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Efficacy and Safety of Henagliflozin in Chinese Adults with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and aims: Henagliflozin (SHR3824) is a novel sodium–glucose cotransporter-2 (SGLT2) inhibitor approved in China for type 2 diabetes mellitus (T2DM). Its efficacy and safety relative to placebo have not been quantitatively synthesized. We addressed this gap with a systematic review and meta-analysis**.**

Methods: We searched PubMed, Embase, Web of Science, Scopus, ClinicalTrials.gov, the Cochrane Library, and the Chinese Clinical Trial Registry through June 2026 for randomized controlled trials comparing henagliflozin with placebo in adults with T2DM. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane RoB 2 tool. The primary outcome was change in glycated hemoglobin (HbA1c). Random-effects meta-analysis was performed in Review Manager 5.4, and certainty of evidence was rated with GRADE.

Results: Three RCTs (n = 1,077; all conducted in Chinese adults) met the inclusion criteria. Henagliflozin reduced HbA1c by 0.8% versus placebo (95% CI: −0.93 to −0.63; I^2 = 65%; moderate-certainty evidence). Fasting plasma glucose, postprandial plasma glucose, body weight, and systolic and diastolic blood pressure were also significantly improved. Overall adverse events did not differ between groups (RR 1.06, 95% CI: 0.96 to 1.17; low-certainty evidence).

Conclusions: In Chinese adults with T2DM, henagliflozin produced glycemic, weight, and blood-pressure benefits consistent with the SGLT2 inhibitor class effect, with a short-term safety profile comparable to placebo. Larger and longer trials in diverse populations are needed to confirm cardio-renal benefits and long-term safety.

Keywords*:* Adverse events; Glycemic control; Glycated Hemoglobin; Henagliflozin; Diabetes Mellitus, Type 2; Sodium-glucose co-transporter-2 inhibitors.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a major global health burden driven by peripheral insulin resistance and progressive pancreatic beta-cell dysfunction [1–3]. Beyond hyperglycemia, T2DM drives microvascular and macrovascular complications and reduces life expectancy [4–6]. Despite expanding pharmacotherapy, durable glycemic control remains difficult to achieve [7], and contemporary management has moved toward agents with pleiotropic metabolic, cardiovascular, and renal benefits [8].

The kidney, long underappreciated in diabetes care, is now recognized as a key effector organ in glucose homeostasis. Beyond fluid and electrolyte balance, renal gluconeogenesis contributes meaningfully to endogenous glucose production, and the proximal tubule reabsorbs nearly all filtered glucose [9]. In insulin-resistant states both processes become maladaptive: renal gluconeogenesis rises and sodium–glucose cotransporter-2 (SGLT2) is upregulated, driving excessive glucose reabsorption and hyperglycemia [10,11]. This understanding provided the mechanistic rationale for SGLT2 inhibitors as a therapeutic class [12].

Henagliflozin (SHR3824) is a novel, highly selective SGLT2 inhibitor [13]. By inhibiting SGLT2 in the S1 segment of the proximal tubule, henagliflozin lowers the renal threshold for glucose excretion and induces insulin-independent glucosuria. These pharmacodynamic effects translate into reductions in glycated hemoglobin (HbA1c) and improvements in body weight, blood pressure, and other cardiometabolic parameters in early-phase trials [14,15].

Despite this mechanistic rationale and growing clinical use in China, the available randomized evidence for henagliflozin has not been quantitatively synthesized or rated for certainty using GRADE. A formal evidence synthesis is needed to inform clinicians and regulators outside China [16,17,18].

We therefore conducted a systematic review and meta-analysis of randomized controlled trials comparing henagliflozin with placebo in adults with T2DM, evaluating efficacy on HbA1c and cardiometabolic outcomes, safety on adverse events, and certainty of evidence using GRADE.

2 Methods

2.1 Protocol and Reporting Standards

We conducted this systematic review and meta-analysis in accordance with the PRISMA 2020 statement and the Cochrane Handbook for Systematic Reviews of Interventions [19,20], following a protocol prospectively registered in PROSPERO (CRD420251173385).

The protocol was amended after registration to add GRADE-based assessment of evidence certainty; the amendment was logged before any analysis was performed.

