



**BRIEF REPORT**

# Risk of a first-ever acute myocardial infarction and all-cause mortality with sulphonylurea treatment: A population-based cohort study

Judith van Dalem MSc<sup>1,2</sup>  | Martijn C. G. J. Brouwers MD<sup>3</sup> | Coen D. A. Stehouwer MD<sup>4</sup>  |  
André Krings PharmD<sup>5</sup> | Olaf H. Klungel PhD<sup>6</sup> | Johanna H. M. Driessen PhD<sup>1,2,6,7</sup> |  
Frank de Vries PharmD<sup>1,2,6</sup> | Andrea M. Burden PhD<sup>1,2,6</sup>

<sup>1</sup>Department of Clinical Pharmacy, Maastricht University Medical Centre+, Maastricht, The Netherlands

<sup>2</sup>Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands

<sup>3</sup>Department of Internal Medicine, Division of Endocrinology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre+, Maastricht, The Netherlands

<sup>4</sup>Department of Internal Medicine, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre+, Maastricht, The Netherlands

<sup>5</sup>Department of Clinical Pharmacy, Zuyderland MC, Heerlen, The Netherlands

<sup>6</sup>Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

<sup>7</sup>NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

**Correspondence**

Frank de Vries, PharmD, PhD, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences Utrecht University, 3508 TB Utrecht, The Netherlands.  
Email: f.devries@uu.nl

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We investigated the association between the current use of individual sulphonylureas and the risk of a first-ever acute myocardial infarction (AMI) and all-cause mortality, in a population-based cohort study, using primary care data from the Clinical Practice Research Datalink database (2004–2012). New users ( $N = 121\,869$ ), aged  $\geq 18$  years, with at least one prescription for a non-insulin antidiabetic agent were included. The first prescription defined start of follow-up. Time-dependent Cox proportional hazard models were used to estimate the risk of a first-ever AMI and all-cause mortality associated with the use of individual sulphonylureas, and other non-insulin glucose-lowering drugs. No differences in risk of a first-ever AMI (adjusted hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.70–1.50) or all-cause mortality (adjusted HR 0.97, 95% CI 0.80–1.17) were observed when comparing gliclazide use with non-gliclazide sulphonylurea use. Similar results were found for each individual sulphonylurea. As evidence is accumulating that gliclazide is no safer than other sulphonylureas, current guidelines suggesting superiority should be carefully evaluated.

**KEYWORDS**

acute myocardial infarction, all-cause mortality, sulphonylureas, type 2 diabetes mellitus

## 1 | INTRODUCTION

Despite the arrival of new therapeutic options, sulphonylureas are still a commonly used second-line therapy for type 2 diabetes

mellitus.<sup>1,2</sup> In recent decades, however, there has been an on-going debate about the safety profile of sulphonylureas.<sup>3–6</sup> Of all sulphonylureas, gliclazide is considered to be associated with the lowest risk of severe side effects, including hypoglycaemia and all-cause

mortality.<sup>7</sup> Consequently, gliclazide is the first-choice sulphonylurea in many clinical guidelines. However, we have recently shown that, among gliclazide users, the risk of hypoglycaemia, a risk factor for serious cardiovascular events including all-cause hospitalization and all-cause mortality,<sup>8,9</sup> does not appear to differ from other sulphonylureas when compared with metformin use.<sup>1</sup> Furthermore, there is great inconsistency in literature, which primarily consists of studies with small sample sizes, regarding the association of individual sulphonylureas and the risk of all-cause mortality and cardiovascular events.<sup>7,10-12</sup> A clear conclusion, therefore, cannot currently be made, and additional large studies are needed.

The objective of the present study was to evaluate the association between current use of individual sulphonylureas and the risk of a first-ever acute myocardial infarction (AMI) and all-cause mortality.

## 2 | METHODS

### 2.1 | Data

We conducted a cohort study using the Clinical Practice Research Datalink (CPRD). (Trial registration: CPRD reference 16\_266R.) The CPRD contains prospectively collected computerized medical records of 674 primary care practices in the UK and holds data on 6.9% of the British population. It comprises valid information on a wide range of medical information, including diagnoses, referrals, laboratory test results, prescription details, and data on mortality.<sup>13</sup>

### 2.2 | Study population

The study population consisted of patients aged  $\geq 18$  years with at least one non-insulin glucose-lowering drug prescription during the period of valid CPRD data collection ( $N = 231\,065$ ). Data collection started in April 2004, and ended in August 2012. The index date was defined as the date of the first prescription. Patients were followed until: a primary outcome event occurred; end of the scheduled data collection; end of study period; or end of registration with the general practice.

### 2.3 | Exposure

The exposure status of every patient was classified at index date; therefore, all patients were current users of at least one of the eligible non-insulin glucose-lowering drugs on the index date. Follow-up was divided into 90-day intervals to define patients' exposure status time-dependently.<sup>1</sup> Exposure status was assessed at the start of each 90-day time interval as current use (use in the last 1-90 days), recent use (91-180 days ago), or past use (>180 days ago). Further details are provided in the Supporting Information, File S1.

### 2.4 | Outcomes

The primary outcomes were the occurrence of a first-ever AMI event (defined using read codes) and all-cause mortality, with separate models run for each outcome. When considering AMI as an outcome, patients with a documented history of AMI before the index date were excluded from analysis, as survivors of AMI are known to be at

increased risk of recurrent infarctions. Additional information is provided in File S1.

