript.

DECLARATION OF INTERESTS

Jinling Tang is an editorial board member of The Innovation Medicine. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this editorial board member and their research groups. The other authors declare that they have no conflicts of interest.

DATA AND CODE AVAILABILITY

More details can be found at https://github.com/PelikanM400/XINNmedicine-2024-0099/blob/main/README.md.

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