2.2 Search Strategy

We searched PubMed, Embase, Web of Science, Scopus, ClinicalTrials.gov, Chinese Clinical Trial Registry (ChiCTR; https://www.chictr.org.cn) and the Cochrane Library for relevant trials from inception to June 2026. Search terms included combinations of “henagliflozin,” “SHR3824,” “type 2 diabetes.” The strategy for PubMed database was ((henagliflozin) or (SHR3824) or (SHR-3824)) and ((diabetes mellitus) or (type 2 diabetes) or (T2DM)).

2.3 Eligibility Criteria (PICOS)

We included RCTs satisfying the following inclusion criteria in our systematic review:

Population: studies on adults (≥18 years) with T2DM.

Intervention: studies where the intervention group received Henagliflozin (5 mg or 10 mg).

Comparator: studies where the control was a placebo or the standard of care.

Outcomes: studies reporting any of the following outcomes were included:

Primary: Change in HbA1c.

Secondary: FPG, PPG, body weight, systolic and diastolic blood pressure, adverse events.

Study Design: Studies described as RCTs.

2.4 Screening and Study Selection Process

We used Rayyan for semi-automated screening of literature search results [21]. Studies were screened in two phases. The first phase is title/abstract screening for potential clinical studies. In the second phase, we retrieved the full text of selected studies for further eligibility criteria screening. We resolved disagreements through discussion.

2.5 Data Extraction

Two reviewers extracted and reviewed data independently on study characteristics, participant demographics, intervention details, and outcomes. Discrepancies were resolved through discussion.

2.6 Risk of Bias Assessment

Two reviewers independently assessed risk of bias using the Cochrane RoB 2 tool, evaluating the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting; disagreements were resolved by discussion [22].

2.7 Statistical Analysis

Random-effects meta-analysis using the DerSimonian–Laird estimator was performed in Review Manager 5.4 [23]. Continuous outcomes were summarized as mean differences (MD) and dichotomous outcomes as risk ratios (RR), each with 95% confidence intervals. Heterogeneity was quantified with the I^2 statistic and interpreted per the Cochrane Handbook (0–40% low; 30–60% moderate; 50–90% substantial; 75–100% considerable). A pre-specified subgroup analysis compared the 5-mg and 10-mg henagliflozin doses. For trials reporting medians and interquartile ranges, we estimated means and standard deviations using the methods of Wan et al. (BMC Med Res Methodol 2014).

2.8 Certainty of Evidence (GRADE)

Certainty of evidence for each outcome was assessed using the GRADE approach [24], considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. RCT evidence started at high certainty and was downgraded according to these domains.

3 Results

3.1 Literature Search and Study Characteristics

Database searches identified 225 records, of which 83 were duplicates. After title and abstract screening of 142 records, 40 full-text articles were assessed for eligibility and 37 were excluded with reasons (Supplementary Table 1). Three placebo-controlled RCTs (n = 1,077) satisfied the inclusion criteria and were included in the qualitative and quantitative synthesis (**Fig**. **1**). Trial duration ranged from 12 to 24 weeks. Baseline characteristics were balanced between the henagliflozin and placebo groups (Tables 1 and 2).

