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Effect of metformin on the clinical outcomes of stroke in patients with diabetes: a systematic review and meta-analysis

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ABSTRACT

Objectives Stroke is a major cause of death and disability globally, especially among diabetic patients. In this study, we aim to scrutinise the effects of metformin on the clinical outcomes of stroke in diabetic patients.

Design This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources PubMed, Embase and Web of Science databases were searched between their inception and 5 December 2023.

Eligibility criteria for selecting studies Studies investigating the effect of metformin on the clinical outcomes of stroke in patients with diabetes were included.

Data extraction and synthesis The effect of metformin on the clinical outcomes of stroke in patients with diabetes was identified using combined ORs and 95% CIs.

Results A total of 11 studies involving 18 525 participants were included in this review. Pooled analysis has demonstrated that prestroke metformin use could reduce the probability of poor course after stroke by 34% in diabetes mellitus (DM) patients (OR=0.66, 95% CI: 0.61 to 0.72) and reduce the probability of death by 43% (OR=0.57, 95% CI: 0.51 to 0.64).

Conclusions Prestroke metformin use is beneficial for the improvement of clinical outcomes in patients who had a stroke with DM, although the potential bias should be carefully considered.

PROSPERO registration number CRD42024496056.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The effect of metformin on the clinical outcomes of stroke in patients with diabetes was identified using combined ORs and 95% CIs.
⇒ This study was processed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was prospectively registered on PROSPERO.
⇒ Most of the included studies were retrospective, which is likely to increase the risk of confirmation bias, making it difficult to confirm causality.
⇒ The frequency and duration of metformin use may be influence on the results, but this information was not adequate for consideration in this study, because few included studies provided this information.

INTRODUCTION

Stroke, ischaemic or haemorrhagic, is one of the primary causes of mortality and morbidity in the world.[1] Globally, the annual number of strokes and deaths due to stroke increased substantially from 1990 to 2019, particularly among people older than 70 years.[2] An estimated 17.8 million adults in China had experienced a stroke in 2020, with 3.4 million experiencing their first-ever stroke and another 2.3 million dying as a result.[3] In Europe, the prevalence of stroke was 9.2%, and the incidence was 191.9 per 100 000 person-years.[4] In the USA, stroke mortality trends increased by 0.5% annually from 2012 through 2020 based on the national mortality data.[5] Despite advances in therapy, the clinical outcome for patients with stroke is still unfavourable. A large prospective observational study showed that the 5-year mortality rate after stroke was 51.7%.[6] The in-hospital mortality was 1.9% for stroke inpatients, and the 12-month fatality rate was 8.6%.[7] In light of this, it is crucial to identify in advance neuroprotective agents that can reduce neurological severity and improve clinical outcomes in stroke.

Disorders of glucose metabolism, highly prevalent and growing worldwide, are well-recognised risk factors for stroke, including type 1 and 2 diabetes mellitus (DM) and prediabetes.[8] These disorders are very common among patients who had a stroke: 28% have prediabetes, and 25% to 45% have DM.[9] Additionally, an association between DM and increased mortality, length of hospital stay and poorer functional outcomes after stroke has also been demonstrated.[10–13] To decrease the disparity between patients who had a stroke with DM and without, much attention,

to date, were paid to the influence of antidiabetic agents on the severity of stroke and acute-phase outcomes in DM patients. Metformin, the first-line antidiabetic drug, improves energy metabolism and reduces oxidative stress, leading to an improved balance of survival and death signalling in neurons.[14] A meta-analysis that included 21 studies with 1 392 809 patients demonstrated that metformin monotherapy is effective in reducing stroke risk, but combined administration of metformin with other antihyperglycaemic agents has no significant effect on stroke prevention in DM.[15] Besides serving as protective factors for stroke, metformin may also be related to the clinical outcomes of stroke. Animal experiments showed that metformin plays a neuroprotective role in stroke and improves clinical outcomes triggered by stroke.[16 17] In recent years, clinical studies have examined the effects of metformin on stroke outcomes, with some evidence that metformin pretreatment is associated with less severe strokes, improved functional outcome and lower mortality.[18 19] In contrast, several studies showed that metformin use is not associated with in-hospital mortality and 1-year prognosis in diabetic intracerebral hemorrhage (ICH) patients.[20 21] In the context of existing inconsistencies between studies, the benefits of prestroke metformin use for improving the clinical outcome of stroke remain controversial.

