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Comparative analysis of linagliptin *vs* gliclazide on incidence of hypoglycemia and major adverse cardiovascular events in type 2 diabetes: Systematic literature review

Mohan V *et al*. Systematic literature review of Linagliptin *vs* Gliclazide

Vishwanathan Mohan, Subhash Wangnoo, Sambit Das, Rajnish Dhediya, Kumar Gaurav

Abstract

BACKGROUND

Cardiovascular outcome trials (CVOTs) have demonstrated cardiovascular safety of glimepiride (a sulfonylureas) against dipeptidyl peptidase-4 (DPP4) inhibitor linagliptin. Gliclazide (another newer sulfonylureas) has shown similar glycemic efficacy and 50% lesser hypoglycemia risk than glimepiride.

AIM

To conduct a systematic review of literature to assess the cardiovascular (CV) safety by assessing the risk for major adverse CV events (MACE) and hypoglycemia risk of gliclazide *vs* linagliptin in patients with type 2 diabetes (T2D).

METHODS

This systematic review, followed the current PRISMA guidelines to analyze all the clinical studies published from 2008 which compared the two drugs in patients with T2D with no risk of CV disease (CVD). We included only evidence designated high quality by the Oxford Center for Evidence-based Medicine (OCEBM)-Levels of Evidence.

RESULTS

Eight clinical studies were included in the narrative descriptive synthesis (gliclazide 5 and linagliptin 3). The CV safety of gliclazide in the ADVANCE trial and of linagliptin

in the CARMELINA and CAROLINA trials were excluded from the comparative analysis as these trials demonstrated CV and hypoglycemia benefits in patients at high risk of CVD. However, since these are landmark trials, they were discussed in brief to show the CV benefits and low hypoglycemia risk of gliclazide and linagliptin. We did not find any study comparing gliclazide with linagliptin. Hence, direct comparison of their MACE and hypoglycemia risk could not be carried out. However, the literature meeting the inclusion criteria showed that both drugs were effective in achieving the desired glycemic control, and had low MACE and hypoglycemia risk in adult patients with no history of CVD.

CONCLUSION

Gliclazide can be considered as an effective and safe GLD in T2D patients with no established CVD but at high risk of CVD due to their T2D status. Future randomized controlled trials comparing gliclazide with linagliptin or DPP4 inhibitors can confirm these findings.

Key Words: Linagliptin; Gliclazide; Hypoglycemia; Major cardiovascular adverse events

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Core Tip: This systematic review shows the lack of high-quality evidence and head-to head trials comparing the cardiovascular safety and hypoglycemia risk of gliclazide (a sulfonylurea) *vs* linagliptin [dipeptidyl peptidase-4 inhibitor (DPP4i)] in adults with type 2 diabetes (T2D) and no cardiovascular disease. While DPP4i have proven to be cardiovascular neutral, sulfonylureas like gliclazide are commonly prescribed and recommended glucose lowering drugs in low resource settings. Hence, it is important to

establish the cardiovascular safety and hypoglycemia risk of gliclazide *vs* DPP4i to highlight that gliclazide if a cost-effective yet safe treatment option for patients with T2D.

INTRODUCTION

Type 2 diabetes (T2D), characterized by chronic hyperglycemia, and impaired insulin secretion, is often associated with disease related microvascular and macrovascular complications and treatment related complications like hypoglycemia[1,2]. Consequently, patients with T2D are at increased risk for cardiovascular (CV) complications and hypoglycemia. Hence, glucose-lowering drugs (GLDs) should not have CV complications and higher hypoglycemic episodes (HE) as adverse effects (AEs) and should ideally provide CV benefits or neutrality[1,2].

Sulfonylureas (SUs) are the most prescribed T2D pharmacotherapy, especially in resource limited setting[3]. Apart from their cost benefit, SUs have an exceptional glycemic efficacy with average glycosylated hemoglobin (HbA1c) reduction by 1%-2%, good safety profile and gastrointestinal tolerability[3]. However, hypoglycemia, weight gain and decreasing efficacy over time are the main concerns with SUs; due to their insulinotropic mechanism of action[3-5]. On the other hand, newer oral GLDs like dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors provide comparably less glycemic control than SUs (average HbA1c reduction 0.5%-0.8%), are costlier than SUs and often need to be combined with SUs to achieve the required glycemic control[3].

However, since, the time of their inception into T2D treatment regime, SUs have been subjected to criticism for CV safety[3,6]. The CV safety of SUs has been derived from small, inadequately powered randomized controlled trials (RCTs) and observational studies[3]. However, formal cardiovascular outcome trials (CVOTs) are not available for SUs[3,6].

Then, in 2008, US Food and Drug Administration (FDA) mandated the assessment of CV safety of newer GLDs[7]. Hence, large multinational, CVOTs of newer oral GLDs like

DPP4 inhibitors[8-12] and SGLT2 inhibitors[13-15] were conducted and showed their CV benefits. DPP4 inhibitors and SGLT2 inhibitors prove to be costly options in resource limited settings because of the chronic disease nature of T2D and because most patients pay from their pocket for the treatment[16,17].