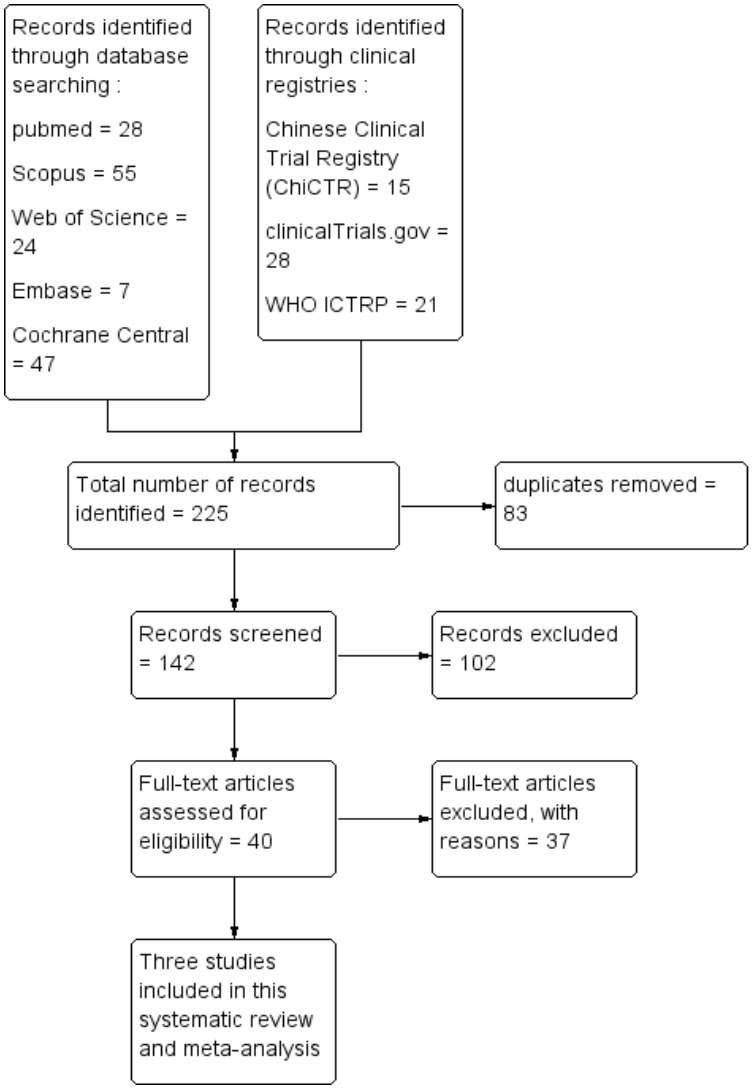


Fig. 1 PRISMA Flow Diagram

Table 1. Summary of included studies

Study Id	Location	Population	Intervention	Control	Outcomes	Study Design
Zhang 2025	China	Middle-aged to older adults with T2DM with evidence of metabolic/aging biomarker elevation (e.g., elevated IL-6 ≥ 2pg/mL).	Henagliflozin 10 mg.	Placebo	Change in aging and metabolic biomarkers (eg., Telomere length, IL-6, TNF-alpha, mitochondrial function markers), Change in HbA1c.	Randomized, double-blind, placebo-controlled mechanistic-trial.
Weng 2021	China	Adults with T2DM inadequately controlled.	Henagliflozin 5 mg and 10 mg as add-on therapy to metformin.	Placebo	Change in HbA1c (%) from baseline to Week 24 Change in FPG, PPG, Body Weight, SBP/DBP- % achieving HbA1c <7%- and safety outcomes.	Phase 3 trial RCT included a 24-week period, followed by a 28-week extension period.
Lu 2021	China	Adults with T2DM who were drug-naïve or had discontinued oral antidiabetic drugs for ≥8 weeks before screening.	Henagliflozin 5mg and 10 mg.	Placebo	Change in HbA1c (%) from baseline to Week 24 Change in FPG, PPG, Body Weight, SBP and DBP. Proportion achieving HbA1c<7%- Safety outcomes.	Phase 3 RCT included a 24-week period, followed by a 28-week extension period

Abbreviations: DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; IL-6: interleukin-6; PPG: postprandial plasma glucose; RCT: randomized controlled trial; SBP: systolic blood pressure; T2D: type 2 diabetes; TNF-α: tumor necrosis factor-alpha.

Table 2. Baseline characteristics of included randomized controlled trials.

Study Id	Group	N	Age mean ± SD	Gender(male)	Body weight (kg)	BMI (kg/m2)	Hba1c%	FBG mmol/l	SBP mmHg	DBP mmHg	eGFR ml/min
Zhang 2025	Henagliflozin10 mg	69	51.78 ± 9.37	46 (66.7%)	72.41 ± 11.95	27.38 ± 4.12	8.01 ± 0.75	8.95 ± 1.76	-	-	99.23 ± 14.39
	Placebo	73	51.67 ± 8.60	51 (69.9) M	73.06 ± 11.09	28.15 ± 4.31	8.09 ± 0.72	9.10 ± 1.74	131.12 ± 14.80	81.60 ± 10.37	102.19 ± 13.36
Weng 2021	Henagliflozin 5 mg	162	54.3 ± 9.5	103 (63.6%)	69.8 ± 11.7	25.5 ± 2.9	8.5 ± 0.8	10.0 ± 2.0	126.8 ± 13.7	78.3 ± 9.6	125.4 ± 31.3
	Henagliflozin 10 mg	160	54.7 ± 10.7	101 (63.1%)	70.2 ± 12.0	25.6 ± 3.2	8.4 ± 0.9	10.0 ± 2.0	127.3 ± 12.1	79.2 ± 8.7	128.9 ± 32.6
	Placebo	161	55.3 ± 9.5	93 (57.8%)	68.9 ± 11.2	25.4 ± 3.1	8.5 ± 0.9	9.8 ± 2.0	127.4 ± 13.6	79.1 ± 9.3	128.0 ± 34.1
Lu 2021	Henagliflozin 5 mg	150	53.3 ± 9.6	88 (58.7%)	70.1 ± 12.5	25.4 ± 3.1	8.59 ± 0.89	9.90 ± 2.05	123.6	78.2	120 ± 32
	Henagliflozin 10 mg	151	52.2 ± 9.4	115 (76.2)	70.4 ± 11.8	25.5 ± 3.1	8.59 ± 0.91	9.88 ± 2.17	122.8	78.3	122 ± 31
	Placebo	151	52.4 ± 10.2	100 (66.2%)	71.6 ± 10.6	26.0 ± 2.9	8.63 ± 0.89	9.83 ± 2.01	123.7	78.2	124 ± 30

