UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

AVALIAÇÃO DA SEGURANÇA DAS SULFONILURÉIAS DE SEGUNDA E TERCEIRA GERAÇÃO NO TRATAMENTO DO DIABETES MELITO TIPO 2: REVISÃO SISTEMÁTICA COM META-ANÁLISE

DISSERTAÇÃO DE MESTRADO

DIMITRIS RUCKS VARVAKI RADOS

Porto Alegre, 2015

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Mestre em Endocrinologia.

Orientadores: Profa Dra. Cristiane Bauermann Leitão e Prof Jorge Luiz Gross.

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Esta dissertação de mestrado será apresentada no formato exigido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela será constituída de uma introdução em português e um artigo em inglês, este formatado conforme as exigências da respectiva revista médica à qual será submetido para avaliação e posterior publicação. O artigo em inglês desta tese é um artigo do tipo Revisão Sistemática e Meta-Análise.

DEDICATÓRIA

"Ensinar é um exercício de imortalidade.

De alguma forma continuamos a viver naqueles cujos olhos aprenderam a ver o mundo

pela magia da nossa palavra.

O professor, assim, não morre jamais..."

Rubem Alves

Aos que me ajudam a encontrar o caminho.

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LISTA DE ABREVIATURAS

ACCORD	*Action to Control Cardiovascular Risk in Diabetes*
ADA	*American Diabetes Association*
ADOPT	*A Diabetes Outcome Progression Trial*
CAROLINA	*Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes*
CI	*Confidence interval*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DM2	Diabetes melito tipo 2
EASD	*European Association for the Study of Diabetes*
GRADE	*Grading of Recommendations, Assessment, Development and Evaluation*
NNH	*Number Needed to Harm*
OR	*Odds ratio*
PRISMA	*Preferred Reporting Items in Systematic Reviews and Meta-analysis*
RCT	*Randomized Clinical Trial*
TSA	*Trial Sequential Analysis*
UGDP	*University Group Diabetes Program*
UKPDS	*United Kingdom Prospective Diabetes Study*

Capítulo 1 - Introdução

Nos últimos 10 anos tem-se observado o surgimento de uma gama de novas medicações para o manejo glicêmico dos pacientes com diabetes melito tipo 2 (DM2) (1). Para tanto, um grande número de ensaios clínicos randomizados foram conduzidos abordando a eficácia dessas drogas com diferentes estratégias terapêuticas (monoterapia ou combinações) e em diferentes momentos da história natural da doença (diagnóstico recente ou longa duração de doença, alto ou baixo risco de eventos cardiovasculares) (2-5).

Se, por um lado, essa grande quantidade de opções é benéfica, por outro a decisão individual junto ao paciente de qual novo tratamento será usado torna-se difícil. A grande quantidade de estudos a serem considerados no momento da decisão terapêutica e a ausência de comparação direta de diversas dessas drogas são dois fatores principais nessa situação.

Neste contexto, estudos de revisão sistemática com meta-análise são úteis para avaliar os benefícios de diferentes intervenções. Além disso, o uso da técnica de *trial sequential analysis* (TSA) permite avaliar se os dados disponíveis são suficientes para conclusões definitivas – uma estimativa do poder total dos estudos incluídos (6, 7).

O efeito hipoglicemiante das sulfas foi descrito há mais de 60 anos (8) e, como classe, as sulfoniluréias foram as primeiras drogas orais disponíveis para o tratamento do DM2. Sua ação se dá através do bloqueio de canais de potássio na célula beta na ilhota pancreática, estimulando a liberação de insulina na circulação. São drogas bastante potentes em termos de efeito glicêmico, baixando em média 1,5% de hemoglobina glicada, tanto como monoterapia, como em combinação (9). Além disso, em análises fármaco-econômicas são a segunda opção no tratamento do DM2 (após a metformina) com melhor relação custo-efetividade (10).

Apesar do efeito benéfico na glicemia, sua segurança é questionada há vários anos, em especial após a divulgação dos resultados do estudo *University Group Diabetes Program*

(UGDP) na década de 1970, mostrando aumento de mortalidade nos pacientes randomizados para tolbutamida (11). Com o surgimento das sulfoniluréias de segunda e terceira geração, com menor risco de hipoglicemia e mais seletivas, essa discussão perdeu força, até o resultado de um dos subgrupos do estudo *United Kingdom Prospective Diabetes Study* (UKPDS) que novamente mostrou aumento de risco de morte por todas as causas nos pacientes alocados para a associação sulfoniluréias e metformina (12).

Desde então, estudos observacionais (13), meta-análises de estudos observacionais (14, 15) e meta-análises de ensaios clínicos (16, 17) vem sendo publicados, com resultados conflitantes ou inconclusivos. Desta forma, considerando as limitações dos estudos prévios e a persistente dúvida em relação à segurança das sulfoniluréias, planeja-se analisar o risco de mortalidade e eventos cardiovasculares relacionados com o uso de sulfoniluréias de segunda e terceira geração em pacientes com DM2.

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Capítulo 2 – Artigo original

Sulfonylurea use is not associated with all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials

Short Title: Sulfonylureas and all-cause mortality

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ABSTRACT

BACKGROUND: Sulfonylureas are an effective and inexpensive treatment for type 2 diabetes. There is conflicting data about the safety of these drugs regarding mortality and cardiovascular outcomes. The objective of the present study was to evaluate the safety of sulfonylureas most frequently used, and to analyse if the available sample is powered enough to support the results through trial sequential analysis (TSA).

METHODS AND FINDINGS: Electronic databases (Pubmed, Embase, Cochrane Library) were reviewed from inception to December 2014. Randomised clinical trials (RCT) of at least 52 weeks in duration evaluating second- or third-generation sulfonylureas in the treatment of adults with type 2 diabetes and reporting outcomes of interest were included. Primary outcomes were all-cause and cardiovascular mortality. Additionally, myocardial infarction and stroke events were evaluated. Data was summarized with Peto odds ratio and the reliability of the results was evaluated with TSA. Forty-seven RCTs with 37,650 patients and 890 deaths in total were included. Sulfonylureas were not associated with all-cause (OR 1.12 [95% CI 0.96 to 1.30]) or cardiovascular mortality (OR 1.12 [95% CI 0.87 to 1.42]). Sulfonylureas were also not associated with increased risk of myocardial infarction (OR 0.92 [95% CI 0.76 to 1.12]) or stroke (OR 1.16 [95% CI 0.81 to 1.66]). Individually, glipizide was the only sulfonylurea associated with increased all-cause mortality (OR 1.68 [95% CI 1.06 to 2.66]). Excluding glipizide trials from analysis the ORs for all-cause mortality was reduced (OR 1.03 [95% CI 0.86 to 1.23]). By using TSA we discarded the absolute risk of harm of 0.5% for mortality and cardiovascular events.

CONCLUSION: Sulfonylureas are not associated with increased risk for all-cause and cardiovascular mortality, myocardial infarction or stroke. Current evidence supports the safety of sulfonylureas; an absolute risk of 0.5% could be firmly discarded. PROSPERO registry CRD42014004330.

