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Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials

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Abstract

Objective and Design: Gliclazide has been associated with a low risk of hypoglycemic episodes and beneficial long-term cardiovascular safety in observational cohorts. The aim of this study was to assess in a systematic review and meta-analysis of randomized controlled trials the safety and efficacy of gliclazide compared to other oral glucose-lowering agents (PROSPERO2013:CRD42013004156).

Data Sources: Medline, EMBASE, Clinicaltrials.gov, Trialregister.nl, Clinicaltrialsregister.eu and the Cochrane database.

Selection: Included were randomized studies of at least 12 weeks duration with the following outcomes: HbA1c change, incidence of severe hypoglycemia, weight change, cardiovascular events and/or mortality when comparing gliclazide with other oral blood glucose lowering drugs. Bias was assessed with the Cochrane risk of bias tool. The inverse variance random effects model was used.

Results: Nineteen trials were included; 3,083 patients treated with gliclazide and 3,155 patients treated with other oral blood glucose lowering drugs. There was a considerable amount of heterogeneity between and bias in studies. Compared to other glucose lowering agents except metformin, gliclazide was slightly more effective (−0.13% (95%CI: −0.25, −0.02, I² 55%)). One out of 2,387 gliclazide users experienced a severe hypoglycemnic event, whilst also using insulin. There were 25 confirmed non-severe hypoglycemic events (2.2%) in 1,152 gliclazide users and 22 events (1.8%) in 1,163 patients in the comparator group (risk ratio 1.09 (95% CI: 0.20, 5.78, I² 77%)). Few studies reported differences in weight and none were designed to evaluate cardiovascular outcomes.

Conclusions: The methodological quality of randomized trials comparing gliclazide to other oral glucose lowering agents was poor and effect estimates on weight were limited by publication bias. The number of severe hypoglycemic episodes was extremely low, and gliclazide appears at least equally effective compared to other glucose lowering agents. None of the trials were designed for evaluating cardiovascular outcomes, which warrants attention in future randomized trials.

Introduction

At present, metformin is the pharmacological cornerstone for patients with type 2 diabetes (T2DM) [1]. When metformin does not suffice or is contra-indicated, the next oral treatment options are: sulphonylureas (SUs), meglitinides, α-glucosidase inhibitor, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium glucose transporter-2 receptor (SGLT-2) inhibitors. SUs are the preferred second treatment option in for example the current NICE guidelines, whereas no specific choices have been made in the American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) position statement [1,2].

The new Dutch type 2 diabetes management guideline specifically advises gliclazide as the preferred second treatment option and not SUs as a group. Specifically advising gliclazide is – amongst others - based on evidence from observational studies showing cardiovascular benefits of gliclazide over other SUs [3–8]. Individual SUs express a different selectivity for pancreatic and myocardial SU receptors; gliclazide seems the most selective with respect to pancreatic receptor stimulation [7,9]. Non-selective SUs like glibenclamide also block the myocardial SU receptor, and it is known that closure of these channels during myocardial ischemia worsens post-ischemic wall function by shortening the action potential [10–12]. Haemorheological and fibrinolytic properties of
gliclazide [13], a lower incidence of hypoglycemic events and less
weight gain while using gliclazide were also proposed as
explanations for a possible favorable cardiovascular safety profile
[14]. Furthermore, no dose adjustments appears necessary in case
of impaired renal function [15]. The role of gliclazide in the new Dutch
guideline, the presumed differences between individual SUs, the possibility of a lower
hypoglycemia risk, possible cardiovascular safety benefits together
with the absence of a systematic review or meta-analysis examining gliclazide specifically, brought us to summarize the
results from randomized studies comparing gliclazide with other
oral glucose lowering agents.

**Methods**

**Protocol**

The eligibility criteria, outcomes, main and sensitivity analyses were pre-specified and published on PROSPERO
(2013:CRD42013004156), see Attachment S1. The presentation of the methods and results is according to the PRISMA
recommendations (available at www.prisma-statement.org).

