Effects of PCSK9 Inhibitors on Glucose Metabolism in Hyperlipidaemic Patients: A Meta-Analysis

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ABSTRACT

This review assessed the impacts of PCSK9 inhibitors on glucose metabolism in patients with dyslipidaemia. A comprehensive search was conducted using PubMed, Embase, Cochrane Library, and ClinicalTrials.gov to find randomised controlled studies investigating the indicators of glucose metabolism. All RCTs comparing PCSK9 inhibitors with other lipid-lowering drugs or placebo from January 2018 to December 2023 were included. In total, 12 randomised controlled trials were included, and the authors used a fixed-effects model to evaluate the potential impacts of PCSK9 inhibitors on glucose metabolism. Compared with the control group, FPG (MD = 0.08, 95% CI -0.07~0.24) and HbAlc (SMD = 0.02, 95% CI -0.09~0.12) slightly increased in patients treated with PCSK9 inhibitors, with no statistical significance. The PCSK9 inhibitor group also did not exhibit a statistically significant difference in risk between deteriorating pre-existing diabetes (RR = 0.92, 95% CI 0.84-1.01) and developing new-onset diabetes (RR = 0.95, 95% CI 0.86-1.05) from the control group. The results were not affected by the type of PCSK9 inhibitors or treatment duration.

Key Words: *PCSK9 inhibitors, Glucose metabolism, Diabetes mellitus.*

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INTRODUCTION

Globally, cardiovascular diseases (CVDs) are the most prevalent non-communicable illnesses and account for one-third of global deaths annually. One important risk factor for the onset and advancement of atherosclerotic cardiovascular disease (ASCVD) is low-density lipoprotein (LDL-C). According to meta-analyses, there is a 20–23% drop in ASCVD occurrences for every 1 mmol/L decrease in LDL–C.[1,2] Numerous lipid-lowering agents and interventions have been developed, such as statins, cholesterol uptake inhibitors (ezetimibe, *etc*.), and bile acid sequestrants (colestipol, *etc*.), which predominantly lower cholesterol levels. There are also medicines that primarily lower triglyceride levels, such as fibrates (fenofibrate, *etc*.), niacin, and highly purified fish oil preparations.

Proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors are novel lipid-lowering agents targeting hyperlipidaemia and cardiovascular risk. They reduce LDL-C levels by inhibiting PCSK9. PCSK9 was first discovered and proposed by Abifadel *et al*.[3] It is a serine protease that the liver primarily synthesises and releases.

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On human chromosome, close to the third genetic locus, is where its gene is found.[1] PCSK9 and familial hypercholesterolaemia are tightly associated. It primarily attaches to the extracellular structural domain of LDLR, promoting LDLR's lysosomal degradation and raising the amount of LDL-C in the blood. PCSK9 inhibitors can attenuate PCSK9's effects and lower LDL-C levels.[4]

However, a Mendelian randomisation study found that PCSK9 gene variants are associated with increased fasting glucose, weight gain, and increased risk of diabetes,[5] suggesting that PCSK9 inhibitors affect glucose metabolism. The conclusion of previous research regarding the impacts of PCSK9 inhibitors on glucose metabolism remains controversial. De Carvalho *et al*. carried out a pooled analysis of 20 RCTs up to March 2017 and found that compared with placebo, PCSK9 inhibitors caused significantly increased glycosylated haemoglobin (HbA1c) and fasting blood glucose (FBG).[6] Another study analysing studies up to 2018 showed that PCSK9 monoclonal antibody did not significantly lead to new-onset diabetes nor change fasting plasma glucose (FPG) and HbAlc levels.[7]

Recent clinical trials have focused on the changes in FPG and HbAlc in patients using PCSK9 inhibitors or placebo. They also focused on the potential impacts of PCSK9 inhibitors on the development and deterioration of diabetes after treatment with PCSK9 inhibitors. Except for the three well-known PCSK9 inhibitors, including alirocumab, evolocumab, and inclisiran, a new PCSK9 monoclonal antibody, tafolecimab, was approved for marketing in August 2023 by the National Drug Administration (NMPA). Because of inconsistent results and updates in clinical trials, more recent and thorough data is required to evaluate how PCSK9 inhibitors affect glucose metabolism. Therefore,

this study was conducted to analyse the effects of various PCSK9 inhibitors and different therapy durations on the development and deterioration of diabetes and identified the most recent RCTs from January 2018 to December 2023 to provide a more accurate treatment.