Despite their unquestionable glucose lowering efficacy, current diabetes guidelines no more favor the use of SUs because of CV safety concern, except when cost is an issue[3,6]. SUs have been recommended as the add-on of choice after metformin for adequate glycemic control in resource limited settings by the World Health Organization (WHO) Guidelines and the Research Society for the Study of Diabetes in India/Endocrine Society of India (RSSDI-ESI) (2020) guidelines from India[18,19], International Task Force (ITF) Consensus[20] and International Diabetes Federation (IDF)[21]. The ITF recommend glimepiride and gliclazide modified release (MR) as SU of choice to be added to metformin while, IDF give equal importance to SU (except glibenclamide/glyburide), a DPP4i inhibitor or an SGLT2i inhibitor[20,21].

The American Diabetes Association (ADA) (2021) guidelines recommend various add-on pharmacotherapies for T2D patients poorly controlled on metformin, including DPP4 inhibitors, SGLT2 inhibitors and SUs[22]. The ADA guidelines recommend T2D patients with CV and renal morbidities should ideally be prescribed SGLT2 inhibitors or Glucagon-like peptide-1 (GLP-1) agonists as the next oral GLDs after metformin[22]. However, the choice of add on therapy in patients without CV risk is not clear.

Of the various DPP4 inhibitors used in T2D, landmark linagliptin trials have demonstrated CV safety and safety against HE, in T2D patients with high risk of CV disease (CVD)[8,9]. On the other hand, a landmark non-CVOT trial in patients with high CV risk showed that high intensity gliclazide treatment conferred low CV risk[23].

Many systematic reviews (SRs) and/or meta-analyses (MAs) have assessed the efficacy and safety [hypoglycemia and major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction/ischemia/acute coronary syndrome, or nonfatal stroke)] of SUs *vs* DPP4 inhibitors with mixed results[5,24-28]. These SRs and MAs identified a need for randomized trials comparing individual SU

with a DPP4 inhibitor. Hence, this SR was carried out to assess the CV safety and hypoglycemia risk of gliclazide *vs* linagliptin in T2D patients, both in monotherapy and as add-on to metformin setting.

MATERIALS AND METHODS

Methodology

MEDLINE database was searched on September 9, 2021 for records on gliclazide or linagliptin with no filter added. This retrieved 2578 records. Advanced search filter was then applied to filter by English language only, clinical trials, randomized controlled trials (RCT), Human studies, and adult age (19 + years). These filters retrieved 2054 records. The records were further filtered by applying adverse events of interest: Hypoglycemia, low blood sugar, myocardial infarction/myocardial ischemia (MI), transient ischemic attack (TIA), CV death and stroke. This retrieved 615 records; 223 duplicates were removed and remaining 392 records were screened. It was seen that linagliptin records were available from 2008 onwards only. Hence, to standardize the time period for the entire literature search, gliclazide records published before 2008 were removed. The remaining 248 records were assessed for eligibility over the next few days and after excluding records that did not meet the eligibility criteria as mentioned in Table 1, eight records were included (gliclazide 5 and linagliptin 3). The details of literature search and study selection are outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1). Google Scholar was searched for any additional manuscript that was missed on MEDLINE. This retrieved no additional records as per study selection criteria.

Two independent reviewers used the current PRISMA guidelines for SRs[29,30] to independently carry out the literature search on the same day. Any conflict in the number of records at identification, screening, eligibility and inclusion were mutually discussed and resolved by consensus. We do note that the protocol for this systematic review has not been published.

Quality of evidence and risk of bias

As shown by the PRISMA flow chart, there is a lot of literature on both gliclazide and linagliptin. Hence, we included only high-quality evidence. Randomized controlled trials (RCTs) are designated the highest quality by the Oxford Center for Evidence-based Medicine (OCEBM)-Levels of Evidence[31] followed by a randomized design of any type. Hence, we included only randomized studies. Placebo controlled studies were not included as there were no gliclazide *vs* placebo studies. The main reason for this could be that trials in the initial trajectory of drug development were missed by standardizing the study period from 2008 onwards. Additionally, studies comparing gliclazide or linagliptin with metformin were also not included because both drugs have a known and comparable efficacy and safety profile *vs* metformin.

Further, risk of bias assessment was independently carried out by two researchers who assessed the scientific quality of the records using the Cochrane Collaboration's tool for risk of bias assessment[32]. The Cochrane Risk of Bias tool assesses seven domains of bias and stratifies the risk of bias as low, high and unclear risk. Discrepancies between reviewers at any stage were resolved by discussion and consensus.

All the studies clearly defined and reported the outcomes of interest (hypoglycemia and MACE) and clearly mentioned all the CVDs that were assessed as exclusion criteria. Only one gliclazide[33] did not have any CVD as an exclusion criteria. The trials clearly explained the randomization schedule and were largely double-blind studies. Number of participants for which the outcomes of interest were reported was clearly stated.

However, most studies were not designed to report the outcome of interest (hypoglycemia and MACE) as their main primary and/or secondary endpoint. These outcomes of interest were primarily reported as AEs or safety endpoints.