In order to obtain insight into the issue mentioned above, we, in this study, searched for relevant published studies and performed a meta-analysis to scrutinise the effects of metformin on stroke outcomes.

METHODS

This study was processed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was prospectively registered on PROSPERO (CRD42024496056).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Literature search strategy

We systematically searched PubMed, Embase and Web of Science databases for studies published from inception to 5 December 2023. The search strategy divided by each database is provided in online supplemental material 1. In addition to database searches, we hand-searched the reference sections of included studies in the full-text review and undertook forward and backward citation tracking to find further eligible studies. All search results were imported into EndNote (X9), with any duplicates removed.

Eligibility criteria and study selection

The exposure of interest was the prestroke metformin use, and the primary outcome was the clinical outcome of stroke. Studies meeting the following criteria were included in this study: (1) reported the effect of prestroke metformin use on the outcomes of patients with stroke; (2) included patients with diabetes; (3) the sample size was beyond 10; (4) the report was not a review, comment, case report or letter; and (5) full-text articles were available, with no limit to the type of study designs. We did not place limitations on its country of origin, nor did we limit the age or gender of the included patients.

Data extraction

First, two authors independently performed a screening of articles by reviewing titles and abstracts. Second, the full text of potentially eligible articles was retrieved, and relevant articles were assessed based on inclusion criteria. Any discrepancy between two authors was resolved by consensus or by consulting a third author. The following data from included studies were extracted: first author, study title, publication year, country, study design, sample size, patient demographics (ie, gender distribution and mean/median age) and clinical outcomes (functional outcome and death). Where articles reported the outcome at multiple time points, the longest follow-up one was selected. The functional outcome after stroke was graded using a modified Rankin Scale (mRS) score ranging from 0 (no symptoms) to 6 (death). The mRS score was used to classify functional outcome as good course (score of 0–2) or poor course (score of 3–6).

Quality assessment

The quality of each included study was assessed using an eight-item modified version of the Newcastle-Ottawa Scale (NOS) for observational studies.[22] This scale estimates the quality of each study through three perspectives: the selection of sample, the comparability of groups and the ascertainment of outcome (details were displayed in online supplemental material 2). Two authors independently scored each study on every item in the scale. The higher the score, the better the methodological quality of the study.

Statistical analysis

All statistical analyses were performed using the R software V.4.0.2, and a two-sided p value of 0.05 or less was considered statistically significant. Data were recorded as the number of events in metformin use and non-metformin use groups. The pooled OR and 95% CI were calculated. This study used I^2 statistics and χ^2 test to evaluate between-study heterogeneity, with I^2>50% or p<0.10, indicating obvious heterogeneity; a random-effects model was used to evaluate the pooled results; otherwise, the fixed-effects model was applied. Publication bias was visually assessed using funnel plots and quantified by Egger's test. Additionally, sensitivity analysis of the pooled ORs was conducted by omitting one study in each turn to estimate the impact of an individual study on the pooled results. A series of subgroup analyses and meta-regressions according to region, publication year, study