Abbreviations**:** BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; SD: standard deviation; SBP: systolic blood pressure.

3.2 Risk of Bias Assessment

Two reviewers independently performed RoB 2 assessment. Risk of bias was low to moderate across most domains, with all trials reported as double-blind. The Zhang 2025 trial was rated high risk in two domains (Incomplete outcome data and selective reporting), while the other two trials were judged low risk overall. Domain-level judgments are presented as a traffic-light plot in Supplementary Figure 1.

3.3 Primary Efficacy Outcome (change in HbA1c)

Henagliflozin reduced HbA1c by 0.8% (–8.4 mmol/mol) compared with placebo (95% CI: –0.93 to –0.63; p <

0.001).

Heterogeneity was substantial (I^2 = 65%, p = 0.02; Fig. **2**).

GRADE certainty: moderate.

Test for subgroup differences (5 mg vs 10 mg) was not significant (p = 0.52), suggesting no additional glycemic benefit from the higher dose.

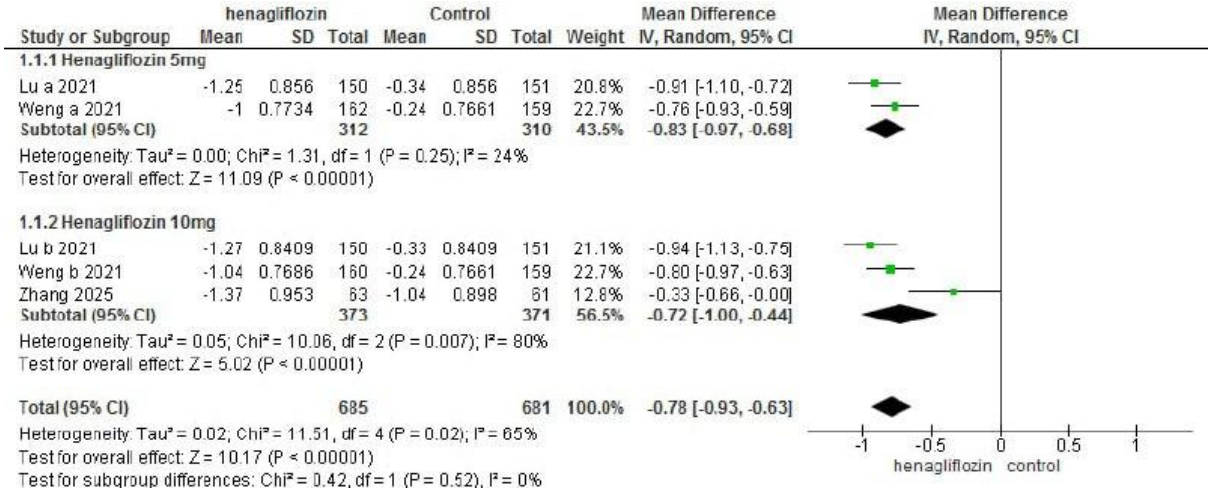


Fig. 2 Forest plot of mean change in HbA1c comparing henagliflozin versus placebo.

3.4 Primary Safety Outcomes (Adverse events)

Overall adverse events did not differ between henagliflozin and placebo (RR 1.06, 95% CI: 0.96 to 1.17; p = 0.22).

Heterogeneity was moderate (I^2 = 58%, p = 0.05; **Fig. 3**).

GRADE certainty: low.