METHODOLOGY

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[8] The authors searched PubMed, Cochrane Library, Embase, and the clinicaltrials.gov databases for all original articles from January 2018 to December 2023 to identify all RCTs using PCSK9 inhibitors. The authors used a combination of keywords and MeSH subject terms, including PCSK inhibitors, proprotein convertase subtilisin/kexin Type 9, inclisiran, evolocumab, AMG 145, alirocumab, REGN727, SAR236553, recaticimab, SHR-1209, siRNA, tafolecimab, glucose metabolism disorders, new-onset diabetes, diabetes mellitus, and hyperglycaemia, to identify articles. No language restrictions were considered. Separately, two researchers extracted the data. Arguments were resolved through discussion and review of trial information. When necessary, authors were contacted for clarification. The protocol of this study was registered in PROSPERO (registration number: CRD42023480909).

The inclusion criteria were being an RCT, subjects in the intervention group treated with PCSK9 inhibitors, and the control group treated with other lipid-lowering drugs or placebo trials, trials which measured glycaemic outcome. The trials which measured either pre- and post-treatment HbA1c or FPG levels or number of worsening of diabetes or poor control of diabetes after treatment and any group of patients including poorly controlled or new-onset diabetes. Exclusion criteria were a single-arm trial observational and non-human studies case reports and systematic reviews; agents that have been discontinued after development or shown to be ineffective in clinical studies, e.g., bococizumab, and studies whose data could not be obtained.

Two researchers retrieved the following information: First author, registration number, publication year, number of patients with diabetes, number of participants, patients' characteristics, duration of treatment type, and dose of PCSK9 inhibitors trial, control group treatments, and background lipid-lowering regimen, which were assessed and documented for the results. Any disagreements between the two reviewers regarding screening or data extraction were resolved *via* a group discussion between all team members to reach a final decision. Patients' age, gender, body mass index (BMI), mean FPG, mean LDL cholesterol, and HbAlc were among their baseline data. The number of new-onset diabetes and diabetic exacerbations were tallied, which were often described in the original articles as worsening of Diabetes or diabetes mellitus with inadequate control. If the published paper did not report the outcomes, information was searched on ClinicalTrials.gov, if it was accessible. Two reviewers independently evaluated the risk of bias based on the Cochrane Collaboration tool.[9]

This review was performed using ReMan 5.4 and assessed heterogeneity using the Cochran q-test and I^2 statistic. According to the results of heterogeneity (I^2 <50%), authors used fixed-effects models to analyse the risk of new-onset diabetes and inadequate control of diabetes. For continuous variables, MD was used as the effect size of FPG. Due to the non-uniformity of the unit of measurement of HbAlc, the authors used SMD as the effect size. Subgroups were analysed on the basis of the type of PCSK9 inhibitor and therapy duration.

RESULTS

A database search identified 2,120 publications from January 2018 to December 2023. In total, 12 trials from 11 reports were included.[10-20] The exclusion criteria are shown in Figure 1. Finally, 26,913 participants from 12 trials were enrolled, of which, 9,356 were diabetic (35.4%) and 17,577 were non-diabetic (65.3%). Five trials used alirocumab, 3 trials used evolocumab, 3 trials used inclisiran, and one trial used tafolecimab. Five trials reported baseline FPG levels, 4 trials reported baseline HbAlc levels, 10 trials reported the number of cases with worsened diabetes mellitus or inadequate glycaemic control, and 3 trials provided the number of cases with new-onset diabetes. In the control group, 11 trials used a placebo, and 1 trial used ezetimibe. Table I displays the general features of the studies that were recruited. Participants' average age was 55.3 years, and the follow-up period was 51.5 weeks on average. The experimental and control groups had comparable baseline levels of FPG, HbAlc, and mean L-LDL. Other baseline features of the studies are reported in Table II. The risk of bias was low in most studies (Figure 2).

Four studies reported the changes in HbAlc levels of 1,656 patients from baseline, 1,101 in the intervention group, and 555 in the control group. Since the units were not standardised, SMD was used as the effect size. Figure 3A illustrates the results which indicated that although the change in HbAlc was marginally higher in the PCSK9 inhibitor group than in the control group (SMD = 0.02, 95% CI -0.09 ~ 0.12), it was not statistically significant (p = 0.76). Similarly, comparing the PCSK9 inhibitor group to the control group, there was a minor increase in FPG levels (MD = 0.08, 95% CI -0.07 ~ 0.24, Figure 3B), nevertheless, there was no statistically significant difference between the two groups (p = 0.29).