Statistical analysis

The systematic literature search (Figure 1) did not retrieve any head-to-head trials comparing gliclazide ± metformin with linagliptin ± metformin. Hence, direct comparison of their outcomes was not possible. The gliclazide and linagliptin trials that met the inclusion criteria could not be compared to reach a statistical analysis due to various reasons. The studies captured for the two drugs were heterogeneous with respect to study design and duration; the outcomes of interest being evaluated as primary or secondary or safety (as AE) endpoints or as incident findings; definition of outcomes [*e.g.*, definition of hypoglycemia-cut off blood glucose (BG) level], and the statistical method used for analysis. The study population of the various studies differed in age, ethnicity, patient profile (*e.g.*, treatment naïve, or after failure of SU). Hence, a meta-analysis or a network meta-analysis could not be carried out. Therefore, key outcomes were described in a narrative manner for each drug separately, with due consideration given to the PRISMA checklist[29].

RESULTS

Gliclazide studies

This section aimed to include randomized trials that compared gliclazide *vs* linagliptin or a DPP4 inhibitor in monotherapy setting or compared gliclazide as add on to metformin *vs* linagliptin/DPP4 inhibitor as add-on to metformin.

Gliclazide *versus* linagliptin or DPP4 inhibitors: There were no records comparing gliclazide with linagliptin. One study compared gliclazide with vildagliptin, a DPP4 inhibitor[34] (Table 2). Foley and Sreenan[34] compared the efficacy and safety of two years of monotherapy with vildagliptin *vs* gliclazide in 1092 drug-naïve patients with T2D, having HbA1c of 7.5%-11.0%. In this vildagliptin non-inferiority trial, vildagliptin group had lower incidence of Grade 1 hypoglycemia than gliclazide group (0.7% *vs* 1.7%).

Two patients in the gliclazide group and none in vildagliptin group had ≥ 2 HEs[34]. Though the baseline HbA1c values were slightly higher in the group treated with gliclazide *vs* the vildagliptin group (HbA1c of 8.7% ± 0.1% *vs* 8.5% ± 0.1%), the mean

HbA1c reduction from baseline to Week 104 was -0.5% and -0.6% in the vildagliptin *vs* gliclazide group[34]. Study could not show the non-inferiority of the DPP4 inhibitor over gliclazide.

Gliclazide + metformin *vs* linagliptin/DPP4 inhibitors + metformin: There were no records comparing gliclazide + metformin with linagliptin + metformin. Vianna *et al*[35] compared the glycemic variability of gliclazide MR and vildagliptin and their effect on bone metabolism. This study was the single center part of the BoneGlic Trial which reported hypoglycemia and MACE as AEs in 42 postmenopausal Brazilian women with T2D and treated with a stable metformin dose for ≤ 3 mo. The study found no difference in time to hypoglycemia and the number of HEs in both the groups (P = 0.062). The investigator did not consider MACE events (Table 2) to be related to study drugs.

The study also found that gliclazide MR group had significantly longer time within the target BG range [> 3.9 mmol/L and ≤ 10.0 mmol/L (> 70.27 mg/dL and ≤ 180.18 mg/dL)] and significantly lower percentage of time with BG > 10 mmol/L (180.18 mg/dL) (P = 0.038 and P = 0.029). In comparison, time within the target BG was insignificantly increased and percentage of time with BG > 10 mmol/L (180.18 mg/dL) was insignificantly lower in the vildagliptin group (P = 0.111 and P = 0.133, respectively). However there were no differences between gliclazide and the DPP4 inhibitor for both the parameters[35].

The STEADFAST study conducted on 557 T2D patients fasting during the holy month of Ramadan found that both gliclazide and vildagliptin as add on therapy to and safety profile[36]. However, confirmed and/or severe HE during Ramadan were significantly higher (Table 2) in the glicalzide group[36]. The HEs observed with gliclazide were lower than reported from observational studies. The authors of the STEADFAST study concluded that HEs with gliclazide could be avoided through frequent patient-physician contacts and Ramadan-focused advice[36].

A vildagliptin non-inferiority trial in patients with T2D uncontrolled with metformin demonstrated that as an add-on to metformin, vildagliptin was non-inferior to

gliclazide in achieving glycemic control [95% confidence interval (CI) 0.11%, 0.20%][37]. However, more patients in the vildagliptin group discontinued treatment due to an unsatisfactory effect compared with gliclazide group (n = 22 *vs* 13, respectively). HEs were lower in vildagliptin *vs* gliclazide group (6 events *vs* 11 events)[37].

All the three trials[35-37] comparing gliclazide + metformin with DPP4 inhibitor + metformin described in this section were specific to a patient population (post-menopausal women) or in special situation (fasting during Ramadan). Therefore, these trials did not meet the strict inclusion criteria of this narrative synthesis. They were included because there were no other trials retrieved that compared gliclazide with a DPP4 inhibitor as an add-on therapy. The results on these trials may have been influenced by the patient population or the fasting state of the patients.

Linagliptin studies

This section aimed to include randomized trials that compared linagliptin *vs* gliclazide/SU in monotherapy setting or compared linagliptin as add on to metformin *vs* gliclazide/SU as add-on to metformin.