Introduction

Sulfonylureas are still used frequently in the treatment of patients with type 2 diabetes because they are effective in both improving glycaemic control [1] and reducing the microvascular complications of diabetes;[2] in addition, they have the advantage of being inexpensive.[3] It is estimated that sulfonylureas are currently used by 20-30% of patients with diabetes in developed countries.[7,8] Furthermore, it can be assumed that its use in type 2 diabetic patients is 40-45% around the world based on the results of recent multinational cardiovascular studies.[9-11]

There are concerns regarding the safety of sulfonylureas that have persisted since the results of the first randomized controlled trial (RCT) in the evaluation of diabetes treatment (University Group Diabetes Program)[12] until the present time.[13-15] Observational studies reported conflicting results,[16-19] some of them disclosing an association of sulfonylurea use with increased risk of cardiovascular events.[17,18] However, observational studies have limitations because of selection and attrition bias, and the results inferred only association, and not causation.[20] There is still a current and intense debate surrounding these safety issues.[13,14]

Recent meta-analyses evaluating the safety of sulfonylureas as group [5,21-23] or in association with metformin [24] also reported contradictory results. Probably, this was due to the inclusion of observational studies,[23,24] inclusion of first generation sulfonylureas [21,22] and lack of evaluation of the optimal sample size.[5,22,23] Studies that included second or third generation sulfonylureas did not reported higher risk.[5,21-23]

When dealing with negative results it is important to evaluate the statistical reliability of the finding, i.e. the power of the analysis. Trial sequential analysis (TSA) is a tool that is increasingly being used [25] to assess whether optimal sample sizes – and benefit or harm boundaries – have been reached by an available sample assuming a minimal clinical

significant difference.[26] It has the potential to increase data reliability, [26] and its use might be of great benefit in determining whether the currently evaluable evidence about the safety of sulfonylureas is enough to discard falsely positive or negative conclusions.[27] Therefore, the aim of this study was to evaluate the safety of second and third generation sulfonylureas use in all-cause and cardiovascular mortality and cardiovascular events (myocardial infarction and stroke), and to quantify the statistical reliability of available data.

Methods

Protocol and registration

We conducted this study using a preconceived protocol according to the Cochrane recommendations [28] and registered it on the PROSPERO registry (CRD42014004330). This report follows the Preferred Reporting Items in Systematic Reviews and Meta-analysis (PRISMA) statement.[29]

Data sources and searches

The present study was intended to evaluate the overall safety of most frequently used sulfonylureas (both second- and third-generation) in type 2 diabetes through a review of RCTs. Therefore, the search strategy included the terms '*type 2 diabetes'*, '*sulfonylureas'* (second- and third-generation) and used the recommended, highly sensitive *Cochrane Collaboration* strategy for RCT systematic reviews.[28] No outcome or comparator was added in the search terms.

We searched the on-line databases of MEDLINE (through PubMed), EMBASE, and the Cochrane Library, as well as a manual review of reference lists of published studies up to December 2014. The terms used for searching PubMed are described in the additional material (S1 Appendix). We also searched the clinicaltrials.org registry and the 2014 abstract

books of international diabetes meetings (American Diabetes Association [ADA] and European Association for the Study of Diabetes [EASD]) for unpublished studies. No time period restrictions were made. All potentially eligible studies were considered for review, limited to the English, Spanish, German, French, Japanese or Portuguese languages.

Study selection

We included RCTs that evaluated patients with type 2 diabetes who were randomized to receive a second- or third-generation sulfonylurea for at least 52 weeks, and which reported all-cause or cardiovascular mortality, myocardial infarction or stroke data. As most of the studies were not specifically designed to evaluate these outcomes, absence of information was frequently observed. In these cases, we attempted to contact the corresponding authors before excluding any study due to lack of data.

We excluded studies where the comparator drug was withdrawn from the market due to safety issues (troglitazone). Duplicate reports and extensions of RCTs were also not considered for this review.

Data extraction

Two investigators (D.V.R. and L.C.P.) independently evaluated the titles and abstracts of the articles retrieved using the search process. Abstracts that did not meet the inclusion criteria or meeting exclusion criteria were discarded. We selected the remaining studies for full text evaluation and data extraction. Any disagreements regarding inclusion or exclusion of a study were solved by consensus and, if doubt persisted, a third reviewer (C.B.L) evaluated the reference.

We used a standardized form to extract the following details from retrieved studies: first author's name, publication year and journal, study characteristics (i.e. comparator, co-

intervention), patient characteristics (mean age, proportion of men/women, proportion of patients with hypertension, dyslipidaemia and active smoking), study methodology (intervention dosages, frequency and duration), number of patients included and lost to follow-up, and number of patients with outcomes of interest (all-cause and cardiovascular death, myocardial infarction and stroke).

Quality assessment

We assessed the included studies in six domains according to The Cochrane Collaboration's tool for assessing risk of bias:[28,30] i) random sequence generation, ii) allocation concealment, iii) blinding, iv) incomplete outcome data, v) selective reporting and vi) other bias; for other bias we evaluated if the study was conducted with funding support from the pharmaceutical industry. We evaluated the quality of the evidence for each meta-analysis using the **Grading of Recommendations, Assessment, Development and Evaluations (GRADE)** approach. The quality of evidence was classified as 'high', 'moderate', 'low' or 'very low'.

Limitations of design or implementation (risk of bias), indirectness of evidence, inexplicable heterogeneity, inconsistent results and presence of significant publication bias were assessed and, if present, decreased the quality of the result. On the other hand, if present, the following items were considered to increase the quality of the evidence: large magnitude of effect, presence of a dose-response gradient and plausible confounding that increased confidence in an estimate.[31]

Data synthesis and analysis

We compared the outcomes of interest in patients treated with sulfonylureas with a control group (diet, placebo or other antihyperglycemic medication). We also performed a meta-

analysis separating the controls in classes (diet or placebo, insulin, metformin, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, glucagon-like peptide-1 analogues, dipeptidyl peptidase-4 inhibitors and sodium-glucose transporter-2 inhibitors) and for each sulfonylurea (glibenclamide, glimepiride, glipizide and gliclazide). Furthermore, as sulfonylureas are commonly used as a second agent in addition to metformin,[1,6,32] we assessed the effects of sulfonylureas when used as an add-on to metformin.

As recommended,[28] if a study had more than two intervention groups using different comparators (e.g. rosiglitazone vs. metformin vs. sulfonylurea), we split the sulfonylurea group sample into two or more groups to avoid falsely increasing the sample size and thereby maintaining the randomization.[28]

To evaluate if the present meta-analysis had sufficient sample size for establishing firm conclusions about the effect of interventions,[26,27] we performed TSA for the major outcomes. Traditionally, interim analysis of a single trial evaluates if the monitoring boundaries for a predefined estimated effect are reached before the whole trial population (optimal sample size) has been accrued.[26,27] Similarly, TSA performs a cumulative meta-analysis, which creates a Z curve of the summarized observed effect (the cumulative number of included patients and events) and the monitoring boundaries for benefit, harm and futility and it estimates the optimal sample size.[26,27] These boundaries and analyses are adjusted to account for the amount of available evidence and to control for repeated analyses, while maintaining type I error at 5% and the power at 80%.[26,27] Therefore, they are initially very wide, but as more information (trials, patients and events) is included, they become narrower converging to the unadjusted significance interval. If the Z curve of the cumulative meta-analysis crosses one of the boundaries, no further studies are required and there is sufficient information to support the conclusions. Most importantly, when evaluating treatments that are expected to be not different, the futility boundary allows identifying the “no effect area” as

early as possible. As the required number of observations (patients, events) is available, the Z curve crosses the futility boundary and identifies that further randomization is not necessary and that it can be affirmed that the intervention does not have the established effect.[26,27]

We performed an initial analysis to evaluate the heterogeneity (I^2)-adjusted optimal sample size for confirming or discarding a harm of an absolute difference between groups of 0.5%, which would lead to a number needed to harm (NNH) of 200 patients.

The current study deals with rare event data and with studies reporting zero events in both arms (double-zero studies). Usual methods (Mantel-Haenszel OR) used to summarize and aggregate dichotomous variables do not perform as expected in meta-analysis of rare events and the risk of finding false positives is increased.[28,33,34] Therefore, the studies were summarized using the Peto OR method. This method seems to be better suited to these situations, especially when the incidence of events is near 1% and the effects of intervention are of a small magnitude.[34] As a sensibility analysis we performed the analysis with Mantel-Haenszel OR and the results remained unchanged.