**Eligibility criteria**

A study was considered eligible if it was a randomized controlled
trial that: treated non-pregnant adults (aged 18 or older) with type
2 diabetes; excluded patients during Ramadan; had a study
duration of at least 12 weeks; reported change in glycated hemoglobin (HbA1c); compared gliclazide with other oral glucose
lowering drugs. Trials comparing gliclazide with placebo, diet, insulin androsiglitazone were excluded. The two preparations of
gliclazide (gliclazide regular formulation and gliclazide MR) were
grouped for all analyses.

**Data sources and searches**

An electronic search without language restrictions was per-
fomed in Medline (using PubMed), EMBASE and the Cochrane
Library (April 17 2013). See Attachment S2. for our search strategy.
References list of selected articles were searched. Additional
studies were searched for by hand searching the abstracts of the
2010, 2011 and 2012 annual meetings of the American Diabetes
Association and the European Association for the Study of
Diabetes. Completed but unpublished trials were searched
for by hand searching the abstracts of the
2004 [17], with September 13, 2005 as the last date for trials not
registered at inception [18]. Studies without registration after this
period were considered at high risk for selective reporting.
Additional studies were also searched for by contacting the authors
of the included studies. In case of not
responding, the pharmaceutical companies, if applicable, were
contacted and ITT or modified ITT data were requested.
In case of missing, incomplete or per protocol (PP) data
regarding the primary and secondary outcomes, the corresponding
authors were contacted (three attempts maximum). In case of not
responding, the pharmaceutical companies, if applicable, were
contacted and ITT or modified ITT data were requested.

**Data collection and data items**

A data extraction form was designed and two reviewers (GL and
PvD) independently performed the study selection. Differences between the reviewers were resolved by consensus with a third author (NK). One reviewer (GL) searched conference abstracts and trial registries.

**Results**

The Cochrane Collaboration’s risk of bias tool was used to
assess risk of bias [16]. This tool considers the presence of bias
caused by: random sequence generation, allocation concealment,
blinding of participants and personnel, incomplete outcome data
(because of high rate of discontinuation, type of analysis, or
imputation of missing data), selective reporting and a category
‘other forms of bias’. Study registration became mandatory in
2004 [17], with September 13, 2005 as the last date for trials not
registered at inception [18]. Studies without registration after this
period were considered at high risk for selective reporting.

The risk of bias was regarded high in case of the presence of
high bias in any domain, low if all key domains (all domains except
random sequence generation and allocation concealment) were of
low bias, and unclear in all other cases. When only the risk of bias
in the 7th domain (other bias) was unclear it was regarded as low
risk of bias [16,19]. Two authors (GL and PvD) independently

**Summary measures - Safety**

The primary safety outcome was the number of patients
experiencing at least one severe hypoglycemic event. A hypogly-
cemic event was considered severe when treatment by a third
party was necessary.

Secondary safety outcomes included total number of confirmed
non-severe hypoglycemic events, cardiovascular events and
mortality. A non-severe confirmed event was defined as an event
with symptoms and a glucose measurement with a plasma blood
glucose <4.0 mmol/L. Cardiovascular events were defined as a
combined endpoint of unstable angina, acute myocardial infar-
ction, stroke and fatal cardiovascular events.

**Summary measures - Efficacy**

The primary outcome was change in HbA1c from baseline to
to endpoint of the intervention, and its difference with the active
comparator(s). The secondary efficacy outcome was the change in
body weight from baseline to endpoint of the intervention. Time
between baseline and endpoint measurements was considered as a
covariate between studies.

**Missing data and multiple reports**

Data from intention to treat (ITT) (all participants randomized)
or modified ITT (all randomized participants who received
intervention and had at least one measurement after baseline)
were used when these were available either in a published paper or
on websites of pharmaceutical companies and trial registries.
In case of missing, incomplete or per protocol (PP) data
regarding the primary and secondary outcomes, the corresponding
authors were contacted (three attempts maximum). In case of not
responding, the pharmaceutical companies, if applicable, were
contacted and ITT or modified ITT data were requested.
In case of multiple reports or companion papers of the same
study (published results of an extension period) outcome data from
the original study were extracted, unless the first report was a
planned interim analysis.
assessed the risk of bias, when necessary consensus was determined through help of a third author (GoB).