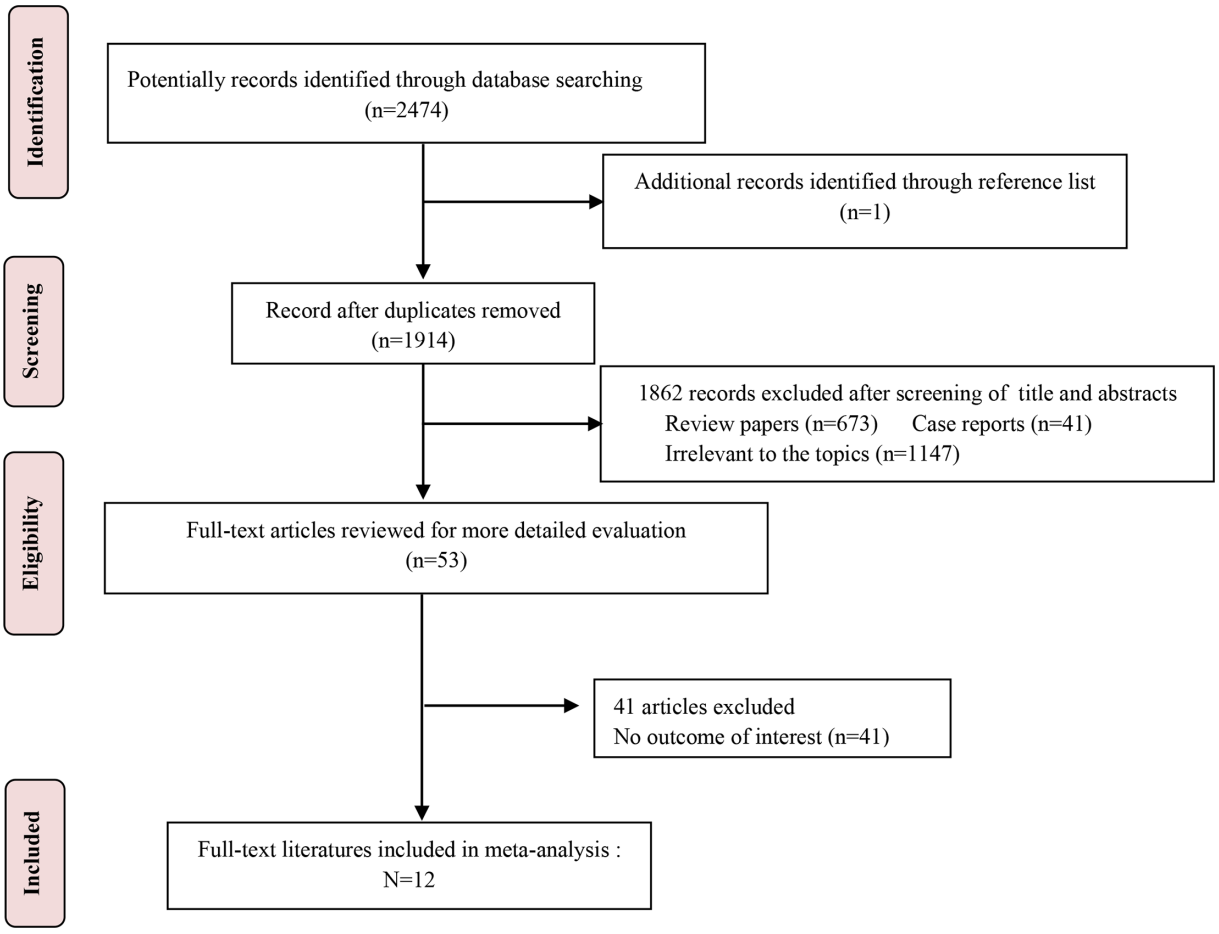

Figure 1 Flow diagram to illustrate the study selection procedure.

design, the type of stroke, follow-up duration and sample size were performed to explore the potential sources of heterogeneity, and the pooled ORs between subgroups were compared using the χ^2 test.