When dealing with double-zero studies, the Peto OR is not able to use the information, and the trial is therefore excluded from the analysis. In this setting, it is suggested that a sensitivity analysis with continuity correction is performed.[35] TSA software does however include double-zero events trials in the analysis, using empirical continuity correction.[27] Therefore, although our forest plots were constructed using the Peto OR analysis (double-zero studies not plotted) double-zero studies *were* included in the TSA analysis and graphics.

We evaluated the heterogeneity using a Cochran Q test with a threshold P-value of 0.1 and an I^2 test, with a value >50% indicating of high heterogeneity.

We assessed publication bias by using a contour-enhanced funnel plot and asymmetry by using Begg and Egger tests. A significant publication bias was considered if the $P<0.10$. A

trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of results.

The main analyses were conducted using Stata version 12.0 (Stata Inc., College Station, Texas, USA) and RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The Begg and Egger test and the trim-and-fill tests were conducted using Stata software version 12.0. The empirical continuity correction and TSA were conducted using TSA software version 0.9 [beta] (Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Literature search

We identified 5572 studies through both the literature and manual searches (Figure 1). After excluding duplicate references and reviewing titles and abstracts, we selected 192 references for full-text evaluation. One-hundred-and-nine trials either did not meet the inclusion criteria or met the exclusion criteria. The main reasons for exclusions were: short duration (40 references, 37%), duplicated records (24 references, 22%) and non-randomised study (17 references, 15%). In addition, 36 studies did not report outcome data and this data was not forthcoming after contacting the relevant corresponding authors. These studies were mostly of short duration (75% of the studies within 52 weeks) and represented only 10% of the total sample. The reviewers had a high agreement rate (κ=0.917). The final number of studies included was 47 (or 55 pair-wise comparisons),[2,36-81] representing 37,650 patients (16,037 randomized to sulfonylureas and 21,613 to comparators). There were 890 all-cause deaths, 354 cardiovascular deaths, 589 myocardial infarctions and 275 strokes.

Study characteristics and risk of bias

The included trials were published from 1986 to 2014. The duration varied from 12 to 133 months. The mean age of the patient population was 57.3 years and mean baseline HbA_{1c} was 7.2% (minimum 6.8%, maximum 12.2%). Most studies compared sulfonylureas with an active control group. Detailed information about included studies is depicted in S1 Appendix. We present details regarding the assessment of quality for individual studies and across studies in the additional material (S1 Appendix). Random sequence generation, allocation concealment and blinding of outcome assessment were unclear in most studies; blinding of participants and personnel, incomplete outcome data and selective reporting were considered as having a low chance of bias in most studies.

Sulfonylureas and all-cause or cardiovascular mortality

Our meta-analysis did not show an association between use of sulfonylureas and all-cause (OR 1.12 [95% CI 0.96 to 1.30]) or cardiovascular mortality (OR 1.12 [95% CI 0.87 to 1.42]; figures 2 and 3). Both analyses have low heterogeneity (all-cause mortality: $I^2 = 0\%$, $P = 0.67$; cardiovascular mortality: $I^2 = 12\%$, $P = 0.30$). The inclusion of double-zero studies with empirical continuity correction analysis did not affect the results (OR 1.11 [95% CI 0.96 to 1.29] and OR 1.12 [95% CI 0.87 to 1.42] for all-cause and cardiovascular mortality, respectively). When restricting the analysis for studies with follow-up longer than 2 years, the results were similar for all-cause (OR 1.05 [95% CI 0.89 to 1.24]) and cardiovascular mortality (OR 1.07 [95% CI 0.83 to 1.39]). We identified publication bias for all-cause mortality. Despite this, the results were unaffected by the trim-and-fill computation: in reality, the point estimation after the computation of theoretical unpublished studies for all-cause mortality was smaller (OR 1.08 [95% CI 0.93 to 1.25]). There was no publication bias for cardiovascular mortality.

Sulfonylureas and myocardial infarction or stroke

A smaller number of trials reported myocardial infarction and stroke data (23 studies each, comprising 26,521 and 26,175 patients for myocardial infarction and stroke, respectively). We found no difference for myocardial infarction in patients treated with sulfonylureas (OR 0.92 [95% CI 0.76 to 1.12]). Including double-zero studies with empirical continuity correction left the results unaffected (OR 0.92 [95% CI 0.76 to 1.12). In addition, no association was observed between sulfonylureas and stroke (OR 1.16 [95% CI 0.81 to 1.66]). The inclusion of double-zero studies with empirical continuity correction did not change these results as well (OR 1.16 [95% CI 0.89 to 1.63]). Publication bias was present for myocardial infarction, but the results were similar with the trim-and-fill computation (OR 0.90 [95% CI 0.74 to 1.09]). No publication bias was identified for stroke events.

All-cause and cardiovascular mortality with different classes of antihyperglycemic agents or diet/placebo as comparators

We found no difference in all-cause mortality across all comparator classes (S1 Appendix). The results were similar for cardiovascular mortality outcomes. In both analyses heterogeneity was low.

Sulfonylureas as add-on to metformin and all-cause and cardiovascular mortality

Sulfonylureas as add-on to metformin were considered safe in terms of overall and cardiovascular mortality (Figure 4) with little heterogeneity. Including double-zero studies with empirical continuity correction in the analysis did not change these results.

Individual sulfonylurea agents and mortality

All-cause mortality analysis for each individual sulfonylurea is shown in S1 Appendix. Results are similar for cardiovascular mortality. In both analyses, heterogeneity was small.

Glipizide was the only sulfonylurea associated with increased all-cause (OR 1.68 [95% CI 1.06 to 2.66]) and cardiovascular mortality (OR 2.1 [95% CI 1.09 to 3.72]).

A sensitivity analysis excluding glipizide trials from the main analyses was performed. We observed a reduction in ORs for all-cause (OR 1.03 [95% CI 0.86 to 1.23] and cardiovascular mortality (OR 1.00 [95% CI 0.77 to 1.30]). Of note, the futility boundary was still reached in this situation.

Trial sequential analysis

TSA evaluates if there is enough information size to establish firm conclusions and this analysis was performed for the main outcomes in this review. For all-cause and cardiovascular mortality TSA showed that a NNH of 200 could be discarded, as the number of patients evaluated for all-cause (n = 37,650) and cardiovascular mortality (n = 21,893) surpassed the optimal sample sizes (n = 29,819 for all-cause mortality and n = 21,593 for cardiovascular mortality), as shown in Figures 5A and 5B. The combination of sulfonylureas and metformin was evaluated with TSA as well. The Z-curve surpassed the optimal sample size boundary and a NNH of 200 could be discarded for all-cause mortality (Figure 5C) but not for cardiovascular mortality. Similarly, for myocardial infarction and stroke the futility boundaries were reached.

Meta-analysis quality evaluation and summary of findings

The GRADE quality of evidence for all-cause and cardiovascular mortality was high. The identified publication bias does not appear to have skewed the results of the meta-analysis. Financial support from pharmaceutical industry is a conservative bias, as it might have increased the risk of benefit for the comparator drug.[82]

We graded the myocardial infarction and stroke meta-analysis as being of moderate quality. As these outcomes are at greater risk of being skewed due to the identified bias (especially due to underreporting and misdiagnosis) we downgraded the evidence by one point.

Discussion

The data presented here suggest that most frequently used sulfonylureas (second and third generations) are not associated with increased all-cause and cardiovascular mortality in patients with type 2 diabetes. By using TSA we were able to discard harm at a rate of 1 in every 200 treated patients (i.e. 0.5% of absolute risk) for mortality (all-cause and cardiovascular) and major events (myocardial infarction and stroke). Furthermore, this finding did not change when sulfonylureas were compared with almost every drug class currently available for the treatment of type 2 diabetes or as an add-on to metformin.