Linagliptin *vs* gliclazide or sulfonylureas: There were no studies comparing linagliptin with gliclazide or another SU. The landmark "CARdiovascular Outcome study of LINAgliptin *vs* glimepiride in patients with type 2 diabetes" (CAROLINA)[9] trial and studies[38,39] trial did not meet the inclusion criteria of the narrative synthesis as the study primarily focused on cardiac and renal patient population. Therefore, other studies[38,39] analyzing the outcomes of interest from the CAROLINA trial were also not included in the narrative synthesis. However, this non-inferiority of linagliptin to glimepiride trial merits discussion as it compared linagliptin with a SU, glimepiride. The trial is covered under excluded trial section.

However, a study by Barnett *et al*[40] (2012) in "metformin contraindicated" T2D patients compared linagliptin 5 mg once daily with placebo for 18 wk and then compared linagliptin with glimepiride after week 18 for 34 wk. The study defined

hypoglycemia according to the 2005 ADA guidelines[41]. The linagliptin group experienced less hypoglycaemia [≤ 70 mg/dL (≤ 3.9 mmol/L)] (2.2% *vs* 7.8%) and clinical event committee (CEC) confirmed CV events (0.7% *vs* 1.6%) than glimepiride group[40]. However, the difference did not reach clinical significance and more patients in the linagliptin group discontinued treatment due to an AE.

Linagliptin + metformin *versus* gliclazide/sulfonylurea + metformin: The literature search did not retrieve any linagliptin + metformin *vs* gliclazide/SU + metformin study meeting the inclusion criteria.

Gliclazide/Linagliptin ± metformin

The literature search did not retrieve any gliclazide *vs* placebo study meeting the inclusion criteria. The main reason for this could be that trials in the initial trajectory of drug development were missed by standardizing the study period from 2008 onwards. Also, there were no trials comparing gliclazide ± metformin with linagliptin ± metformin. Hence, this section aimed to include trials evaluating gliclazide alone or gliclazide + metformin without a comparator and linagliptin alone or linagliptin + metformin without a comparator. These trials were then assessed separately to see if the outcomes of interest could be compared.

Gliclazide ± metformin: Only one trial met the inclusion criteria and is detailed in Table 3. The multicentre, randomized, parallel-group "Diamicron MR in NIDDM: Assessing Management and Improving Control" (DINAMIC 1)[33] trial compared the efficacy, tolerability and acceptability of gliclazide MR for T2D management in the self-monitoring of BG (SMBG) *vs* non SMBG group. HEs were reported as a safety outcome and were classified as follows: Grade 1: Suspected mild hypoglycemia; Grade 2: Suspected moderate hypoglycemia; Grade 3: Suspected severe hypoglycemia with need of third-party assistance; and Grade 4: Suspected severe hypoglycemia with need of medical assistance. In 610 T2D patients (aged 40-80 years) followed up for six months,

8.7% patients in the SMBG group had a total of 51 HEs and 7.0% of patients in the non-SMBG group had a total of 66 HEs. There were no severe (Grade 3 or 4) HEs in any group.

Symptoms suggestive of nocturnal hypoglycemia were experienced by 3 and 7 patients in the SMBG *vs* non-SMBG. Two patients withdrew from the study because of hypoglycemia and both were in the non-SMBG group. The study highlighted the importance of SMBG in T2D management.

Linagliptin ± metformin: Only one trial met the inclusion criteria and is detailed in Table 3. This study compared linaglitin + metformin with only linagliptin and hence was included. Ross *et al*[42] (2015)conducted a randomized study to evaluate the efficacy and safety of initial treatment with linagliptin/metformin combination in newly diagnosed T2D patients with marked hyperglycemia. Hypoglycaemia occurred in 1.9 of patients in the linagliptin/metformin and 3.2% of patients in the linagliptin group. No severe HE was reported[42]. At week 24, there was a significant reduction in HbA1c from baseline in linagliptin/metformin versus linagliptin group ($P < 0.0001$ for treatment difference)[42]. Target HbA1c of < 7.0% was achieved by 61% of patients in the linagliptin/metformin arm and 40% of patients in linagliptin arm[42].

Other studies of linagliptin + metformin[43-45] compared the combination with either metformin or with placebo and hence were not included.

Landmark trials not meeting inclusion criteria but requiring special mention

Some landmark and important gliclazide and linagliptin trials were excluded from the narrative synthesis due to the applied exclusion criteria. However, given their importance in the drug trajectory, they need a special mention to get a clear picture regarding the HE and MACE AEs associated with gliclazide and linagliptin.

Excluded gliclazide trials

ADVANCE trial: Gliclazide studies retrieved during literature search that reported MACE as an outcome were the "Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation" (ADVANCE)[23] trial and its analyses[46-53]. However, the ADVANCE trial and its analyses were excluded from the narrative synthesis because the ADVANCE trial compared high intensity glucose control (with gliclazide) with standard glucose control (with other sulfonylureas). Also, in the high intensity group, those not achieving the targeted HbA1c with highest gliclazide dose were further given metformin, thiazolidinediones, acarbose, or insulin as add on therapy[23]. Comparison studies of gliclazide *vs* other GLDs (except DPP4 inhibitors) and studies analyzing gliclazide in combinations with other GLDs (except metformin) were excluded from the analysis.