The incidence of worsening diabetes or inadequate control of diabetes mellitus was measured in 10 trials. Of the 13,852 cases in the PCSK9 inhibitor group, 901 cases experienced deterioration or inadequate management of diabetes. Of 13,027 cases in the control group, 935 experienced deterioration or inadequate control of diabetes. The PCSK9 inhibitor group had a somewhat reduced risk of exacerbation or poor control of pre-existing diabetes than the control group (RR = 0.92, 95% CI 0.84 ~ 1.01, p = 0.07), nonetheless, there was no statistically significant change (Figure 3C). The authors assessed the possibility of publication bias, and the funnel plot was basically symmetrical (Figure 4A), which was verified by the results of Egger's test (Figure 4B). The findings indicated that there was no publication bias (t = -1.98, p = 0.083).

Table I: Features of the research studies included in the meta-analysis.

Trial	Registration number	Year	Number	Diabetes no.	Included population	Treatment intervention	Control	Treatment duration	Background treatment
Odyssey DM-Dyslipidemia Ray *et al.*[10]	NCT02642159	2018	413	413	T2DM with mixed dyslipidaemia	Alirocumab 75 mg / 150 mg Q2W	Usual care	24 weeks	Any statin
Burggraaf *et al.*[11]	NTR6709	2020	12	12	Male patients with T2DM on intensive insulin treatment	Alirocumab 150 mg Q2	Place	6 weeks	NA
Banting Rosenson *et al.*[12]	NCT02739984	2019	421	421	T2DM	Evolocumab 420 mg QM	Placebo	12 weeks	Any statin
Odyssey East Han *et al.*[13]	NCT02715726	2019	615	169	Hypercholesterolaemia	Alirocumab 75 mg / 150 mg Q2W	Ezetimibe	24 weeks	Maximally tolerated statin
Berson Chen *et al.*[14]	NCT02662569	2019	451	451	T2DM with hyperlipidaemia	Evolocumab 420 mg Q4W / 140 mg Q2	Placebo	12 weeks	Stain
Odyssey Outcomes Schwartz *et al.*[15]	NCT01663402	2018	18924	5444	patients with acute coronary syndrome	Alirocumab 75 mg / 150 mg Q2W	Placebo	48 months	High-intensity dose or maximum tolerated stain
Hao *et al.*[16]	-	2022	136	50	diagnosed with ACS and receiving PCI treatment	Evolocumab 140 mg Q2W	Placebo	12 weeks	Stain, ezetimibe
Janik *et al.*[17]	-	2021	2171	1063	Patients with heterozygous familial hypercholesterolaemia (HeFH) or non-FH	Alirocumab 75 mg / 150 mg Q2W	Placebo	96 weeks	Stain
Orion-9 Raal *et al.*[18]	NCT03397121	2020	482	48	Heterozygous familial hypercholesterolaemia	Inclisiran 300 mg at day 1, day 90, then every 6 months	Placebo	18 months	Stain, ezetimibe
Orion-10 Ray *et al.*[19]	NCT03399370	2020	1561	702	Patients with elevated LDL cholesterol concentrations.	Inclisiran 300 mg at day 1, day 90, then every 6 months	Placebo	18 months	Stain, ezetimibe
Orion-11 Ray *et al.*[19]	NCT03400800	2020	1617	568	ASCVD or an ASCVD risk equivalent	Inclisiran 300 mg at day 1, day 90, then every 6 months	Placebo	18 months	Stain, ezetimibe
Credit-1 Huo *et al.*[20]	NCT04289285	2023	614	225	Patients with non-familial hypercholesterolaemia	Tafolecimab 450 mg Q4W, 600 mg Q6W	Placebo	48 weeks	Stain

Table II: Baseline characteristics of patients included in randomised controlled trials.