Other systematic reviews also evaluated this topic.[5,21-24] Although some of these studies identified increased risk of occurrence of mortality or cardiovascular events with sulfonylurea use,[21,22,24] other did not found an increased risk.[5,23] These contradictory results may be explained by the inclusion of first generation sulfonylureas,[21,22] observational studies [23,24] and short-term studies.[5,21-23] Furthermore, most systematic reviews did not evaluate if the data presented had enough power to support the conclusions.[5,22,23] We included only RCTs evaluating sulfonylureas from second and third generations as monotherapy or in combination. We chose to include only these sulfonylureas, because they are more frequently used than the first generation;[18] alone or in combination with metformin.[8]

A particular aspect our meta-analysis was the use of TSA. This analysis explores the possibility of a false negative result and evaluates the statistical reliability of present data. To perform this analysis it is necessary to establish a minimal clinically significant difference in the outcomes between the groups. Therefore, we chose to discard an absolute difference of

0.5%, which means a NNH of 200, based on the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[83] where an absolute difference of 1% (a NNH of 100) in mortality was found. We believe discarding this amount of risk is clinically meaningful and is an useful information. This assumption allowed us to exclude a risk as small as 1 death in every 200 treated patients for the evaluated outcomes. Ideally, it would be desirable to discard a smaller risk, for example a NNH of 500. However, this approach would require a sample of almost 195,000 patients randomized. Such amount of individuals will probably never be enrolled, as it is more than five times the amount of patients enrolled in sulfonylurea trials in the last 30 years.

Some limitations of the present study must be acknowledged. Unfortunately, we were not able to include all the identified studies in the meta-analyses because the mortality outcomes were not available, even after trying to contact the authors. However, these studies represented only 10% of the study population. It seems unlikely that these data would change the results as optimal sample size was reached for most analyses. Finally, most studies were not designed for cardiovascular safety but all of them have a duration of 52 weeks, which partially controls for this limitation.

Our study findings are reassuring, as we could discard a significant increased risk with the use of a frequently prescribed antihyperglycemic medication. However, sensitivity analyses disclosed that glipizide was associated with increased risk of mortality, but only few studies with a small number of events were included in this analysis. We believe that the finding of reduction of the ORs with the exclusion of the glipizide trials can reassure the clinician when prescribing other second or third generation sulfonylurea.

Another important unresolved question is which drug should be added to patients who are failing metformin monotherapy. The EMPA-REG study suggests empagliflozin might be the preferred drug, as this drug reduced cardiovascular events and all-cause mortality in patients

with diabetes and cardiovascular disease. [84] To date, no antihyperglycemic agent reduced mortality or cardiovascular events in association with metformin. Even the recent published trials of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes and high cardiovascular risk did not reduce cardiovascular events,[9-11] but there was a concern regarding heart failure incidence in two of them.[10,85] To clarify the question of which should be the preferred drug for patients failing metformin, The Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) and the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) results are awaited.[86,87]

In conclusion, the present study suggests that the use of second and third generation sulfonylureas in patients with type 2 diabetes is not associated with cardiovascular risk and all-cause mortality, irrespective of comparator or background medication.

Acknowledgement

Author contributions

DVR was responsible for study design, data acquisition, analysis, interpretation and drafting of the manuscript. LCFP contributed to study design, reference selection and data acquisition and analysis. LRR contributed to study design and data analysis. CBL contributed to study design, data analysis and interpretation and drafting of the manuscript. JLG contributed to study design, data analysis and interpretation and drafting of the manuscript. All authors have read and approved the final manuscript. Drs. Dimitris Varvaki Rados and Jorge Luiz Gross are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data.

Ethical Approval

Not needed.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no support was received from any organisation for the submitted work; JLG reports grants from *Conselho Nacional de Desenvolvimento Científico e Tecnológico*, during the conduct of the study; grants and other from Eli Lilly, grants from Bristol-Myers Squibb, grants and other from Boehringer Ingelheim, grants from GlaxoSmithKline, grants and other from Novo Nordisk, grants from Janssen, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work are reported.

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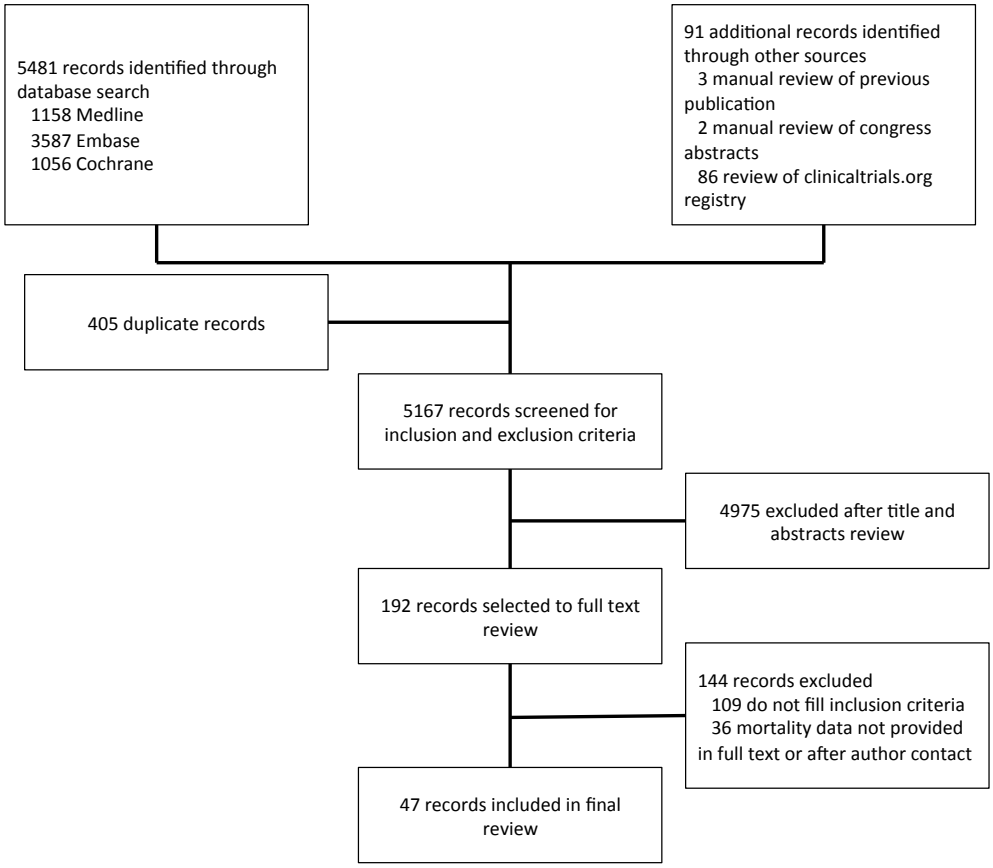

Figure 1. Studies flowchart.