Additionally, the ADVANCE trial recruited patients at high cardiovascular risk[23,54]. Patients with history of stroke, MI, unstable angina, transient ischemic attack, coronary or peripheral vascularization met the inclusion criteria for the study[23,54]. Thus, ADVANCE trial evaluated the MACE outcome in patients at high risk for MACE. However, ADVANCE trial also recruited patients with no history of CVD, but at high risk of MACE as they had T2D for ≥ 10 years or were ≥ 65 years old.

The primary macrovascular endpoint of the ADVANCE trial was composite of CV endpoints (death from CV causes, nonfatal MI, or nonfatal stroke). Individual CV endpoints were evaluated as secondary endpoints[23,54]. The trial also evaluated microvascular endpoints both as a composite and individual endpoint[23,54]. During the 5-years follow-up there were no significant effects of the type of glucose control on major macrovascular events[23].

Hypoglycemia was a secondary endpoint of the ADVANCE trial. It was defined as a BG level of < 2.8 mmol/L (< 50.5 mg/dL) or the presence of typical symptoms and signs of hypoglycemia without other apparent cause. Patients with transient dysfunction of the central nervous system (CNS) requiring external help for treatment were considered to have severe hypoglycemia. During the 5-years follow-up severe

hypoglycemia was uncommon. However, it was significantly more common in the intensive-control than standard-control group (2.7% *vs* 1.5%)[23].

Excluded linagliptin trials

CARMELINA trial: The other study of linagliptin *vs* placebo that reported both HE and MACE as outcomes was the landmark "Cardiovascular and Renal Microvascular Outcome Study With Linagliptin" (CARMELINA) trial. This study was excluded from the narrative synthesis because it evaluated HE and MACE in 6979 T2D patients with high CV and renal risk[8]. However, given that this was a landmark trial, it is discussed excluded linagliptin studies section.

This study evaluated HE and MACE in 6979 T2D patients with high CV and renal risk[8]. The trial, designed as a non-inferiority trial of linagliptin *vs* placebo, assessed the first occurrence of the composite of MACE as a primary endpoint and hypoglycemia was assessed as an AE. Both the outcomes of interest were well defined according to predefined criteria. After a median follow-up of 2.2 years, MACE occurred in 12.4% and 12.1% in the linagliptin and placebo groups, respectively and the difference was statistically significant[8]. The frequency of confirmed HEs including severe hypoglycemia in the linagliptin *vs* placebo group was 15.9% *vs* 16.4%. HE in the placebo group was due to rescue medications that were allowed to control hyperglycemia[8].

CAROLINA trial: In CAROLINA trial, 6042 subjects with T2D and glycated hemoglobin (HbA1c) 6.5%-8.5% who were at high CV risk (had established CV disease and renal impairment but not end stage renal disease) were randomized to linagliptin at 5 mg/d (n = 3028) *vs* glimepiride at doses of 1-4 mg/d (n = 3014)[9]. After a mean follow up of 6.3 years, the primary outcome of the trial (MACE) occurred in 11.8% of subjects in linagliptin *vs* 12% of subjects in glimepiride arm, and the difference was statistically significant[9]. At least one HE occurred in 10.6% *vs* 37.7% of participants in the linagliptin *vs* glimepiride group[9].

DISCUSSION

There were no CVOT trials for gliclazide. The landmark ADVANCE trial[23] compared two levels of glycemic control, intensive (HbA1c < 6.5%) *vs* standard (managed with oral GLD according to local practice). It was not a CV safety trial of gliclazide, but the trial did show that the primary end point of composite of microvascular and macrovascular events was significantly reduced by 18.1% in the intensive control gliclazide arm.

On the other hand CV safety of linagliptin has been demonstrated by two RCTs, namely the CARMELINA[8] (versus placebo) and the CAROLINA[9] (versus glimepiride, a SU) trials. These dual randomized CVOT linagliptin trials in T2D patients, CARMELINA[8] and CAROLINA[9] showed that linagliptin was non-inferior to placebo and glimepiride, respectively, for the composite of MACE.

This CV safety of gliclazide in the ADVANCE trial and of linagliptin in the CARMELINA and CAROLINA trials was demonstrated in patients at high risk of CVD. Hence, gliclazide and linagliptin can be considered as oral GLD that can be given safely in T2D patients with CVD or at high risk of CVD.

In this context, the two RCTs comparing gliclazide with vildagliptin, a DPP4 inhibitor[34,35] were not powered to assess hypoglycemia and MACE as outcomes. Instead, they reported these as AEs. However, both the trials did not report a significant difference in CV safety and/or HE incidence between gliclazide and vildagliptin. In this context, it is important to note that linagliptin and vildagliptin belong to two different class of DPP4 inhibitors[55]. Hence, it is important to compare gliclazide with linagliptin.