**Synthesis of results**

Mean differences between the intervention group and all active comparator groups with standard deviations (SDs) were calculated for continuous outcomes with an inverse variance random effects model. If a specific study did not report standard deviations, this was calculated from the standard error or the 95% confidence interval (CIs). For dichotomous outcomes, risk ratios and 95% CIs were used, again using an inverse variance random effects model.

In the absence of a gliclazide group receiving the maximum approved dose of 240 mg, data regarding the group receiving the highest dose were analyzed.

Statistical heterogeneity (I²) values of 30–60% and between 60–90% represent moderate and considerable heterogeneity, respectively [16]. Potential causes of heterogeneity were explored by looking at outliers and by performing sensitivity analyses, excluding reports with high overall risk of bias. Sensitivity analyses were planned for every outcome based on its overall risk of bias.

All analyses were performed with RevMan 5.1 (Nordic Cochrane Centre).

**Results**

In total, 19 studies were included (see figure 1). 18 studies were retrieved from searching in electronic databases [8,14,20–35] and one study, including Chinese patients, was selected through searching Clinicaltrials.gov [36]. No additional completed trials were retrieved from other sources. The ADVANCE study was not included because the primary goal of the study was to compare a strict control (with gliclazide) to conventional treatment (without gliclazide) and not gliclazide itself [37].

Although some authors or pharmaceutical companies responded [8,27,29], others either did not respond or did not give priority to our requests [26,28,30–35] or stated that intention to treat analyses could not be performed for differences in weight [34,35].

Table 1 summarizes the characteristics of the included studies. Participants’ baseline characteristics show that the studies were heterogeneous in design. The durations of the intervention periods varied between 12 and 104 weeks. All but two studies used the regular gliclazide formulation [8,29].

The primary end point between studies varied, the most common endpoint being change in HbA1c. Five studies had a non-inferiority design [29,30,34–36], four used a 95% confidence interval, with non-inferiority margins of 0.3% [34], 0.4% [35,36] and 0.5% [29] and one used a 90% CI with a non-inferiority margin of 0.2% [30]. All 19 included studies contributed to the HbA1c analysis; 3,083 patients were randomized to gliclazide and 3,155 patients were randomized to another glucose lowering comparator group occurred in a patient using glibenclamide. Few studies described differences in weight with SD’s for the gliclazide group [37].

In those studies, in which severe hypoglycemic events were systematically reported, there was one severe hypoglycemic event in 2,387 gliclazide users and one in the 2,430 patients in the comparator group [8,22,23,26,27,29,31–36]. The one severe hypoglycemic event in the gliclazide group occurred in a patient who also started NPH insulin in the prmonths preceding the incident [27]: the one severe hypoglycemic event in the comparator group occurred in a patient using glibenclamide.

**Confirmed non-severe hypoglycemia**

Symptomatic confirmed hypoglycaemia’s could be evaluated in 7 studies [8,14,22,23,26,34,35]. There were 25 hypoglycemic events (2.2%) in 1,152 gliclazide users and 22 hypoglycemic events (1.8%) in 1,163 patients in the comparator group (risk ratio 1.09; 95% CI: 0.20, 5.78; NS) after 13 to 104 weeks follow-up. There was a high heterogeneity (F 77%) across studies.

Three out of 7 studies were responsible for all symptomatic confirmed hypoglycemic events [14,34,35]. Two studies comparing gliclazide with vildagliptine had a relative long follow-up period of 52 and 104 weeks and used a gliclazide dose of up to 320 mg, well above the official maximum of 240 mg [34,35].

One small study comparing with glibenclamide showed 12 confirmed symptomatic hypoglycemic events in the glibenclamide group and 0 in the gliclazide group [14]. After excluding studies that used a dose above 240 mg, there were no symptomatic confirmed hypoglycemic events in 129 gliclazide users, these studies had a follow-up period between 13 and 26 weeks [14,22,23,26].