RESULTS

Study characteristics

A flow chart describing the selection of articles identified, included and excluded, with reasons, is presented in figure 1. The search in the databases resulted in 1913 non-duplicate articles, 1852 of which were excluded after the screening of the titles and abstracts. The full text of the remaining 52 articles was retrieved and reviewed. Finally, the data from 11 articles were included in this study.[18–21 23–29] One study was included through a manual review of reference lists.[30] Nine studies were retrospective cohort studies, and three were prospective cohort studies. Nine studies reported the functional outcome, and eight articles the survival status (whether the patients had died or not). The eligible articles involved a total of 18 664 patients, 7386 of which were with prestroke metformin use. The articles enrolled patients from a diverse range of geographical locations and ethnic populations. Detailed information on the included studies is summarised and presented in table 1.

Quality assessment

10 included studies scored 7 or above on the NOS checklist (online supplemental material 2), while two studies scored 6. This indicates that all included studies were of at least moderate quality. All patients who met the inclusion criteria in the specific region were consecutively recruited within a certain period and were divided into two groups according to metformin or non-metformin use prior to stroke, ensuring the representativeness and comparability of groups. The ascertainment of metformin use was clearly described in six studies.[18 21 26–28 30] All the included studies had a follow-up longer than 3 months to determine the functional outcome or survival status of the patients, except for two studies that reported discharge outcome only.[25 28]

Effect of prestroke metformin use on prognosis of stroke

The effect of prestroke metformin use on the improvement of functional outcomes after stroke was assessed in nine cohort studies. Figure 2 shows the comparison of functional outcomes between patients with prestroke metformin use and patients without, with individual and pooled ORs with corresponding CIs. Individual ORs ranged from 0.49 (95% CI: 0.24 to 0.97) to 0.87 (95% CI: 0.72 to 1.05), and pooled analysis showed that prestroke metformin use could reduce the probability of poor

Table 1 Characteristics of included studies

Author	Year	Country	Sample size	N (metformin/ control)	Design	Age	Stroke type	Outcomes
Horsdal *et al*	2012	Denmark	3841	563/3278	PCS	MET+: 71.2 (63–79)	Ischaemic stroke	30 days, 1 year
Kuwashiro *et al*	2012	Japan	241	19/222	RCS	71±10	Ischaemic stroke	3 months
Mima *et al*	2016	Japan	355	77/278	RCS	70.1±10.6	Ischaemic stroke	Discharge
Wu *et al*	2016	Multiple	374	148/226	RCS	68 (60–76)	ICH	90 days
Westphal *et al*	2020	European	1919	757/1162	RCS	MET+: 71, MET−: 74	Ischaemic stroke	3 months
Tu *et al*	2021	China	730	281/449	RCS	65 (56–72)	ICH	Discharge, 1 year
Akhtar *et al*	2022	Qatar	2157	1132/1025	RCS	54.5±13.1	Ischaemic stroke	Discharge, 90 days
Curro *et al*	2022	Italy	139	69/70	PCS	NR	Ischaemic stroke	3 months
Kersten *et al*	2022	Netherlands	937	592/345	RCS	MET+: 75 (10), MET−: 76 (11)	Ischaemic stroke	3 months
Tu *et al*	2022	China	7587	3593/3994	PCS	66 (57–73)	Stroke	Discharge, 1 year
Akiyama *et al*	2023	Japan	160	55/105	RCS	MET+: 75, MET−: 73	Ischaemic stroke	Discharge
Jian *et al*	2023	China	224	94/130	RCS	MET+: 64 (54–71), MET−: 65 (56–74)	Ischaemic stroke	90 days

NR, not reported; PCS, prospective cohort study; RCS, retrospective cohort study.

course after stroke by 34% in DM patients (OR=0.66, 95% CI: 0.61 to 0.72, p<0.001). The application of χ^2 test and I^2 statistic showed that no significant heterogeneity existed among studies (p=0.06, I^2=47%), and a fixed-effects model was applied.