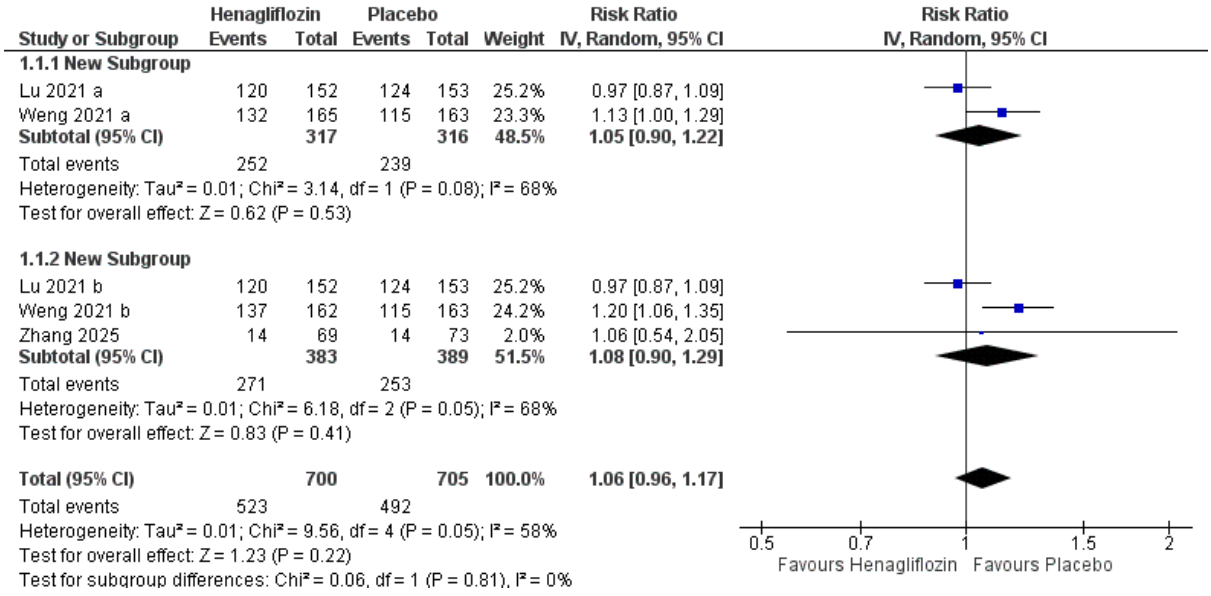


Fig. 3 Forest plot of Adverse Events comparing henagliflozin with placebo.

3.5 Secondary Outcomes

Henagliflozin significantly improved all secondary efficacy outcomes versus placebo: fasting plasma glucose (MD = -1.84 mmol/L, 95% CI: -2.09 to -1.58 for 5mg subgroup and -1.64 mmol/L, 95% CI: -2.45 to -0.84 for 10mg subgroup), postprandial plasma glucose (MD = -2.91 mmol/L, 95% CI: -3.32 to -2.50 for 5mg subgroup and -2.71 mmol/L, 95% CI: -3.12 to -2.30 for 10mg subgroup), body weight (MD = -1.28 kg, 95% CI: -1.61 to -0.95 for 5mg subgroup and -1.37 kg, 95% CI: -1.69 to -1.05 for 10mg subgroup), systolic blood pressure (MD = -4.83 mmHg, 95% CI: -6.39 to -3.27 for 5mg subgroup and -5.40 mmHg, 95% CI: -6.91 to -3.89 for 10mg subgroup), and diastolic blood pressure (MD = -2.45 mmHg, 95% CI: -3.59 to -1.31 for 5mg subgroup and -2.37 mmHg, 95% CI: -3.42 to -1.31 for 10mg subgroup); heterogeneity was low to moderate (Supplementary Figures 2–6).

Serious adverse events, treatment discontinuation, genital infections, urinary tract infections, and hypoglycemia did not differ significantly between groups (Supplementary Figures 7–14).

No outcome showed a significant difference between the 5-mg and 10-mg henagliflozin subgroups. (Supplementary Tables 2 and 3)

3.6 GRADE assessment of the certainty in evidence

GRADE-rated certainty was moderate for HbA1c, ranged from moderate to low for other efficacy outcomes, and ranged from very low to low for safety outcomes (Table 3).

3.7 Publication Bias

Assessment of publication bias using funnel plots or statistical tests was not performed due to the small number of included studies (<10), in accordance with Cochrane recommendations.