Trial	Mean age (year)	Males (%)	BMI, mean (kg/m^2)	Mean LDL-C (mmol/L) PCSK9i	Mean LDL-C (mmol/L) control	Fasting plasma glucose (mmol/L) PCSK9i	Fasting plasma glucose (mmol/L)-control	HbA1c (%) PCSK9i	HbA1c (%) control
Odyssey DM-Dyslipidemia	63.2	52.3	32.9	2.9	3.0	8.1	8.2	7.1	7.1
Burggraaf *et al.*	62.6	100.0	32.8	1.9	2.0	8.3	8.6	8.0	8.1
Banting	62.4	56.1	33.3	2.8	2.9	7.7	7.4	7.3	7.2
Odyssey East	58.6	74.8	25.5	2.9	2.9	NA	NA	NA	NA
Berson	58.5	45.0	25.6	2.3	2.2	7.8	7.3	7.5	7.1
Odyssey Outcomes	58.5	74.7	28.5	2.2	2.2	6.0	6.0	6.1	6.1
Hao *et al.*	62.2	68.4	26.0	3.5	3.5	6.8	6.6	NA	NA
Janik *et al.*	63.0	58.2	30.8	3.1	3.1	NA	NA	NA	NA
Orion-9	56.0	47.1	NA	3.9	4.0	NA	NA	5.6	5.6
Orion-10	66.1	70.4	NA	2.6	2.7	NA	NA	6.2	6.2
Orion-11	64.8	71.7	NA	2.8	2.7	NA	NA	6.0	6.0
Credit-1	57.3	67.0	26.7	2.9	2.8	NA	NA	NA	NA

A total of 14,983 patients did not have diabetes at baseline. Among 7,563 patients in the PCSK9 inhibitor, 706 experienced new-onset diabetes. Among 7,420 patients without pre-existing diabetes in the control group, 733 experienced new-onset diabetes. In contrast to the control population, the results demonstrated that PCSK9 inhibitors did not substantially cause new-onset diabetes. (RR = 0.95, 95% CI 0.86 ~ 1.05, p = 0.33, Figure 3D).

Depending on the type of PCSK9 inhibitors, the authors performed a subgroup analysis to measure changes in FPG values after administering the two medicines, alirocumab and evolocumab. The results showed that changes in FPG were greater in the evolocumab subgroup compared with the alirocumab subgroup; however, there was no statistically significant change (evolocumab: MD = 0.01, 95% CI -0.17 ~ 0.19, p = 0.93, alirocumab: MD = 0.29, 95% CI -0.01 ~ 0.59, p = 0.05). Neither of the two PCSK9 inhibitors significantly changed FPG levels compared with the control population (Figure 5A). Similarly, the patients experienced no apparent increase in HbAlc levels after treatment with either alirocumab (SMD = 0.03, 95% CI -0.11 ~ 0.18, p = 0.65) or evolocumab (SMD = 0.00, 95% CI -0.14 ~ 0.14, p = 1.00). Patients treated with alirocumab exhibited greater changes in HbAlc than those treated with evolocumab (p = 0.75, Figure 5B), but there was no statistically significant change.

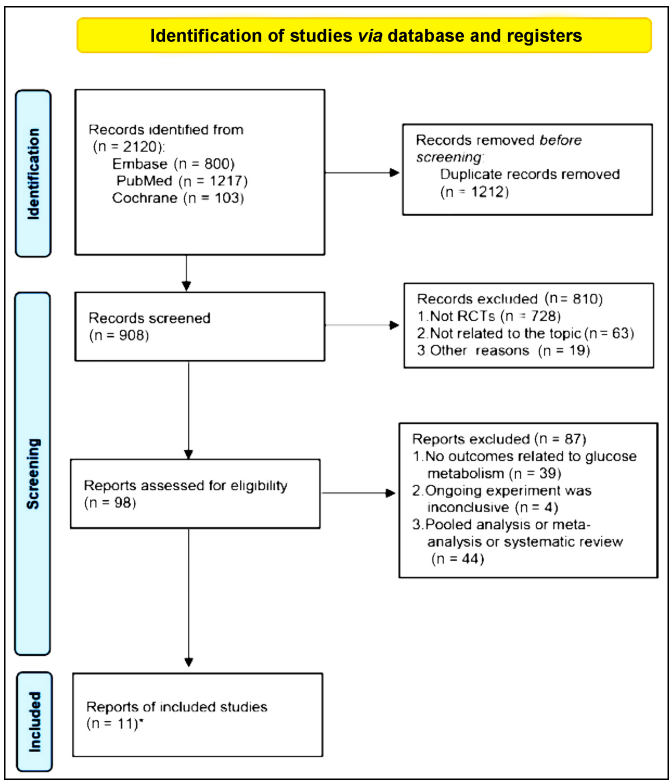

Figure 1: Flow diagram of selection of studies.
These 11 citations included 12 randomised trials.