One study, with low risk of bias, comparing gliclazide (XR 120 mg) with glibenpride showed an advantage regarding non-severe, confirmed symptomatic and confirmed asymptomatic hypoglycaemia episodes in favour of gliclazide. 15 patients experienced a hypoglycaemic episode in 403 gliclazide users compared to 39 patients in 439 glibenpride users (p<0.02) [29].
This study was excluded from the meta-analysis because asymptomatic episodes were also included in the study analysis (despite registered glucose ≤3.0 mmol/L) [29].

**Glycemic efficacy**

Compared to all other interventions, gliclazide was more effective: −0.12% (95% CI: −0.23, −0.01) on the primary outcome measure; change in HbA1c from baseline (see Figure 2). There was moderate heterogeneity with I² of 48%. The study by Kardas [8] and the study by Harrower [20] were mainly responsible for the heterogeneity. After excluding these studies, the effect estimates were −0.09 (95% CI: −0.18, −0.00).

After excluding 3 studies [22,23,25] that used metformin as comparator arm and the metformin comparator arm of the study by Lawrence [28], gliclazide was more effective: −0.13% (95% CI: −0.25, −0.02, I² 55%).

In the 12 studies where the risk for severe hypoglycemia could be evaluated, gliclazide was more effective: −0.11% (95% CI: −0.2, −0.01, I² 26%). When comparing to other SUs, there was no significant difference in HbA1c: −0.21% (95% CI: −0.46, 0.05, I² 74%). Inclusion of studies with a maximum dose set at 240 mg gliclazide [8,21–23,27,29,33,36] resulted in a non-significant difference of −0.14% (95% CI: −0.34, 0.05, I² 50%), compared to all other interventions. After excluding studies that used gliclazide MR, the effect estimate was −0.09% (95% CI: −0.20, 0.02, I² 35%). As second line treatment [24,27,29,31,33,35], gliclazide was not significantly different to comparators: HbA1c −0.07% (95% CI: −0.16, 0.01, I² 0%). After excluding studies with a duration of less than 24 weeks the effect estimate was −0.11% (95% CI: −0.21, −0.00, I² 38%). Compared to metformin monotherapy, the effect estimate of gliclazide monotherapy was 0.26 (95% CI: −0.59, 1.11, I² 0%).

**Weight**

The difference in weight was 0.47 kg (95% CI: −0.75, 1.70) in favor of the control group with high heterogeneity (I² 87%) among the studies. The analysis was based on eight studies including 616 patients using gliclazide and 616 for the reference population [20,23–27,33,36]. The treatment duration varied from 13 to 52 weeks.

When comparing gliclazide to other SUs or metiglinides the effect estimate was: −0.09 kg (95% CI: −1.72, 1.55, I² 87%). This analysis was based on four studies including 401 patients for gliclazide and 411 for SU or metiglinides [20,27,33,36].
Table 1. Summarizes the characteristics of the included studies.