Also, all SUs do not have the same CV risks. SUs like glyburide/glibenclamide inhibit an adenosine triphosphate (ATP)-sensitive potassium (K+) channel (KATP) channels in the heart and pancreas and are therefore associated with increased CV risk as compared to gliclazide which selectively inhibits KATP channels only in the pancreas[56]. The CARMELINA trial compared linagliptin with glimepiride. However, the double-blind head-to head comparison GUIDE study showed that compared to glimepiride, gliclazide had a better safety profile and resulted in 50% fewer HEs[2]. The frequency of

CV AEs was similar in both glimepiride and gliclazide groups and judged by the investigator as not related to the treatment[2].

Strengths and limitations

Literature was searched for using only free resources such as MEDLINE and Google scholar. Hence, the SR is likely to have missed some important articles on the paid sites. The strict inclusion and exclusion criteria is likely to have filtered out important RCTs and real-world studies that could have added value to the CV and hypoglycemia profile of these two drugs. This SR is also limited by its reporting style of narrative synthesis. However, as explained under the "Narrative synthesis of data" section, there were no trials comparing gliclazide and linagliptin. Hence, gliclazide and linagliptin studies were independently assessed for the outcomes of interest. For most studies included in the narrative synthesis, except the CARMELINA[8], ADVANCE[23] and DINAMIC 1 study[33], hypoglycemia, MI and other cardiovascular events were reported as cause of exclusion from the study or withdrawal from study and non-inclusion in analysis. Hence, these trials looked at outcome of interest in patients not at risk of CV and renal events.

Filtering of gliclazide trials by the year (2008) resulted in inclusion of trials in the later trajectory of gliclazide compared to linagliptin trials that were in the earlier stage of drug trajectory. This resulted in exclusion of five randomized gliclazide clinical trials which reported the outcomes of interest in the initial drug trajectory[2,57-60] These included trials comparing various gliclazide formulations[57,60], and trials comparing gliclazide with other SUs such as GUIDE Study[2], and with thiazolidinediones (QUARTET Study Group)[58]. However, none of these randomized trials included a DPP4 inhibitor as a comparator, and hence, their exclusion does not affect the narrative synthesis.

All the records included in this study were RCTs or a factorial randomized design. Hence, quality of records included was good.

CONCLUSION

Although, the head-to-head comparative clinical data between gliclazide and linagliptin is lacking, both the drugs have shown effective glycemic control along with CV safety in patients with T2D. In resource limited settings, SUs are commonly used as first add-on therapy after metformin because of cost constraints. In these settings, there is a need to compare modern SUs like gliclazide, which have a cardiac-sparing action, with drugs with established CV safety in CVOT such as DPP4 inhibitors. Future randomized controlled trial may confirm the comparative CV outcomes between gliclazide and linagliptin and other DPP4 inhibitors.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes (T2D) patients are at increased cardiovascular and treatment related hypoglycemia risk. Various guidelines recommend dipeptidyl peptidase-4 inhibitors (DPP4i) as the first add-on therapy to metformin in T2D due to their confirmed cardiovascular benefits demonstrated through cardiovascular outcome trials (CVOTs). However, in resource limited countries like India, newer sulfonylureas, like gliclazide and glimepiride, are the most commonly used glucose lowering drugs (GLDs) in T2D due to their low cost. Gliclazide and glimepiride have similar glycemic efficacy but gliclazide has 50% lower hypoglycemia risk.

Research motivation

A landmark CVOT demonstrated cardiovascular safety of glimepiride against linagliptin (a DPP4i). However, the cardiovascular safety of gliclazide *vs* linagliptin has not been established through CVOTs. If the cardiovascular safety and lower hypoglycemia risk of gliclazide is established *vs* linagliptin, it will help physicians prescribe it with assurance of safety for their patients.

Research objectives

To assess the cardiovascular safety and hypoglycemia risk of gliclazide as compared to linagliptin (and other DPP4i). The objective was to assess whether gliclazide was as safe as guidelines recommended DPP4i (linagliptin) in providing cardiovascular safety and lowering hypoglycemia risk in T2D. This systematic review is likely to help provide assurance regarding cardiovascular and hypoglycemia safety of gliclazide in T2D as compared to costlier DPP4i.

Research methods

This systematic review, followed the current PRISMA guidelines to analyze all the clinical studies published from 2008 which compared the asrdiovascular safety and hypoglycemia risk of the two drugs in patients with T2D with no CVD. Using keywords such as "linagliptin", "Gliclazide", “hypoglycemia”, “myocardial infarction”, and “Cardiovascular death”, we searched databases MEDLINE and Google Scholar. Two independent reviewers assessed the trials included using the current PRISMA guidelines for systematic reviews. We included only evidence designated high quality by the Oxford Center for Evidence-based Medicine (OCEBM)-Levels of Evidence. The primary outcomes compared were major adverse cardiovascular events (MACE) and hypoglycemia risk.

Research results

We could not find any trial comparing gliclazide with linagliptin, either as monotherapy or as add-on therapy to metformin. The CV safety of gliclazide in the ADVANCE trial and of linagliptin in the CARMELINA and CAROLINA trials were excluded from the comparative analysis as these trials demonstrated CV and hypoglycemia benefits in patients at high risk of CVD. However, since these are landmark trials, their results are important and hence described in detail as a separate section. The final analysis included five gliclazide and three linagliptin trials (total eight studies) that individually studied the outcomes of interest in T2D patients with no established CVD. Statistical comparisons of the results were not possible as the trials

had different designs, different definition of MACE and hypoglycemia, and were conducted in different patient populations. Hence, no direct comparisons were possible. The trials were therefore described individually and their results were compared through narrative synthesis. We assessed that both drugs were effective in achieving the desired glycemic control, and had low MACE and hypoglycemia risk in adult patients with no CVD.