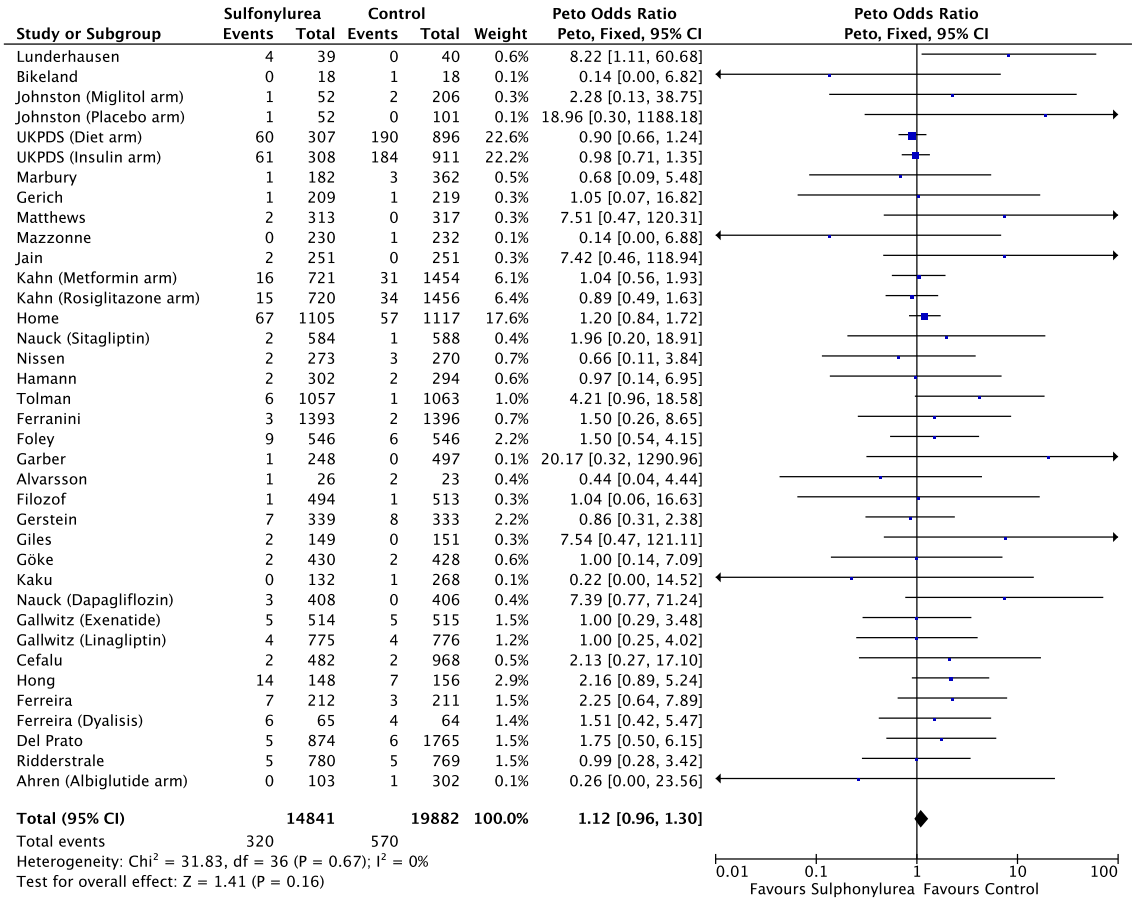

Figure 2. Forest plot for all-cause mortality.

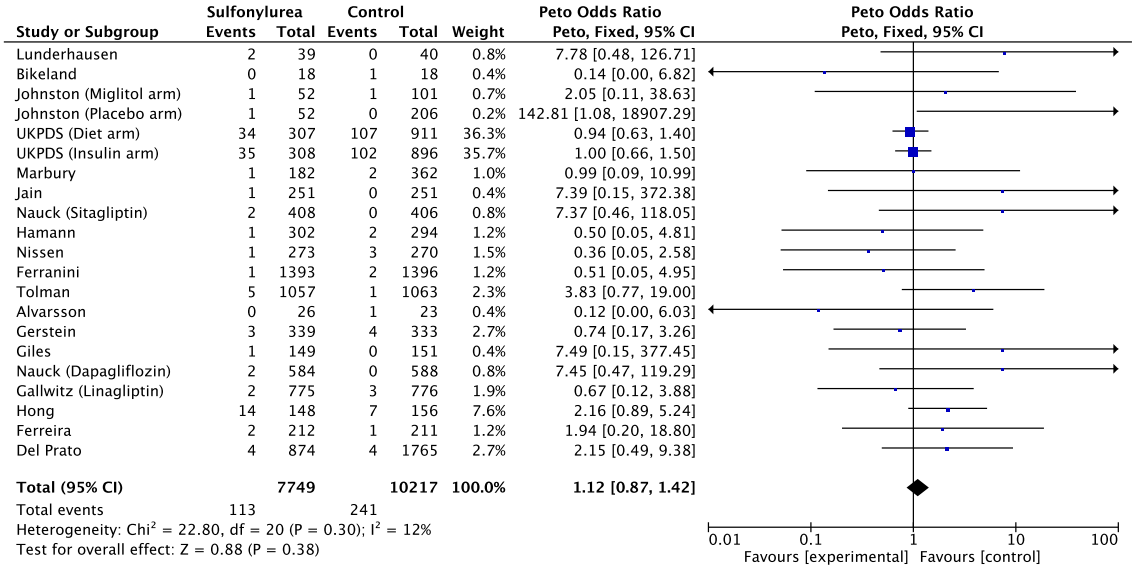

Figure 3. Forest plot for cardiovascular mortality.

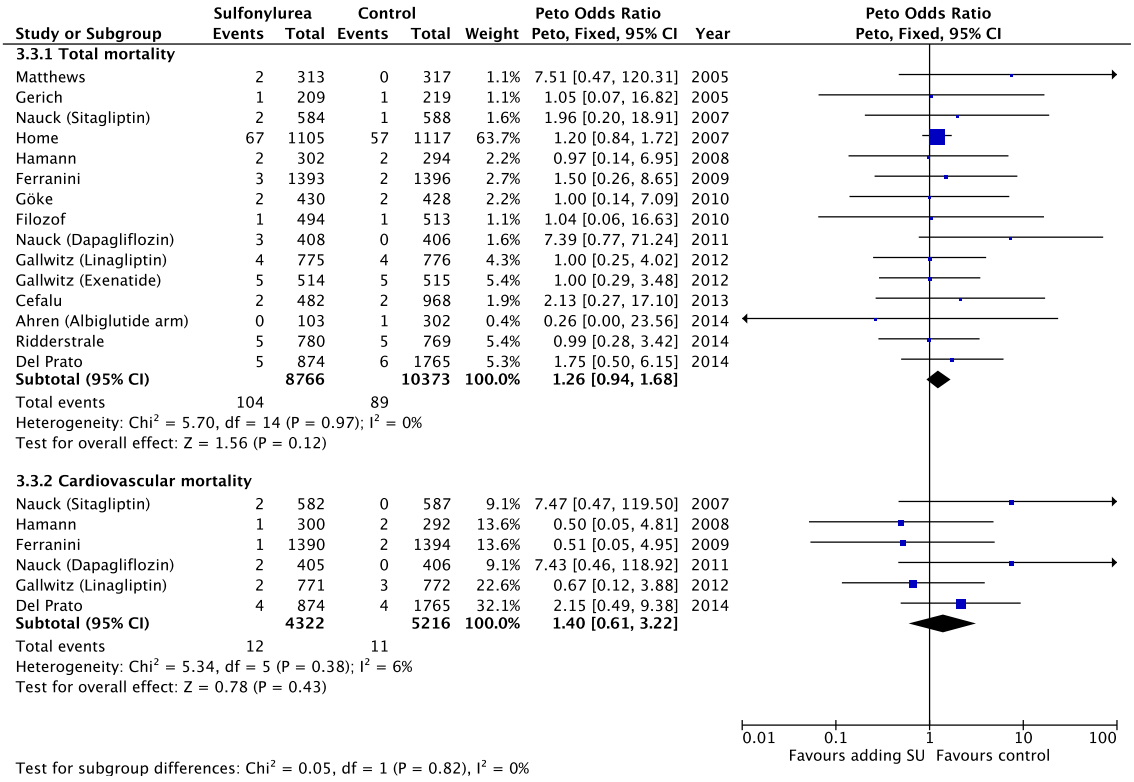

Figure 4. Forest plot of all-cause and cardiovascular mortality of sulfonylureas as add-on to metformin.