Table 3. GRADE Summary of Findings: Henagliflozin vs Placebo in Adults with Type 2 Diabetes Mellitus

Outcome	No. of studies (RCTs)	Participants (n)	Effect estimate (95% CI)	Certainty of evidence (GRADE)	Explanation
HbA1c (%)	3	1,077	MD −0.8%, -8,4 mmol/mol (−0.93 to −0.63)	**Moderate** ⊕⊕⊕◯	Downgraded one level Inconsistency (I-square=65%)
Fasting plasma glucose (mmol/L)	3	1,077	MD −1.71 (−2.10 to −1.32)	**Low** ⊕⊕◯◯	Downgraded inconsistency (I-square=65%) and imprecision
Postprandial plasma glucose (mmol/L)	2	924	MD −2.81 (−3.15 to −2.47)	**Moderate** ⊕⊕⊕◯	Downgraded for imprecision due to the limited number of reporting studies
Body weight (kg)	3	1,077	MD −1.33 (−1.61 to −1.05)	**Moderate** ⊕⊕⊕◯	Downgraded for short study duration.
Diastolic blood pressure (mmHg)	3	1,077	MD −2.41 (−3.18 to −1.63)	**Moderate** ⊕⊕⊕◯	Downgraded for indirectness (short-term outcomes only)
Overall adverse events	3	1,077	RR 1.06 (0.96–1.17)	**Low** ⊕⊕◯◯	Downgraded for imprecision and short follow-up
Hypoglycemia	2	924	RR 2.42 (0.80–7.28)	**Low** ⊕⊕◯◯	Wide confidence intervals; low event rate
Genital infections	2	924	RR 4.72 (0.54–41.28)	**Very low** ⊕◯◯◯	Very low event rate; extreme imprecision
Diabetic ketoacidosis	3	1,077	RR 1.46 (0.23–9.22)	**Very low** ⊕◯◯◯	Rare events

GRADE Interpretation Key

- **High (⊕⊕⊕⊕):** Very confident that the true effect lies close to the estimate
- **Moderate (⊕⊕⊕◯):** True effect likely close to estimate but may differ
- **Low (⊕⊕◯◯):** True effect may be substantially different
- **Very low (⊕◯◯◯):** Very little confidence in the effect estimate

4 Discussion

This systematic review and meta-analysis shows that henagliflozin improves glycemic control and selected cardiometabolic parameters in Chinese adults with T2DM. The HbA1c reduction we observed (–0.8%) is consistent with class-wide effects reported for empagliflozin (approximately –0.6 to –0.7%), dapagliflozin (approximately –0.5 to –0.7%), and canagliflozin (approximately –0.7 to –0.9%), supporting a class-consistent glucose-lowering effect [25–28].

The substantial heterogeneity in HbA1c ($I^2 = 65\%$) likely reflects clinical and methodological differences among the included trials. HbA1c is influenced by baseline glycemic control, duration of diabetes, background therapies, and follow-up length, all of which varied. Because HbA1c reflects average glycemic exposure over several months, short trials may underestimate the steady-state effect.

Study design heterogeneity also contributed. The Zhang et al. trial was a mechanistic study focused on aging biomarkers, recruiting participants with elevated aging biomarkers rather than conventional glycemic endpoints; this design may partly explain its outlying treatment effect.

Safety outcomes were comparable between henagliflozin and placebo. However, short follow-up and low event rates left the analyses underpowered to detect rare but clinically important signals — diabetic ketoacidosis, lower-limb amputation, Fournier's gangrene, and volume depletion — and GRADE certainty ranged from moderate to very low across safety outcomes.

Larger and longer randomized trials in broader and more representative populations are needed to establish the long-term safety and effectiveness of henagliflozin.

None of the included trials were designed or powered to assess cardiovascular or renal outcomes — the principal long-term value proposition of the SGLT2-inhibitor class. Class-effect inferences from EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, DAPA-HF, EMPEROR-Reduced, CREDENCE, and DAPA-CKD provide a biologically plausible but unproven basis for cardio-renal benefit with henagliflozin. A dedicated cardiovascular outcome trial is the key missing evidence.

All included trials enrolled Chinese adults, limiting external validity. East Asian patients with T2DM differ phenotypically from Western patients in body habitus (lower BMI), beta-cell reserve (earlier failure), and dietary carbohydrate exposure, all of which may modify SGLT2 inhibitor efficacy and the urinary/genital infection signal. Confirmatory trials in non-Chinese populations are needed before clinical recommendations can be generalized.