<table>
<thead>
<tr>
<th>Primary study</th>
<th>Study arm (max dose)</th>
<th>Comparison arm (max dose)</th>
<th>Study duration (month)</th>
<th>HbA1c (%)</th>
<th>Age</th>
<th>Add on to:</th>
<th>N</th>
<th>Sex</th>
<th>% female</th>
<th>Diabetes duration (years)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrower 1985</td>
<td>Gliclazide 320 mg</td>
<td>Glibenclamide 30 mg</td>
<td>52</td>
<td>12</td>
<td>60</td>
<td>No</td>
<td>20/19</td>
<td>n.a.</td>
<td>4</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Jerums 1987</td>
<td>Gliclazide 240 mg</td>
<td>Glibenclamide 15 mg</td>
<td>104</td>
<td>9.6</td>
<td>60</td>
<td>No</td>
<td>9/8</td>
<td>35</td>
<td>8</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Collier 1989</td>
<td>Gliclazide 240 mg</td>
<td>Metformin 3 g</td>
<td>24</td>
<td>11.9</td>
<td>54</td>
<td>No</td>
<td>12/12</td>
<td>n.a.</td>
<td>0</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Noury 1991</td>
<td>Gliclazide 240 mg</td>
<td>Metformin 1.7 g</td>
<td>13</td>
<td>9.7</td>
<td>55</td>
<td>No</td>
<td>27/30</td>
<td>51</td>
<td>3</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Tessier 1994</td>
<td>Gliclazide 320 mg</td>
<td>Glibenclamide 20 mg</td>
<td>26</td>
<td>8.6</td>
<td>72</td>
<td>No</td>
<td>11/11</td>
<td>18</td>
<td>5</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Tessier 1999</td>
<td>Gliclazide 320 mg</td>
<td>Metformin 1.7 g</td>
<td>24</td>
<td>7.5</td>
<td>59</td>
<td>No</td>
<td>18/18</td>
<td>31</td>
<td>5</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Guvener 1999</td>
<td>Gliclazide 320 mg</td>
<td>Acarbose 600 mg</td>
<td>26</td>
<td>8.5</td>
<td>56</td>
<td>Insulin</td>
<td>18/20</td>
<td>79</td>
<td>11</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Salman 2001</td>
<td>Gliclazide 320 mg</td>
<td>Acarbose 600 mg</td>
<td>24</td>
<td>8.8</td>
<td>54</td>
<td>No</td>
<td>30/27</td>
<td>42</td>
<td>4</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>NCT01022762 2010</td>
<td>Gliclazide 240 mg</td>
<td>Repaglinide 12 mg</td>
<td>16</td>
<td>7.2</td>
<td>62</td>
<td>Metformin</td>
<td>218/217</td>
<td>46</td>
<td>1</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Furlong 2003</td>
<td>Gliclazide 240 mg</td>
<td>Repaglinide 12 mg</td>
<td>13</td>
<td>9.3</td>
<td>59</td>
<td>Insulin</td>
<td>39/41</td>
<td>47</td>
<td>8</td>
<td>91</td>
<td></td>
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<tr>
<td>Lawrence 2004</td>
<td>Gliclazide 320 mg</td>
<td>Pioglitazone 45 mg</td>
<td>24</td>
<td>7.7</td>
<td>61</td>
<td>Low dose oral glucose lowering agents 66%</td>
<td>20/20/20</td>
<td>35</td>
<td>n.a.</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Schertnhamer 2004</td>
<td>Gliclazide 120 mg XR</td>
<td>Glimepiride 6 mg</td>
<td>27</td>
<td>8.3</td>
<td>61</td>
<td>Metformin/acarbose</td>
<td>388/427</td>
<td>49</td>
<td>6</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Charbonell 2004</td>
<td>Gliclazide 320 mg</td>
<td>Pioglitazone 45 mg</td>
<td>52</td>
<td>8.6</td>
<td>57</td>
<td>Metformine</td>
<td>313/317</td>
<td>50</td>
<td>6</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Mteews 2005</td>
<td>Gliclazide 320 mg</td>
<td>Pioglitazone 45 mg</td>
<td>52</td>
<td>8.6</td>
<td>57</td>
<td>Metformine</td>
<td>140/135</td>
<td>35</td>
<td>9</td>
<td>80</td>
<td></td>
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<tr>
<td>Kardas 2005</td>
<td>Gliclazide MR 90</td>
<td>Glibenclamide 10 mg</td>
<td>16</td>
<td>7.2</td>
<td>62</td>
<td>Metformine in 28%</td>
<td>49/50</td>
<td>60</td>
<td>3</td>
<td>77</td>
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<tr>
<td>Pierucci 2006</td>
<td>Gliclazide 320 mg</td>
<td>Pioglitazone 45 mg</td>
<td>52</td>
<td>8.8</td>
<td>59</td>
<td>Diet or 1 oral drug</td>
<td>133/129</td>
<td>48</td>
<td>7</td>
<td>n.a.</td>
<td></td>
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<tr>
<td>Ristic 2006</td>
<td>Gliclazide 240 mg</td>
<td>Nateglinide 180 mg</td>
<td>24</td>
<td>7.6</td>
<td>62</td>
<td>Metformin</td>
<td>133/129</td>
<td>48</td>
<td>7</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Foley 2009</td>
<td>Gliclazide 320 mg</td>
<td>Vildagliptine 100 mg</td>
<td>104</td>
<td>8.5</td>
<td>59</td>
<td>Metformin</td>
<td>533/530</td>
<td>44</td>
<td>2</td>
<td>84</td>
<td></td>
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<tr>
<td>Filozof 2009</td>
<td>Gliclazide 320 mg</td>
<td>Vildagliptine 100 mg</td>
<td>52</td>
<td>8.5</td>
<td>59</td>
<td>Metformin</td>
<td>490/503</td>
<td>48</td>
<td>7</td>
<td>85</td>
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</tbody>
</table>