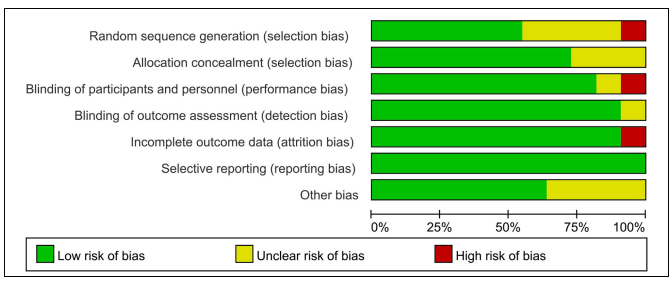

Figure 2: Risk of bias in the included trials.

The authors conducted a subgroup analysis to assess whether the four PCSK9 inhibitors, including alirocumab, evolocumab, inclisiran, and tafolecimab, worsened diabetes or led to poor glycaemic control. According to the findings, the patients' risk of inadequate control of diabetes was slightly lower in the alirocumab and tafolecimab-treated group than in the control group (alirocumab: RR = 0.89, 95% CI 0.76 ~ 1.04, p = 0.16; tafolecimab: RR = 0.95, 95% CI 0.48 ~ 1.86, p = 0.87). In contrast, the risk of poor control of diabetes was slightly higher in patients treated with evolocumab and inclisiran than in the control group (evolocumab: RR = 1.68, 95% CI 0.37 ~ 7.52, p = 0.50; inclisiran: RR = 1.02, 95% CI 0.85 ~ 1.22, p = 0.83) (Figure 5C), but none of these differences were statistically significant.

Analysing the duration of treatment showed that regardless of long-term treatment (MD = 0.33, 95% CI -0.09 ~ 0.24, p = 0.13) or short-term treatment (MD = 0.05, 95% CI -0.12 ~ 0.21, p = 0.59), the changes in FPG were not significantly different contrasted to the control population (Figure 5D).

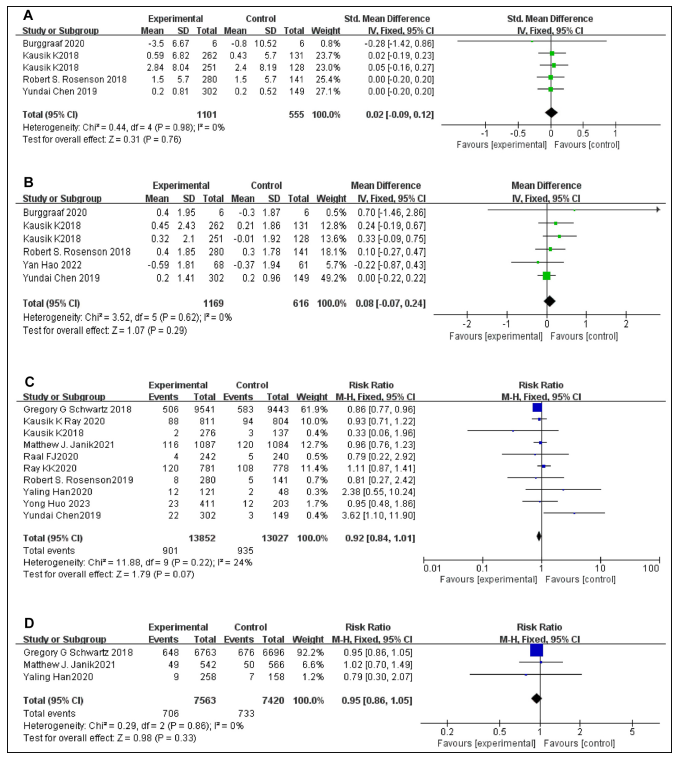

Figure 3: Forest plot. (A) Absolute change in HbAlc. (B) Absolute change in FPG. (C) Worsening of diabetes mellitus. (D) New-onset diabetes mellitus.