Also, eight studies with a total of 15 908 patients reported the difference in survival status between patients with or without prestroke metformin use. The comparison of survival status between patients with prestroke metformin use and those without is presented in figure 3, with individual and pooled ORs with corresponding CIs. Individual ORs ranged from 0.16 (95% CI: 0.02 to 1.33) to 0.73 (95% CI: 0.47 to 1.13), and the pooled analysis indicated a 43% reduction in the probability of death after stroke (OR=0.57, 95% CI: 0.51 to 0.64, p<0.001). There was also no

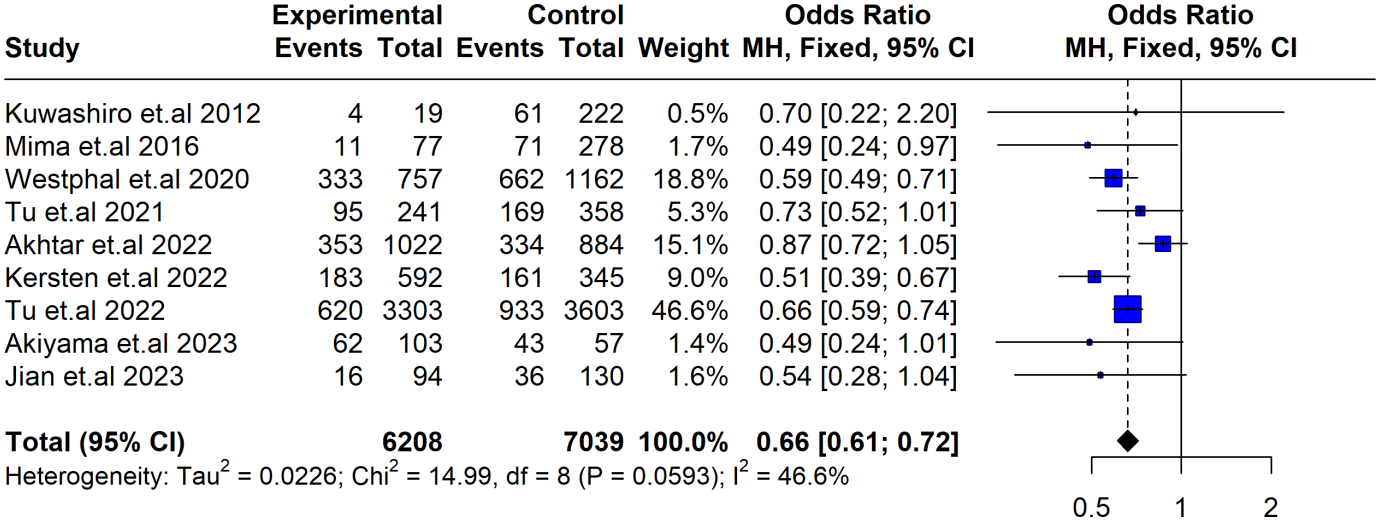

Figure 2 Forest plot for functional outcomes between patients with metformin use and patients without.