Research conclusions

Gliclazide can be considered as an effective and safe GLD in T2D patients with no established CVD but at high risk of CVD due to their T2D status.

Research perspectives

Future randomized controlled trials comparing gliclazide with linagliptin or DPP4 inhibitors can add value to the findings of this systematic review.

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Figure Legends

Figure 1 PRISMA flow-chart of literature search and selection. DPP4 inhibitor: Dipeptidyl peptidase-4 inhibitor; GLD: Glucose lowering drug; MA: Meta-analysis; PBO: Placebo; PD: Pharmacodynamic; PK: Pharmacokinetic; RCT: Randomized controlled trials; SR: Systematic review; SU: Sulfonylurea.

Table 1 Inclusion, exclusion criteria of the records included in the systematic review

Inclusion criteria	Exclusion criteria
Age 19 years and < 70 years; Male and Female; Type 2 diabetes	Age below 19 years or ≥ 70 years; type 1 diabetes; no diabetes
Human studies: Any race, ethnicity	Clinical trials evaluating gliclazide or linagliptin in patients with specific comorbidites including CVD[1]
Randomized clinical trials on safety of: -Gliclazide monotherapy versus linagliptin monotherapy -Gliclazide + metformin versus linagliptin + metformin	Review articles, systematic reviews and meta-analysis, network meta-analysis, pooled analysis of trials, case studies, non-randomized trials
Randomized clinical trials on safety of: -Gliclazide versus DPP4 inhibitors -Linagliptin versus sulfonylureas	Pharmacokinetic, pharmacodynamic and bioequivalence study; retrospective chart review; observational real-world study; case study; trials studying mechanism of action of gliclazide or linagliptin; Literature reporting only study design; trial summaries and implications; animal studies; preclinical studies
Randomized clinical trials on gliclazide or linagliptin monotherapy evaluating the following outcomes: Hypoglycemia or low blood sugar	Clinical trials evaluating gliclazide or linagliptin versus PBO Clinical trials evaluating gliclazide or linagliptin in combination with other GLDs except metformin Clinical trials evaluating gliclazide or linagliptin versus other GLDs except: DPP4 inhibitors for gliclazide; Sulfonylureas for linagliptin
Occurrence of 3 point major	Clinical trials evaluating other glycemic, cardiac,

adverse cardiovascular events (3P-MACE): Cardiovascular death, nonfatal myocardial infarction/ischemia/acute coronary syndrome, or nonfatal stroke (transient ischemic attack included)	cardiovascular outcomes than those of interest; other outcomes (*e.g.*, microvascular complications)

[1]History of myocardial infarction, stroke, unstable angina, transient ischemic attack, percutaneous coronary intervention for coronary occlusion, or coronary artery bypass graft.

Note: Efficacy was synthesized from the gliclazide and linagliptin studies that met the inclusion criteria. CVD: Cardiovascular disease; DPP4: Dipeptidyl peptidase-4; GLD: Glucose lowering drugs; PBO: Placebo.

Table 2 Gliclazide versus dipeptidyl peptidase-4 inhibitor /Linagliptin versus sulfonylurea

Ref.	Primary study objective	Study design	Study population	CVD excluded	Number of participants	Study duration	Endpoint (hypoglycemia)	Hypoglycemia definition	Hypoglycemia results	Endpoint (MACE)	MACE definition	MACE results
Gliclazide *vs* DPP4 inhibitor (vildagliptin)												
Foley *et al*[34], 2009	Compare the efficacy and safety of vildagliptin versus gliclazide	Randomized, multi-center, double-blind, active-controlled study	Drug-naïve patients with T2D, HbA 1c of 7.5%-11.0 %	CHF NYHA class III or IV, ECG abnormalities	1092	104 wk	AEs were safety endpoints	Grade 1 hypoglycemic events per week: Symptoms suggestive of low blood glucose confirmed by SMBG measurement of < 3.1 mmol/L plasma glucose equivalent not requiring the assistance of another party; Grade 2 hypoglycemic event (requiring the assistance of another party) or if there were 3 or more asymptomatic glucose values < 3.1 mmol/L per week	Grade 1 hypoglycemia: 4 patients (0.7%) in the vildagliptin group and 14 (1.7%) in the gliclazide group. ≥ 2 HEs: 2 patients in the gliclazide group and none in vildagliptin group No grade 2 HEs in either group	-	-	-
Gliclazide +metformin *vs* DPP4 inhibitor (vildagliptin) + metformin												
Vianna *et al*[61], 2018	Compare the effects on glycemic variability and bone metabolism	Single center, randomized, controlled, open-label (blinded to the observer)	Postmenopausal Brazilian women with T2D and treated with a stable metformin	CV complications	56 (42 randomized)	2-wk pre-randomization period followed by 24 wk	As AE	Major hypoglycemia: Glucagon, carbohydrates administration by another person or other resuscitative measures; minor hypoglycemia: BG ≤ 3.9 mmol/L with or without typical symptoms or hypoglycemia symptoms without BG test	-No differences from baseline in time to hypoglycemia (% of time ≤ 3.9 mmol/L)	As SAE		Vildagliptin: 1 hemorrhagic stroke gliclazide MR group: 1 death due to AMI,