5 Strengths and Limitations

This systematic review and meta-analysis had several important strengths. First, the study protocol was prospectively registered in PROSPERO, which enhances methodological transparency and reduces the risk of selective reporting. Second, the review was conducted in accordance with PRISMA 2020 guidelines and the Cochrane Handbook for Systematic Reviews of Interventions, ensuring adherence to internationally recognized methodological standards. Third, only the randomized controlled trials were included, which strengthens the internal validity of the findings and reduces confounding compared with observational evidence. Additionally, the certainty of evidence was formally assessed using the GRADE framework, providing a structured evaluation of the reliability and clinical applicability of the findings.

Several limitations should be acknowledged. First, only three randomized trials were available, restricting statistical power and generalizability.

Second, follow-up was short (12–24 weeks), limiting inference about long-term efficacy and safety. Third, moderate to substantial heterogeneity was observed for several outcomes, reflecting differences in trial design, populations, and background therapy. Fourth, the analyses were underpowered to detect rare but clinically important adverse events such as diabetic ketoacidosis, lower-limb amputation, Fournier's gangrene, and genitourinary infection. Fifth, all trials enrolled Chinese adults, limiting external validity to other ethnic and geographic populations. Finally, no dedicated cardiovascular or renal outcome trial of henagliflozin has been completed; class-effect extrapolation from other SGLT2 inhibitors should be considered hypothesis-generating only.

6 Clinical Implications

Henagliflozin offers an additional option for glycemic control in adults with T2DM and may produce modest weight and blood-pressure benefits. Until cardio-renal outcome data are available, the choice of henagliflozin

over established SGLT2 inhibitors with proven cardio-renal efficacy (empagliflozin, dapagliflozin, canagliflozin) cannot be recommended on the basis of long-term outcomes.

7 Conclusion

In Chinese adults with T2DM, henagliflozin significantly improves glycemic control and selected cardiometabolic parameters compared with placebo, with a short-term safety profile comparable to placebo. Heterogeneity, short follow-up, and a single-population evidence base reduce the certainty of these findings. Larger and longer trials in diverse populations — and a dedicated cardiovascular outcome trial — are needed to establish the long-term and cross-population value of henagliflozin.

8 Declarations

8.1 Funding

No funding was received for this study.

8.2 Conflict of Interest

The authors declare that they have no conflicts of interest.

8.3 Ethical Approval

This article was based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

8.4 Consent to Participate

Not applicable.

8.5 Consent for Publication

All authors approved the final manuscript and consented to publication.

8.6 Acknowledgments

None.

8.7 Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

8.8 Code Availability

Not applicable.

8.9 Authors' Contributions

Mohamed Ahmed: Conceptualization, Methodology, Eligibility criteria development, Study screening, Data extraction and data analysis, Writing – review & editing.

Mohamed Emadeldin: Protocol development and submission, Data extraction, Writing – review & editing.

Moamen Salah: Protocol submission, Data extraction.

Ahmed Adel: Data analysis, Study screening.

Hamed Elsayed: Writing – original draft preparation,

Study screening.

Rehab Khaled: Study screening, Writing – supplementary material.

Abdulhamid Shaban: Writing – original draft preparation, review & editing.

Al-Hassan Kandeel: Writing – original draft preparation, Writing – review & editing.

Aya Kheiarelseed: GRADE certainty assessment, Writing – original draft preparation.

All authors conducted a critical review of the manuscript and provided their approval.

8.10 Use of AI tools

During preparation of this manuscript, the authors used ChatGPT (OpenAI; version GPT-4; accessed [June 2026]) for language editing and to assist with preliminary literature screening. No artificial intelligence tool was used to generate study data, perform statistical analyses, draft scientific arguments, or make editorial decisions about included studies. The authors reviewed and verified all AI-assisted content and take full responsibility for the final manuscript.

9 References

[1] Genitsaridi I, Salpea P, Salim A, Sajjadi SF, Tomic D, James S, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050. Lancet Diabetes Endocrinol 2026;14:149–56. https://doi.org/10.1016/S2213-8587(25)00299-2.

[2] Lu X, Xie Q, Pan X, Zhang R, Zhang X, Peng G, et al. Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Signal Transduct Target Ther 2024;9:262. https://doi.org/10.1038/s41392-024-01951-9.

[3] Dludla PV, Mabhida SE, Ziqubu K, Nkambule BB, Mazibuko-Mbeje SE, Hanser S, et al. Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. World J Diabetes 2023;14:130–46. https://doi.org/10.4239/wjd.v14.i3.130.