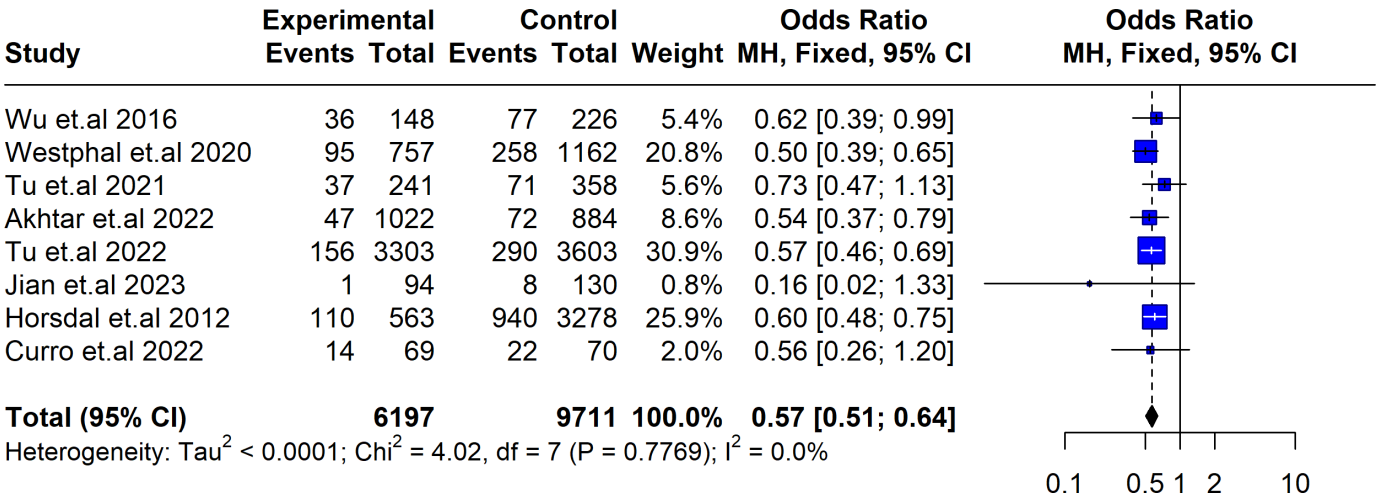

Figure 3 Forest plot for survival status between patients with metformin use and patients without.

significant heterogeneity among studies (p=0.78, I^2=0%), and a fixed-effects model was performed.

Subgroup and sensitivity analysis

The results of subgroup analysis showed that there are no significant differences across different subgroups except for region (online supplemental material 3). Meta-regression was performed for both the two outcomes (functional outcome and survival status). None of the subgroups were significant for studies reporting the association between metformin use and clinical outcomes after stroke; hence, a multivariable meta-regression was not attempted. The results of sensitivity analysis showed that the pooled OR was steady, and removing one study did not change the significance of the pooled OR. For functional outcome, the pooled OR ranged from 0.63 (0.57–0.68) to 0.68 (0.62–0.74); and for survival status, the pooled OR ranged from 0.56 (0.50–0.63) to 0.59 (0.52–0.67). The details are listed in online supplemental material 4.

Publication bias

Publication bias in the included studies was assessed by using Egger's test and a funnel plot. The Egger's test indicated that there was no evidence of publication bias for the assessment of the effect of metformin use on functional outcome (p=0.503) and survival status (p=0.608). Also, the funnel plots revealed evidence of symmetry for functional outcome and survival status (online supplemental material 5).

DISCUSSION

Metformin is a cheap, widely available, safe and first-line antidiabetic drug. Recently, metformin has also been demonstrated to be effective in decreasing the risk of stroke in DM patients.[15] In this study, we summarised evidence from published studies for now through a meta-analysis to prove that DM patients with prestroke metformin use had a better functional outcome and a lower probability of death after stroke compared with those without. Thus, metformin in DM patients may not only be beneficial for reducing the risk of stroke but also for improving clinical outcomes after stroke.

As is well known, hyperglycaemia on admission was related to poor outcomes in patients who had a stroke,[31 32] likely mediated through increased risk of infection and cardiac complications.[23 26 33] Prestroke glycaemic control, as glycosylated hemoglobin type A1C (HbA1c) level on admission, is a useful way to improve clinical outcomes in DM patients with stroke.[34] Thus, one possible pathway for the protective effect of metformin on stroke is through lowering blood glucose in DM patients. Moreover, interestingly, accumulating evidence showed that although there is no statistically relevant difference between admission glucose levels of the metformin group and sulphonylureas group,[25] preadmission use of sulphonylureas does not affect stroke severity and clinical outcome among DM patients admitted with stroke.[30 35] It seems to support the hypothesis that metformin preconditioning results in benefits besides its hypoglycaemic effects.