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When comparing gliclazide to metformin the effect estimate was 1.37 kg (95%CI 0.15, 2.60, I² 28%). This analysis was based on two studies including 45 patients for gliclazide and 48 for metformin [23,25].

Studies with pioglitazone or DPP-4 inhibitors had a high risk for selective reporting; further weight comparisons with these individual drug classes were not performed.

Cardiovascular events and mortality

The incidence of cardiovascular events could be evaluated in 9 studies [8,23,27,28,31–34,36]. There were 11 cases in 1480 gliclazide users and 20 cases in the comparator group of 1508 patients, risk ratio for gliclazide 0.95 (95% CI: 0.57, 1.61). Information on total mortality and cardiovascular mortality was available from 17 and 15 studies, respectively. There were 12 deaths in 2500 gliclazide users and 8 deaths in the comparator group of 2569 patients, risk ratio gliclazide vs. others; 1.50 (95% CI: 0.62, 3.62) [8,14,20–29,31–36]. The number of cardiovascular deaths were 3 in 1602 gliclazide users and 7 in 1619 comparator patients, risk ratio gliclazide 0.81 (95% CI: 0.26, 2.47) [8,14,20–28,31–34,36].

Discussion

Severe hypoglycemic events caused by gliclazide are extremely rare and the occurrence of confirmed symptomatic non-severe hypoglycemic events in gliclazide users could exclusively be ascribed to studies using a gliclazide dose of 320 mg instead of the advised maximum dose of 240 mg. Gliclazide probably has advantages over glimepiride regarding hypoglycemia risk. Gliclazide appears to have a non-relevant beneficial effect on glycemic control compared to other oral glucose lowering agents. There were no trials investigating cardiovascular effects of gliclazide and weight comparisons were limited by a low number of trials and publication bias. The methodological quality of most studies was poor.

Gliclazide appears to be safe regarding severe hypoglycemia risk with one severe hypoglycemic event in 2,387 gliclazide users. Severe hypoglycemiias were defined as the primary outcome, since severe episodes have the most deleterious effects [38]. We acknowledge that the risk of severe hypoglycemia in the comparator groups was also very low. This could either suggest that the risk of severe hypoglycemic events is rare in general, or that randomized trials are not the best way for evaluating hypoglycemic risk and that patients in trials represent a highly selected group.

The maximum dose of gliclazide (regular formulation) between studies varied from 240 to 320 mg. Two industry-sponsored high bias trials, both comparing gliclazide to vildagliptine, were responsible for all symptomatic confirmed non-severe events in gliclazide users; both used the 320 mg gliclazide dose [34,35]. It appears that under the condition of not exceeding the 240 mg dose, gliclazide is safe regarding non-severe confirmed hypoglycemic events. One trial comparing gliclazide with glimepiride showed a definitely lower incidence of confirmed (either symptomatic or not) hypoglycemia events [29]. In patients who are at risk for hypoglycemic episodes, gliclazide is probably preferable to glimepiride.

Regarding hypoglycemic events, it should be noted that cut-off values can have great impact on the event rate [39] and non-symptomatic confirmed hypoglycemic events were not included in the meta-analyses because of concerns for overestimation of the event rate. The definition and recording of hypoglycemic events between studies differed substantially. Asymptomatic confirmed hypoglycemic events below for example 3.0 mmol/L could be relevant and we acknowledge that unconfirmed hypoglycemic events can be clinically relevant in patients with hypoglycemia unawareness.