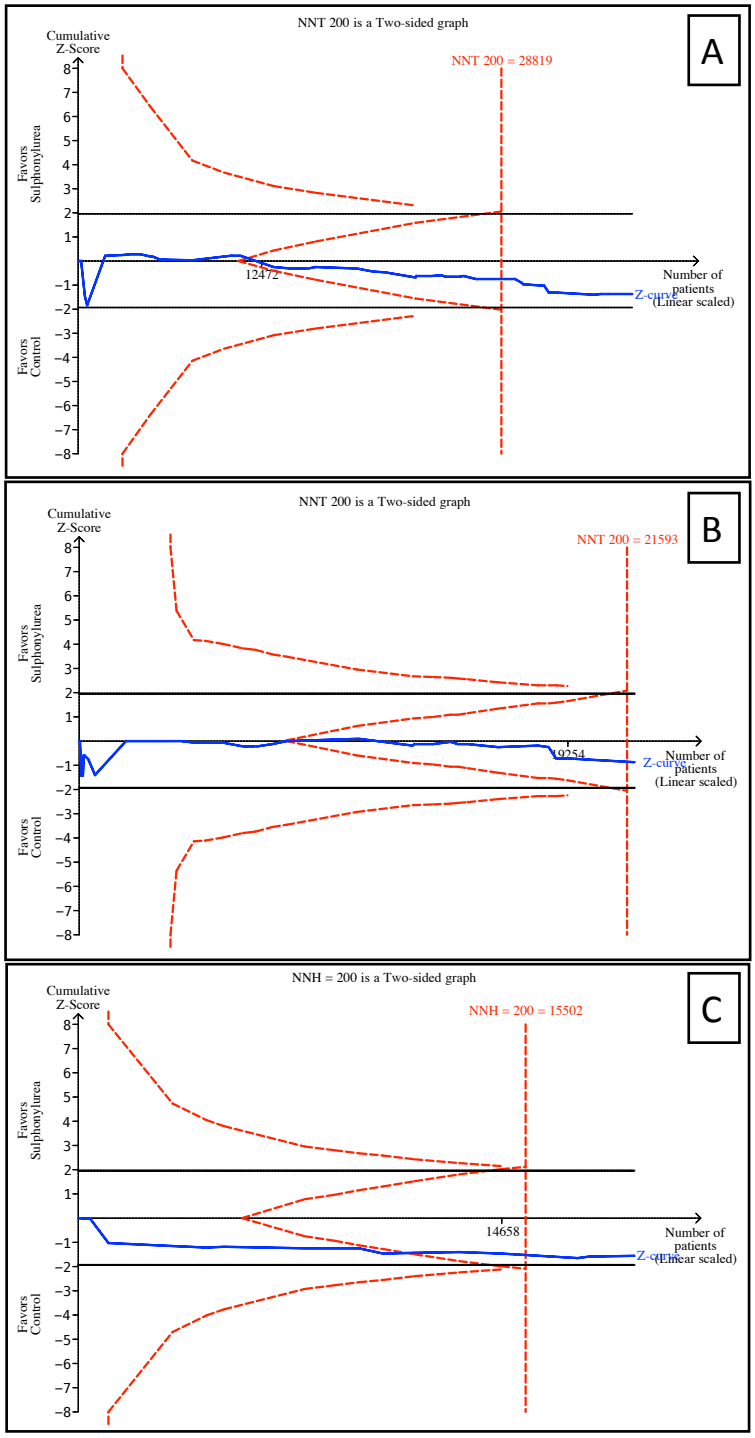

Figure 5. TSA graphics for mortality.

Legend: TSA discarded harm with sulfonylurea use with α of 5%, β of 80% and an absolute difference of 0.5% between the groups (sulfonylurea and comparator). Continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated

analysis and the continuous black lines represent the conventional confidence intervals. (A) Sulfonylureas overall. Futility and optimal sample boundaries size were crossed for all-cause mortality. (B) Sulfonylureas overall. Futility and optimal sample boundaries size were crossed for cardiovascular mortality. (C) Sulfonylureas as add-on to metformin. Futility and optimal sample size boundaries were crossed for all-cause mortality

Online only supplemental data

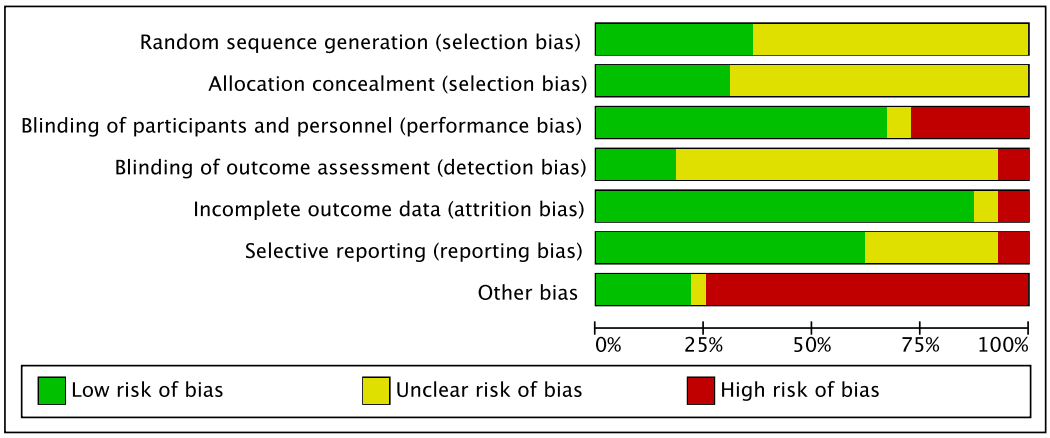

Figure S1. Quality assessment across studies.

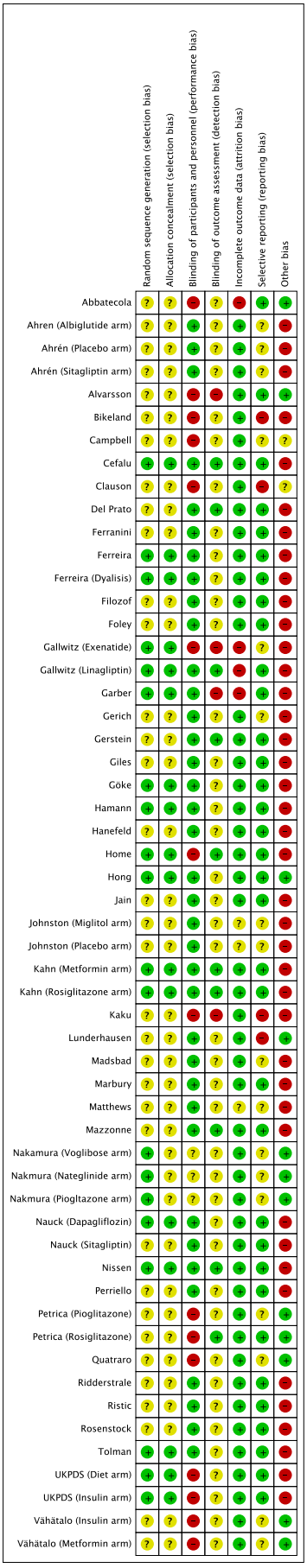

Figure 2. Quality assessment for individual studies.