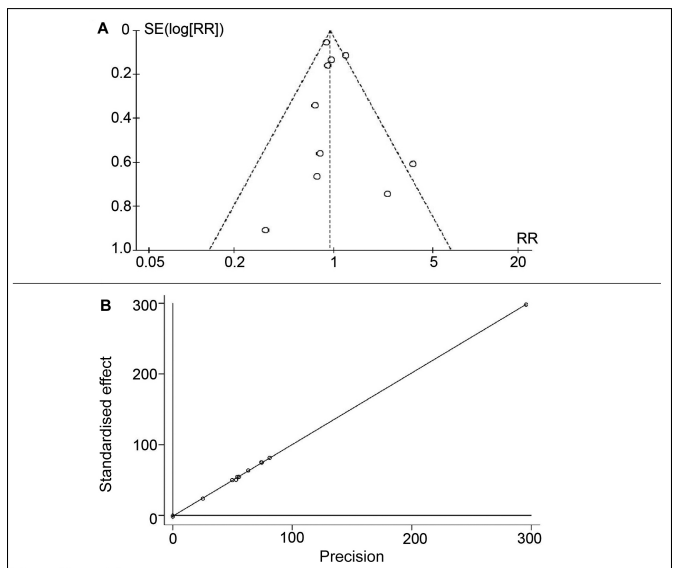

Figure 4: Possibility of publication bias of worsening of diabetes mellitus. (A) Funnel plot analysis. (B) Egger's test.

Likewise, there was no statistically significant variation in HbA1c changes between patients receiving short-term (MD = 0.00, 95% CI -0.11 ~ 0.12, p = 0.94) and long-term treatment (MD = 0.05, 95% CI -0.16 ~ 0.27, p = 0.62) when contrasted with the placebo group (Figure 5E).