			dose for ≤ 3 mo					-No major hypoglycemia -Minor hypoglycemia events: 7 in the gliclazide; 2 in the vildagliptin group (P = 0.062)			the investigator did not consider the SAEs to be related to the study medications
Hassanein et al[36], 2014 (STEADFAST study)	HE during Ramadan	Multiregional, randomized double-blind	Patients fating during Ramadan	CHF (NYHA class III or IV); other significant CVr history within 6 mo	557	4-wk Ramadan period	Primary	Hypoglycemia: Low BG symptoms with or without confirmatory, SMBG measurement < 3.9 mmol/L; PGE, or asymptomatic SMBG < 3.9 mmol/L PGE; confirmed hypoglycemia: Symptomatic/asymptomatic SMBG measurement < 3.9 mmol/L; PGE and severe HE requiring assistance from another party irrespective of whether SMBG value was available or not	Confirmed and/or severe HE during Ramadan: Vildagliptin *vs* glicalzide was 3.0% *vs* 7.0% (P = 0.039; one-sided test), and this was HEs: Vildagliptin *vs* glicalzide was 6.0% and 8.7% (P = 0.173)	-	-	-

Filozof and Gautier[37], 2010	Demonstrate non-inferiority of vildagliptin compared with gliclazide, as an add-on therapy	Randomized, double-blind, active-controlled	T2D uncontrolled with metformin	Serious cardiac conditions (torsades de pointes, sustained and clinically relevant VT or VF, PCI ≤ 3 mo, MI, CABG, unstable angina; or stroke ≤ 6 mo and CHF requiring pharmacological treatment, 2nd- or 3rd-degree AV block or prolonged QTC)	1007	52 wk	AE	Symptoms suggestive of hypoglycaemia and confirmed by SMBG < 3.1 mmol/L	HE vildagliptin *vs* gliclazide (6 *vs* 11 events)	-	-	-

AE: Adverse event; AMI: Acute myocardial infarction; AV: Atrioventricular; BG: Blood glucose; CABG: Coronary artery bypass surgery; CHF: Congestive heart failure; CV: Cardiovascular; CVD: Cardiovascular disease; ECG: Electrocardiogram; HbA1c: Glycated haemoglobin: HE: Hypoglycemia event/episode; MI: Myocardial infarction; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; PGE: Plasma glucose equivalent; SAE: Serious adverse event; SMBG: Self-monitored blood glucose; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

Table 3 Gliclazide ± metformin and linagliptin ± metformin (no comparator)

Trial/treatment	Primary study objective	Study design	Study population	CVD excluded	Number of participants	Study duration	Endpoint (hypoglycemia)	Hypoglycemia definition	Hypoglycemia results	Endpoint (MACE)	MACE definition	M res
DINAMIC 1) (2008)[33]/Gliclazide	Compare the efficacy, tolerability and acceptability of gliclazide in SMBG *vs* non-SMBG group	Multicentre randomized parallel-group	T2D patients managed on diet alone	Not mentioned	610	6-mo	Safety endpoint (AE)	Grade 1: Suspected mild hypoglycaemia	SMBG group: 8.7% patients had 51 HE: symptomatic (27), asymptomatic (11), SMBG-confirmed (11) and non-graded (2)	-	-	-
								Grade 2: Suspected moderate hypoglycaemia	non-SMBG group: 7.0% patients had 66 he: symptomatic (66) and non-graded (2). Two HE-related withdrawals			
								Grade 3: Suspected severe hypoglycaemia with need of third party assistance	No grade 3 or 4 symptoms			
								Grade 4: Suspected severe hypoglycaemia with need of medical assistance	Symptoms suggestive of nocturnal hypoglycaemia: SMBG group: 03 and non-SMBG group: 07			
Ross 2015/linagliptin/metformin *vs* linagliptin monotherapy	Change from baseline in HbA1c	Randomized, double-blind, active-controlled, parallel	Newly diagnosed (≤ 12 mo) T2D and marked	ACS, stroke or TIA < 3 mo	316	24 wk	Safety endpoint (AE)	Severe hypoglycemia: Requiring assistance from another person to administer carbohydrate or other resuscitative action	Linagliptin/metformin: 1.9% of patients and linagliptin: 3.2% of patients no severe	-	-	No de

	group, multinational	hyperglycaemia (≥ 8.5 and ≤ 12.0%)				hypoglycemia

ACS: Acute coronary syndrome; AE: Adverse event; CVD: Cardiovascular disease; HbA1c: Glycosylated hemoglobin; SMBG: Self-monitoring of blood gluose; T2D: Type 2 diabetes; TIA: TTransient ischaemic attack.

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