The effect of metformin on clinical outcomes was at least partially driven by the lower stroke severity on admission. The severity on admission was also a known determinant of chronic clinical outcomes after stroke.[36–38] A study, which included 1281 patients with stroke, reported that the National Institute of Health stroke scale (NIHSS) score on admission, which reflected the severity of stroke, could strongly predict the functional outcome after stroke, and patients with a score of NIHSS≥16 on admission have a higher probability of death or severe disability than those without.[38] Several studies have shown that prestroke metformin use may be related to reduced neurological severity in stroke.[18 25] In a cohort study with a total of 1919 patients who had a stroke, patients with metformin treatment prior to stroke showed less severe strokes demonstrated by a lower NIHSS on admission compared with the non-pretreated patient group.[18] Similarly, a study identified metformin as the only antidiabetic drug to represent a significantly favourable determinant of stroke severity.[25] These results support the view that

metformin may be an active option for DM patients, not only because of its position as a DM treatment but also because of its neuroprotective effects.[28]

One possible mechanism of metformin-induced neuroprotective effect in stroke is related to neuronal adenosine monophosphate-activated protein kinase (AMPK), an important mediator of cellular energy homeostasis, highly expressed in neurons and activated under low cellular energy conditions, for example, cerebral ischaemia.[39 40] Studies have demonstrated that AMPK plays a protective role in the brain.[41 42] Evidence from the animal experiment showed that metformin, in patients who had an acute stroke with DM, could improve neurological function and oxidative stress status by the AMPK/mammalian target of rapamycin (mTOR) signalling pathway and oxidative stress.[43 44] However, it is worth noting that the neuroprotective effects require chronic use of metformin. Acute metformin use exacerbated stroke damage, enhanced AMPK activation and led to metabolic dysfunction. Conversely, chronic metformin use was neuroprotective, improved stroke-induced lactate generation and ameliorated stroke-induced activation of AMPK.[39] Therefore, the timing and duration of metformin use in DM patients should be taken into consideration to achieve neuroprotection. Tian *et al* indicated that a pretreatment time window of no less than 7 days was required for the neuroprotection of metformin against acute brain injury, and the time window cannot be reduced by increasing metformin dosage.[44] The cumulative dynamics of metformin dosage may be a key to the protective effects for stroke by metformin pretreatment. Additionally, chronic metformin use after stroke is also beneficial for clinical outcomes by inhibiting the inflammatory response, such as reduced IL-6 levels, stimulating vascular endothelial growth factor expression and promoting angiogenesis.[25 28] Thus, metformin was a potential target in the therapeutic intervention of stroke.[45]

Strengths and limitations

To the best of our knowledge, this meta-analysis of the effects of prestroke metformin use on the clinical outcomes of stroke in DM represents the first and pooled analysis of available evidence on this issue with a large pooled sample size. Nevertheless, although the results in this study are believed to be highly stable, some limitations are acknowledged. First, only English studies were included in this study, and the quantity of studies included was limited. Second, most of the included studies were retrospective, which is likely to increase the risk of confirmation bias, making it difficult to confirm causality. Third, the frequency and duration of metformin use may be influenced by the results, but this information was not adequate for consideration in this study, because few included studies provided this information. Whether metformin continues to be used after a stroke is also unclear. Fourth, the effects of other diabetes treatments, including insulin and thiazolidinediones, were not evaluated. Given that insulin action might influence stroke prognosis, this may introduce potential treatment bias. Additionally, while metformin is generally well tolerated, it is important to consider any potential risks or adverse effects associated with its use, particularly in the prestroke setting. While the 34% reduction in poor functional outcomes is statistically significant, further analysis and potentially additional research are needed to determine its clinical significance. In future researches, these factors should be considered at length. Therefore, the results of this study should be interpreted with caution.

CONCLUSION

In conclusion, prestroke metformin use is beneficial for the improvement of clinical outcomes in patients who had a stroke with DM, although the potential bias should be carefully considered. Metformin, as a known safety profile, may provide an economical and accessible therapeutic option for DM patients to improve stroke outcomes. Future researches in a large, prospective, randomised controlled trial are warranted to further elucidate the mechanisms underlying these associations and to determine whether metformin use may improve the clinical outcomes after stroke in DM patients.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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