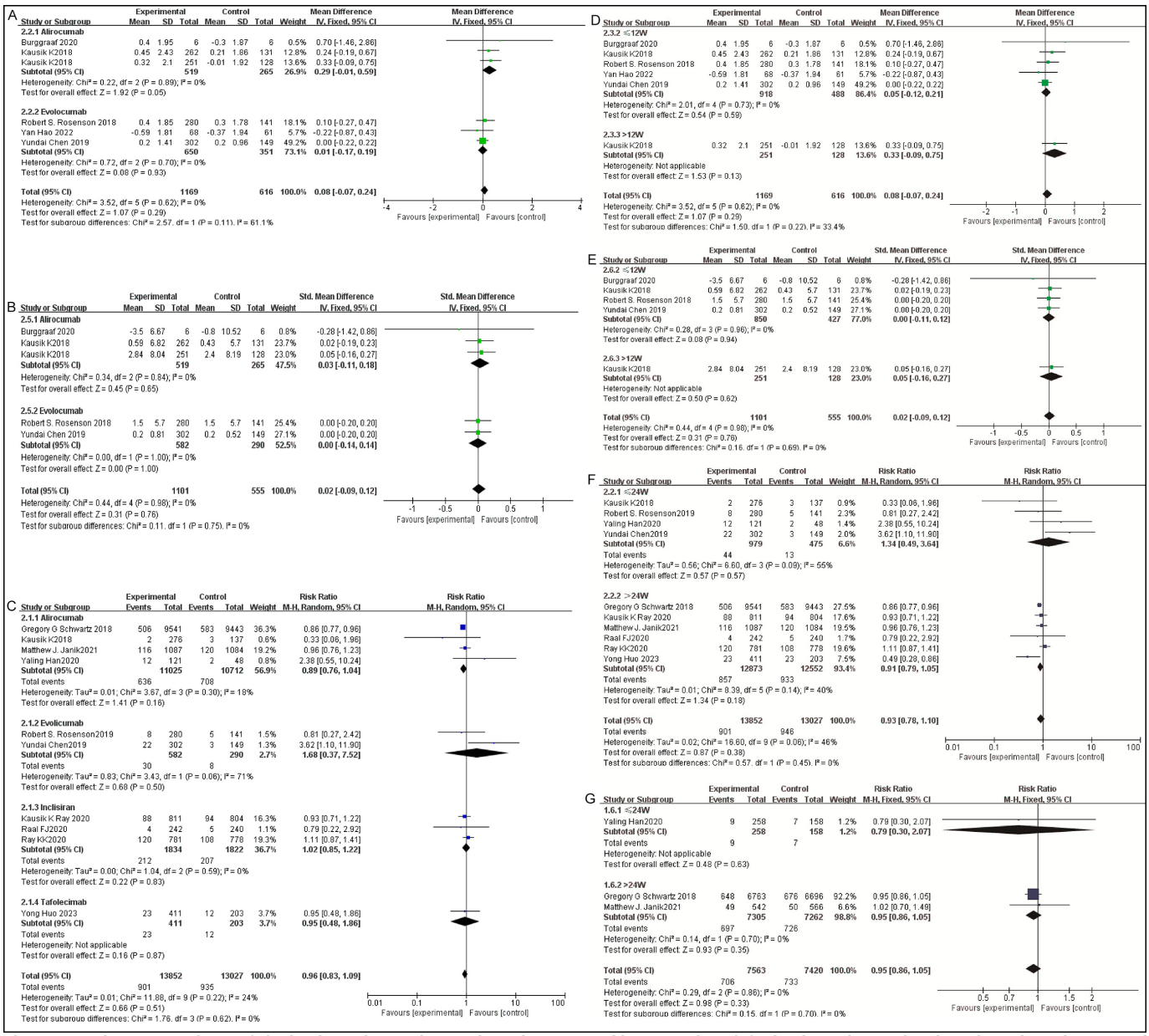

Figure 5: Subgroup analyses. (A) Absolute change in FPG based on type of intervention. (B) Absolute change in HbAlc based on the type of intervention. (C) Worsening of diabetes mellitus based on the type of intervention. (D) Absolute change in FPG based on follow-up duration. (E) Absolute change in HbAlc based on follow-up duration. (F) Worsening of diabetes mellitus based on follow-up duration. (G) New-onset diabetes mellitus based on follow-up duration.

Patients receiving short-term treatment had a slightly greater incidence of poorly controlled diabetic mellitus than the control group (RR = 1.34, 95% CI 0.49 ~ 3.64, p = 0.57), but it was not significantly different. Long-term therapy recipients were marginally less likely than the control population to have poorly controlled diabetes, but this difference was not of statistical importance (RR = 0.91, 95% CI 0.79 ~ 1.05, p = 0.18, Figure 5F). Tests for subgroup differences: p = 0.70, I^2 = 0.0% were conducted to assess whether receiving short-term or long-term treatment was connected with an increased likelihood of new-onset diabetes, showing that the difference was not statistically significant (Figure 5G).

DISCUSSION

This updated meta-analysis with 9,566 diabetic and 17,851 non-diabetic patients from January 2018 to December 2023 showed that PCSK9 inhibitors did not increase FPG and HbAlc levels contrasted to the control population, confirming the findings of combined analysis of 10 Odessey phase III clinical trials.[21] In addition, PCSK9 inhibitors did not worsen diabetes in patients with pre-existing diabetes, nor did they contribute to the development of diabetes in non-diabetic patients. The results were independent of the type of PCSK9 inhibitor and the duration of treatment. These results were in line with those reported by Cao *et al*. in a pooled analysis of trials to December 2017.[22]

Statins combined with therapeutic lifestyle changes are the cornerstone of achieving LDL goals,[23] reducing LDL-C levels by up to 30-50% and effectively reducing the risk of ASCVD.

A large-sized clinical study measuring the effect of statins on blood glucose was published in the JAMA subseries in 2021, which showed that statin therapy increased blood glucose and the prevalence of new-onset diabetes. Moreover, the intensity of statin use was positively associated with the risk of diabetes progression.[24] Pooled analyses of previous clinical research by Sattar *et al*. and Casula *et al*. also clarified that statins elevated blood glucose levels.[25,26] The METSIM study confirmed that statin therapy significantly reduced the insulin sensitivity of patients, which may explain the potential mechanism through which statins contribute to new-onset diabetes.[27] However, the underlying mechanisms have not yet been fully elucidated and deserve more studies. It is crucial to figure out whether PCSK9 inhibitors, which possess greater lipid-lowering properties than statins, increase blood glucose levels and raise the possibility of diabetes. The GLAGOV research by Nicholls *et al*. demonstrated that treatment with evolocumab for 76 weeks significantly increased FPG levels in comparison to the control population.[28] One explanation may be that PCSK9 inhibition increases the number of LDLRs, through which cholesterol enters the pancreatic β-cells, leading to cholesterol overload in pancreatic β-cells and inhibiting glucose-mediated insulin release.[29] These alterations finally elevate blood glucose levels. However, this latest clinical trial meta-analysis from the last few years showed that PCSK9 inhibitors slightly but not significantly elevate blood glucose levels. PCSK9 inhibitors also did not raise the chance of new-onset diabetes or poor control of pre-existing diabetes. Subgroup analyses showed no statistically significant difference in the effect of PCSK9 inhibitors on blood glucose between different durations of treatment. Although further studies and longer duration of clinical trials are needed to elucidate whether PCSK9 inhibitors can lead to new-onset diabetes or worsen blood glucose control, there is no doubt that their lipid-lowering effect provides benefits that far outweigh their impact on blood glucose.