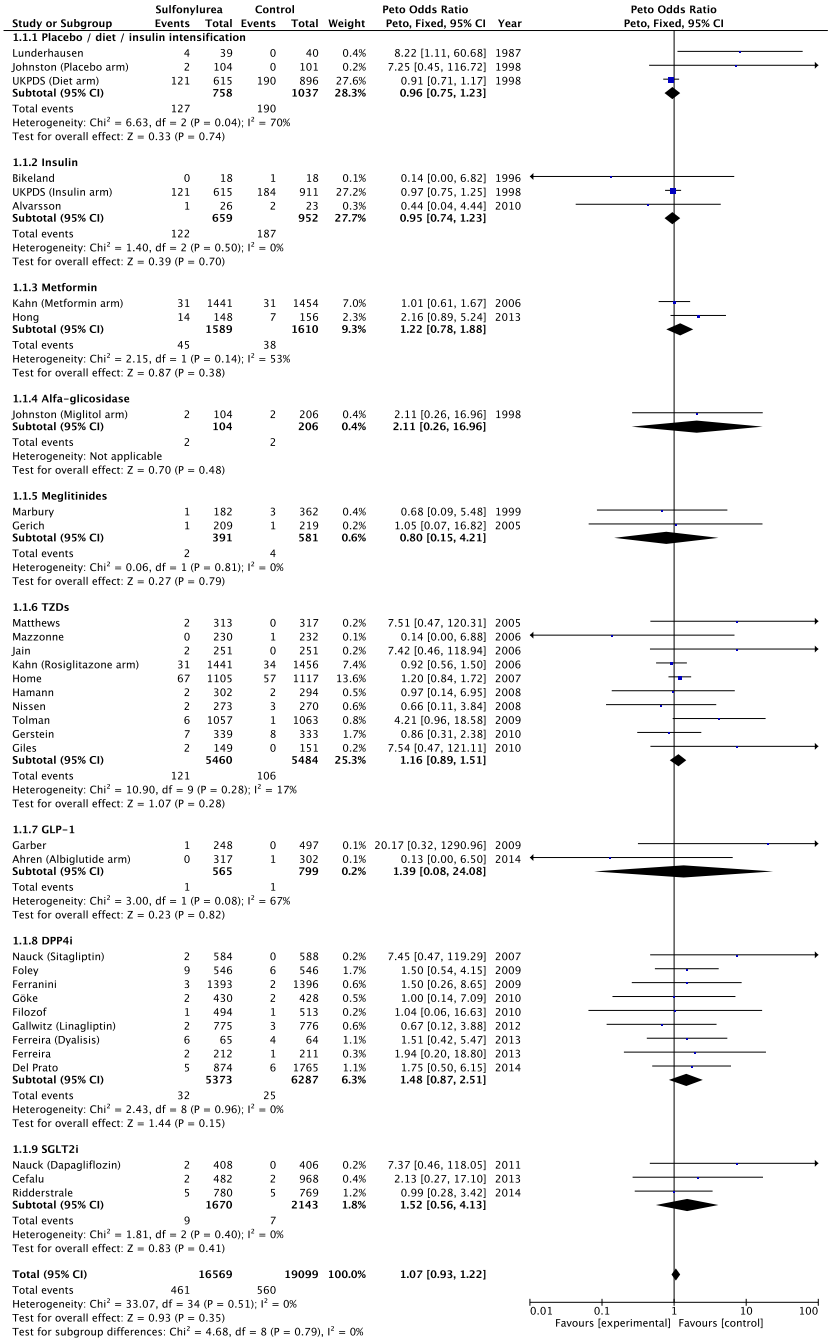

Figure S3. All-cause mortality across comparators.

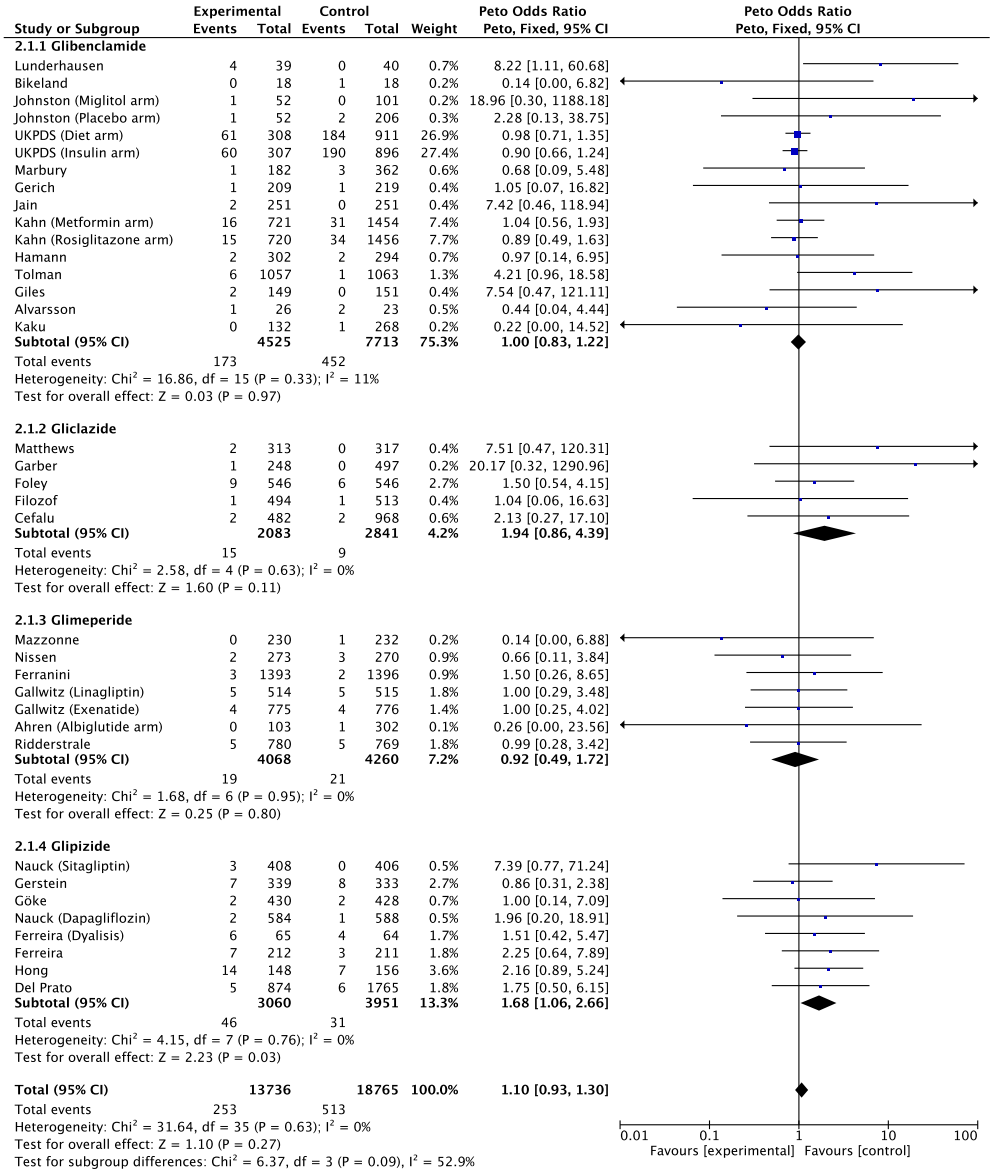

Figure S4. All-cause mortality for different sulfonylureas.

Table S1. Search strategy for PubMed.

("Glyburide"[Mesh]) OR ("glibornuride" [Supplementary Concept]) OR ("Glipizide"[Mesh]) OR ("gliquidone" [Supplementary Concept]) OR ("glisoxepide" [Supplementary Concept]) OR ("glyclopyramide" [Supplementary Concept]) OR ("glimepiride" [Supplementary Concept]) OR ("Gliclazide"[Mesh]) AND ("Diabetes Mellitus, Type 2"[Mesh]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh: noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])

Table S2. Included randomised clinical trials and their baseline characteristics.