There seemed to be a small benefit of metformin compared to gliclazide regarding weight although the effect estimate was small. Most studies either did not report or did not report ITT-analyses on differences in weight between individual drugs (i.e. pioglitazone and vildagliptine) and gliclazide, suggesting a high risk for

Figure 2. Forest plot of the main effect outcome. The main effect outcome HbA1c; gliclazide versus other glucose lowering agents. doi:10.1371/journal.pone.0082880.g002
publication bias in the weight analysis. The lack of cooperation by authors and pharmaceutical companies in providing data after our request is disconcerting [29,30,31,34,35]. Because of concerns for bias, weight comparisons between gliclazide and other individual drug classes, with for example DPP-4 inhibitors, were not performed.

Results from randomized trials in this review could not be used to confirm the observed beneficial cardiovascular effects found in cohort studies. The results regarding cardiovascular end-points and mortality must be interpreted with caution; none of the trials were designed to evaluate cardiovascular events, the number of randomized controlled trials included in the meta-analysis was low and the number of events was limited. Furthermore, study duration was relatively short in most cases. Also, a substantial number of studies did not report on specific adverse events. Randomized controlled trials are possibly not the best way of evaluating these adverse events, at least not when not designed for evaluating such endpoint and not endowed with a sufficiently long study duration [40].

A considerable amount of heterogeneity in the primary efficacy analysis was noted. This heterogeneity could be explained by differences in primary research questions [8], the inclusion of small studies, the use of different doses of gliclazide and varying use of diabetes drugs before randomization between studies.

We did not include the ADVANCE study in the meta-analyses. The ADVANCE investigated intense glucose control with gliclazide to a strategy with standard glucose control without gliclazide. Intensive glucose control itself (irrespective of the drug that is used) is associated with a lower HbA1c, increased risk for hypoglycemic events, weight increase and probably has beneficial effects on cardiovascular outcomes [37,41].

Except for non-severe hypoglycemia risk, we were not able to make clinically relevant recommendations due a low number and quality of trials. Our conclusions regarding gliclazide as a second line treatment were not robust, due to a small number of trials.

We did not conduct separate analyses for each comparator class or looked at within-class difference because of scarcity of data. Furthermore, we did not conduct sensitivity analyses or meta-regression to examine the contribution of participants’ baseline characteristics to the effect estimate of our primary outcome and did not conduct mixed treatment comparison/network meta-analysis. Exclusion of trials at high risk of bias in a sensitivity analysis did not relevantly alter the results of the main analysis, although this analysis included few trials.

Conclusions

Relative few studies used gliclazide as active comparator despite years of clinical experience, no need for dose adjustment in renal dysfunction, low costs and observational studies showing possible cardiovascular benefits. The risk of severe or confirmed hypoglycemia was extremely low with gliclazide. Gliclazide could have a relative favorable short-term safety profile; specifically compared to glimepiride, under the condition of not exceeding the maximum dose of 240 mg, without evidence for a loss of efficacy. The quality of reporting changes in weight in randomized controlled trials could benefit from substantial improvements. Although none of the trials were designed to evaluation cardiovascular end-points, the possibility of cardiovascular benefits as shown in observational studies warrants attention in future randomized trials.

Ethics Statement

An ethics statement was not required for this work.

Data sharing

The full dataset and technical appendix are available at request from the corresponding author.

Supporting Information

Attachment S1 PROSPERO protocol. (TIFF)
Attachment S2 Search strategy. (TIFF)
Attachment S3 Risk of bias summary. Presentation of the risk of bias summary of the review author’s judgments about each risk of bias item for each included study. (TIFF)
Attachment S4 Risk of bias plot. Presentation of the risk of bias graph of the review author’s judgments about each risk of bias item presented as percentages across all included study. Studies in green or + are at low risk of bias. (TIFF)
Checklist S1 PRISMA Checklist. (PDF)

Author Contributions

Conceived and designed the experiments: GL GHdB KJJvH PvD KHG SH ROBG HJGB NK. Analyzed the data: GL KJJvH P vD KHG GHdB. Contributed reagents/materials/analysis tools: GL KHG GHdB. Wrote the paper: GL KJvH P vD KHG SH ROBG HJGB NK. Final approval of the version to be published: GL GHdB KJJvH P vD KHG ROBG SH HJGB NK.

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