Cardiovascular disease is considerably more common in those with diabetes[30] therefore, strict lipid control is needed to reduce the risk of cardiovascular diseases. PCSK9 inhibitors are currently the most effective lipid-lowering agents, and as demonstrated by numerous large clinical trials, PCSK9 inhibitors can greatly lower non-high-density lipoprotein cholesterol (non-HDL-c) levels.[31,32] Furthermore, numerous studies have found that PCSK9 inhibitors can partly decrease the chance of cardiovascular diseases in diabetic patients.[33,34] So far, four PCSK9 inhibitors have been approved by the FDA and introduced to the market, including alirocumab, evolocumab, inclisiran, and tafolecimab. A subgroup analysis of these four different PCSK9 inhibitors was conducted which found that different types of PCSK9 inhibitors could not significantly change blood glucose levels nor deteriorate blood glucose control in patients with pre-existing diabetes. Thus, PCSK9 inhibitors can be actively used in patients with Diabetes to decrease the chance of cardiovascular diseases. At the same time, the risk for developing diabetes mellitus is not increased by PCSK9 inhibitors and they can be used in individuals with dyslipidaemia who do not have diabetes.

There were certain limitations to this study. First, the maximum follow-up time of these included trials was 48 months. Thus, longer follow-up times are required in future RCTs to evaluate the effect of PCSK9 inhibitors on blood glucose. The 2022 FOURIER open-label extension (NCT02867813, NCT03080935) provided longer-term data on the effect of PCSK9 inhibitors on glycaemic control.[35] This trial, with a median follow-up of 5.0 years, reported that the incidence of new-onset diabetes was similar in the experimental and control groups. There was no incremental trend toward the incidence of new-onset diabetes with increasing follow-up time. At the end of the FOURIER study, the incidence of new-onset diabetes in patients using evolocumab was not higher than that of patients in the placebo group. Still, further RCTs with longer follow-up periods are required. Second, there was an imbalance in the distribution of background lipid-lowering treatments between the PCSK9 inhibitor and the control group. Third, inclusion of studies in this meta-analysis was limited. There are some investigational PCSK9 inhibitors, such as the anti-PCSK9 monoclonal antibody recaticimab (SHR-1209) for which specific experimental data are not available. The results of its phase III clinical trial, REMAIN-2 (NCT04885218), were presented orally at the 2023 American Heart Association Annual Scientific Sessions (AHA 2023). Furthermore, a novel oral form of PCSK9 inhibitor, MK0616, has completed its phase II clinical trial (NCT05261126).[36] Injectable PCSK9 inhibitors can slightly increase the risk of serious reactions at the injection site;[37] therefore, oral formulations are more likely to improve safety and convenience.

In addition to monoclonal antibodies, small interfering RNAs, and oral PCSK9 inhibitors, many PCSK9 targeting agents, such as PCSK9 vaccines and small molecule drugs, are being developed. Future studies should provide more data on the impacts of various kinds of PCSK9 inhibitors on blood glucose. Finally, the included RCTs probably had a publishing bias, since positive outcomes are more likely to be published. More RCTs concentrating on glucose metabolism are needed.

CONCLUSION

This meta-analysis of 12 RCTs, including 9,566 diabetic and 17,851 non-diabetic patients, exhibited no statistically significant association between different types of PCSK9 inhibitors and glucose metabolism. PCSK9 inhibitors do not increase the risk of new-onset diabetes nor worsen the control of pre-

existing diabetes independent of treatment duration. Clinically, they can be actively used in lipid-lowering therapy for diabetic or non-diabetic patients.

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COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YB, MH: Searching and selecting the studies.
YB, JZ: Analysing and interpreting data for work.
LZ: Designing the work and revising the article critically for important intellectual content.
All authors approved the final version of the manuscript to be published.

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