Author	Year	Interventions	Number of patients	Mean age	Baseline HbA1c %	Follow-up (months)
Abbatecola[35]	2006	Glibenclamide	79	74.3	7.2	12
		Repaglinide	77	74.5	7.3	
Ahrén[36]	2014	Glimeperide	307	54.5	N.R.	36
		Sitagliptin	302	54.5	N.R.	
		Albiglutide	302	54.5	N.R.	
		Placebo	101	54.5	N.R.	
Alvarsson[37]	2010	Glibenclamide	26	55.9	6.8	72
		Insulin	23	51.7	7.1	
Arjona Ferreira[38]	2013	Glimeperide	65	60	7.8	12
		Sitagliptin	64	60	7.9	
Arjona Ferreira[39]	2013	Glipizide	212	64.2	7.8	12
		Sitagliptin	211	64.2	7.8	
Bikeland[40]	1996	Glibenclamide	18	59.2	8.5	42
		Insulin	18	59.2	9.1	
Campbell[41]	1994	Glipizide	24	57	11.8	12
		Metformin	24	57	11.5	
Cefalu[42]	2013	Gliclazide	482	56.2	7.8	12
		Canagliflozin	968	56.2	7.8	
Clauson[43]	1996	Glibenclamide	20	59.3	10.3	12
		Nothing (both arms on insulin)	19	57.8	9.8	
Delprato[44]	2014	Glipizide	874	55.4	7.6	24
		Alogliptin	1765	55.4	7.6	
Ferranini[45]	2009	Glimeperide	1393	57.5	7.3	12
		Vildagliptin	1396	57.5	7.3	
Filozof[46]	2010	Gliclazide	494	59.5	8.5	12
		Vildagliptin	513	59.5	8.5	
Foley[47]	2009	Gliclazide	546	54.3	8.7	12
		Vildagliptin	546	55.2	8.6	
Gallwitz[49]	2012	Glimeperide	775	59.8	7.7	24
		Linagliptin	776	59.8	7.7	
Gallwitz[48]	2012	Glimeperide	514	60	7.4	24
		Exenatide	515	60	7.4	
Garber[50]	2009	Gliclazide	248	53	8.3	48
		Liraglutide	497	53	8.3	
Gerich[51]	2005	Glibenclamide	209	52.6	8.3	24
		Nateglinide	219	53.5	8.4	
Gerstein[82]	2010	Glipizide	339	61	7.2	18
		Rosiglitazone	333	61	7.1	
Giles[53]	2010	Glibenclamide	149	64	8.3	12
		Pioglitazone	151	64	8.6	
Göke[54]	2010	Glipizide	430	57.6	7.7	12

		Saxagliptin	428	57.6	7.7	
Hamann[55]	2008	Glibenclamide	302	60	8.0	12
		Rosiglitazone	294	60	8.0	
Hanefeld[56]	2007	Glibenclamide	203	60.4	8.2	12
		Rosiglitazone	384	60.4	8.2	
Home[57]	2007	Any 2nd / 3rd generation sulphonylurea	1105	57	N.R	45
		Rosiglitazone	1117	57	N.R	
Hong[58]	2013	Glipizide	148	63.3	7.6	36
		Metformin	156	63.3	7.6	
Jain[59]	2006	Glibenclamide	251	52.1	9.2	13
		Pioglitazone	251	52.1	9.2	
Johnston[60]	1998	Glibenclamide	104	67.7	8.4	12
		Miglitol	206	67.4	8.4	
		Placebo	101	68.5	8.3	
Kahn[61]	2006	Glibenclamide	1441	56.4	7.3	48
		Metformin	1454	57.9	7.3	
		Rosiglitazone	1456	56.3	7.3	
Kaku[62]	2011	Glibenclamide	132	58.3	9.2	12
		Liraglutide	268	58.3	9.3	
Lunderhausen[63]	1987	Glibenclamide	39	61	N.R.	12
		Placebo	40	61	N.R.	
Madsbad[64]	2001	Glipizide	81	62	7.2	12
		Repaglinide	175	60.2	7.3	
Marbury[65]	1999	Glibenclamide	182	58	9.0	12
		Repaglinide	362	58	8.7	
Matthews[66]	2005	Gliclazide	313	56	8.5	12
		Pioglitazone	317	57	8.7	
Mazzonne[67]	2006	Glimeperide	230	59	7.4	18
		Pioglitazone	232	59	7.4	
		Glibenclamide	21	53	7.8	
Nakamura[68]	2006	Voglibose	17	55	7.6	12
		Pioglitazone	17	56	8.0	
		Nateglinide	16	53	7.7	
Nauck[70]	2007	Glipizide	584	56	7.5	12
		Sitagliptin	588	56	7.5	
Nauck[69]	2011	Glipizide	408	58.4	7.7	12
		Dapagliflozin	406	58.4	7.7	
Nissen[71]	2008	Glimeperide	273	59	7.4	18
		Pioglitazone	270	59	7.4	
Perriello[72]	2007	Gliclazide	135	59	8.7	12
		Pioglitazone	140	58	8.7	
Petrica[73]	2009	Glimeperide	17	63	7.6	12
		Rosiglitazone	17	63	7.7	
Petrica[74]	2011	Glimeperide	39	58	7.5	12
		Pioglitazone	39	56	7.7	

Quatraro[75]	1986	Gliclazide	15	56	12.2	12
		Nothing (both arms on insulin)	15	57	11.8	
Ridderstrale[76]	2014	Glimeperide	780	56	N.R.	24
		Empagliflozin	769	56	N.R.	
Ristic[77]	2007	Gliclazide	118	61	7.5	12
		Nateglinide	129	61	7.6	
Rosenstock[78]	2013	Glipizide	219	69	7.4	12
		Alogliptin	222	69	7.5	
Tolman[79]	2009	Glibenclamide	1057	55	9.5	36
		Pioglitazone	1063	55	9.5	
UKPDS[2]	1998	Glibenclamide	615	54	6.3	133
		Diet	911	54	6.2	
		Insulin	896	54	6.1	
Vahatalo[80]	2007	Glipizide	15	62	9.6	12
		Metformin	26	62	9.8	
		Nothing (all arms on insulin)	11	62	10.0	

Capítulo 3 – Considerações finais e perspectivas futuras

Os dados desta revisão sistemática com meta-análise sugerem que o uso de sulfoniluréias de segunda e terceira geração para tratamento da hiperglicemia em pacientes com DM2 é seguro. Além disso, foi possível descartar um dano tão pequeno quanto 1 morte a cada 200 pacientes tratados. Esses resultados não parecem depender da associação com metformina e da classe de medicamento usada como comparador. Por fim, o achado de aumento de mortalidade com a glipizida precisa ser mais bem explorado.

A confirmação da segurança das sulfoniluréias no tratamento do DM2 é um ponto importante (e tranquilizador) no tratamento da doença. São drogas úteis e frequentemente utilizadas no tratamento da hiperglicemia, capazes de reduzir a incidência de eventos microvasculares (1). Entretanto, esse resultado deve ser considerado um pouco limitado, uma vez que reforça novamente o fato de que tratamentos que visem apenas o controle da glicemia são capazes de diminuir a taxa de complicações microvasculares mas não são efetivos para reduzir a mortalidade (2, 3, 4). Neste contexto, entendemos que novos paradigmas no manejo do DM2 devem ser procurados. Esta nova forma de tratar a doença deve incluir tratamentos que sejam eficazes não só para controle da hiperglicemia, mas que também atuem em outras manifestações do desarranjo metabólico do paciente diabético (obesidade, hipertensão, dislipidemia) e, portanto, com maior potencial para diminuir a mortalidade desses pacientes.

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