[4] Arnold SV, Khunti K, Tang F, Chen H, Cid-Ruzafa J, Cooper A, et al. Incidence rates and predictors of microvascular and macrovascular complications in patients with type 2 diabetes: Results from the longitudinal global discover study. Am Heart J 2022;243:232–9. https://doi.org/10.1016/j.ahj.2021.10.181.

[5] Zhang Y, Yang R, Hou Y, Chen Y, Li S, Wang Y, et al. Association of cardiovascular health with diabetic complications, all-cause mortality, and life expectancy among people with type 2 diabetes. Diabetol Metab Syndr 2022;14:158. https://doi.org/10.1186/s13098-022-00934-6.

[6] Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018;379:633–44.

https://doi.org/10.1056/NEJMoa1800256.

[7] American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Suppl 1):S181–S206. https://doi.org/10.2337/dc25-S009.

[8] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022;65:1925–66. https://doi.org/10.1007/s00125-022-05787-2.

[9] Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. Diabetes Care 2001;24:382–91. https://doi.org/10.2337/diacare.24.2.382.

[10] Meyer C, Woerle HJ, Dostou JM, Welle SL, Gerich JE. Abnormal renal, hepatic, and muscle glucose metabolism following glucose ingestion in type 2 diabetes. Am J Physiol Endocrinol Metab 2004;287:E1049-56. https://doi.org/10.1152/ajpendo.00041.2004.

[11] Alsahli M, Gerich JE. Renal glucose metabolism in normal physiological conditions and in diabetes. Diabetes Res Clin Pract 2017;133:1–9. https://doi.org/10.1016/j.diabres.2017.07.033.

[12] Chen LH, Leung PS. Inhibition of the sodium glucose co-transporter-2: its beneficial action and potential combination therapy for type 2 diabetes mellitus. Diabetes Obes Metab 2013;15:392–402. https://doi.org/10.1111/dom.12064.

[13] Yong X, Wen A, Liu X, Liu H, Liu Y-P, Li N, et al. Pharmacokinetics and Pharmacodynamics of Henagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, in Chinese Patients with Type 2 Diabetes Mellitus. Clin Drug Investig 2016;36:195–202. https://doi.org/10.1007/s40261-015-0366-7.

[14] Lu J, Fu L, Li Y, Geng J, Qin L, Li P, et al. Henagliflozin monotherapy in patients with type 2 diabetes inadequately controlled on diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Obes Metab 2021;23:1111–20. https://doi.org/10.1111/dom.14314.

[15] Weng J, Zeng L, Zhang Y, Qu S, Wang X, Li P, et al. Henagliflozin as add-on therapy to metformin in patients with type 2 diabetes inadequately controlled with metformin: A multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Obes Metab 2021;23:1754–64. https://doi.org/10.1111/dom.14389.

[16] Filion KB, Lix LM, Yu OH, Dell'Aniello S, Douros A, Shah BR, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ 2020;370:m3342. https://doi.org/10.1136/bmj.m3342.

[17] Zhang J, Cai W, Liu D, Zheng N, Wang Y, Qiu F, et al. Effect of henagliflozin on aging biomarkers in patients with type 2 diabetes: A multicenter, randomized, double-blind, placebo-controlled study. Cell Rep Med 2025;6:102331. https://doi.org/10.1016/j.xcrm.2025.102331.

[18] Teng Y, Fan X, Yu R, Yang X. Evaluation and comparison of efficacy and safety of tirzepatide, liraglutide and SGLT2i in patients with type 2 diabetes mellitus: a network meta-analysis. BMC Endocr Disord 2024;24:278. https://doi.org/10.1186/s12902-024-01805-z.

[19] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:n71. https://doi.org/10.1136/bmj.n71.

[20] Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.

[21] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.

[22] Sterne JAC, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

[23] Cochrane Collaboration. Review Manager (RevMan) [computer program]. Version 5.4. London: The Cochrane Collaboration; 2020.

[24] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6. https://doi.org/10.1136/bmj.39489.470347.AD.

[25] Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab 2013;15:1154–60. https://doi.org/10.1111/dom.12185.

[26] Laffel LM, Danne T, Klingensmith GJ, Tamborlane WV, Willi S, Zeitler P, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. Lancet Diabetes Endocrinol 2023;11:169–81. https://doi.org/10.1016/S2213-8587(22)00387-4.

[27] Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled,

phase 3 trial. Diabetes Care 2010;33:2217–24. https://doi.org/10.2337/dc10-0612.

[28] Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15:372–82. https://doi.org/10.1111/dom.12054.

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