## 2.5 | Covariates

The presence of risk factors (possible confounders) for AMI or all-cause mortality were identified during follow-up using read codes. The confounders for each outcome are presented in File S1, and were identified to minimize confounding bias.

## 2.6 | Data analysis

Unadjusted incidence rates were identified and summarized as events per 1000 person-years. Cox proportional hazards models (SAS 9.4. PHREG procedure) were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of a first-ever AMI or all-cause mortality associated with current use of individual sulphonylureas. For all models, current use of gliclazide was used as the reference category. Missing data were identified using an indicator variable.

## 3 | RESULTS

In total we identified 121 869 eligible patients with first exposure to a non-insulin glucose-lowering medication during the study period. Of these, 13 379 were sulphonylurea monotherapy users (11 283 gliclazide users and 2096 non-gliclazide users (Table S1). Patient demographics and clinical characteristics of all non-insulin glucose-lowering drug users are shown in Table S2.

Table 1 shows the incidence rates and risk of AMI by exposure group among the 114 249 eligible patients with no history of AMI at baseline. The unadjusted incidence rates for gliclazide and non-gliclazide sulphonylurea use were 7.0 and 6.5 cases per 1000 person-years, respectively. There was no difference in first-ever AMI risk between gliclazide and non-gliclazide sulphonylurea users (adjusted HR 1.02, 95% CI 0.70-1.50). No statistical differences were observed when individual sulphonylureas were analysed. Notably, use of metformin was associated with a lower risk of first-ever AMI compared with use of gliclazide (adjusted HR 0.72, 95% CI 0.61-0.86).

For all-cause mortality, the unadjusted incidence rates in gliclazide and non-gliclazide sulphonylurea users were 24.1 and 23.0 cases per 1000 person-years, respectively (Table 2). No significant differences in risk between gliclazide and non-gliclazide users were identified (adjusted HR 0.97, 95% CI 0.80-1.17). In addition, there were no differences between individual sulphonylureas. Use of metformin did not result in a lower risk of all-cause mortality when compared to use of gliclazide. Results of users of combination therapy and other non-insulin glucose-lowering medication are shown in Table S3.

## 4 | DISCUSSION

This large population-based cohort study showed that the risk of a first-ever AMI or all-cause mortality did not differ between users of the individual sulphonylureas. This study adds to a growing body of

**TABLE 1** Risk of acute myocardial infarction in patients using sulphonylureas or metformin

| Non-insulin glucose-lowering agent exposure | Risk of AMI |                      |                               |   |
|---|-------------|----------------------|-------------------------------|---|
|   | Events      | IR/1000 person-years | Age-/sex-adjusted HR (95% CI) | Fully adjusted HR (95% CI) <sup>a</sup> |
| <b>Sulphonylurea use</b>                    |             |                      |                               |   |
| Current use                                 |             |                      |                               |   |
| Gliclazide                                  | 176         | 7.0                  | Reference                     | Reference                               |
| Non-gliclazide                              | 30          | 6.5                  | 0.97 (0.66-1.43)              | 1.02 (0.70-1.50)                        |
| Glimepiride                                 | 17          | 6.9                  | 1.03 (0.63-1.70)              | 1.04 (0.63-1.71) <sup>b</sup>           |
| Glibenclamide                               | <6          | 8.8                  | 1.27 (0.52-3.08)              | 1.71 (0.70-4.17) <sup>b</sup>           |
| Glipizide                                   | 6           | 5.2                  | 0.77 (0.34-1.73)              | 0.85 (0.38-1.91) <sup>b</sup>           |
| Tolbutamide                                 | <6          | 5.2                  | 0.76 (0.19-3.07)              | 0.67 (0.17-2.69) <sup>b</sup>           |
| Combination of sulphonylureas               | <6          | 25.7                 | 3.84 (0.95-15.47)             | 3.38 (0.84-13.67)                       |
| Recent use                                  | 11          | 4.6                  | 0.70 (0.38-1.28)              | 0.65 (0.35-1.20)                        |
| Past use                                    | 11          | 0.9                  | 0.14 (0.08-0.25)              | 0.19 (0.10-0.35)                        |
| <b>Metformin use</b>                        |             |                      |                               |   |
| Current use                                 | 620         | 3.3                  | 0.50 (0.43-0.59)              | 0.72 (0.61-0.86)                        |
| Recent use                                  | 27          | 2.2                  | 0.34 (0.22-0.50)              | 0.50 (0.33-0.75)                        |
| Past use                                    | 42          | 0.8                  | 0.12 (0.08-0.16)              | 0.22 (0.16-0.31)                        |

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NIAA, non-insulin antidiabetic agent; SU, sulphonylurea. All analyses adjusted for current, recent, past use of all exposure groups (metformin only, SU only, metformin + SU, metformin + other NIAA, SU + other NIAA, and other NIAA). Current use (1-90 days), recent use (91-180 days), or past use (>180 days) defined by time since most recent prescription.

<sup>a</sup> Statistically adjusted for age, sex, body mass index, alcohol use, smoking status, acute coronary syndrome, atrial fibrillation, cancer, cardiovascular disease, cerebrovascular disease, chronic heart failure, chronic kidney disease, hypertension, ischaemic heart disease, peripheral vascular disease, stroke, total cholesterol and use of aspirin,  $\beta$ -blockers, calcium channel blockers, digoxin, dipyridamole, insulin, loop diuretics, nitrates, renin-angiotensin-aldosterone system inhibitors, spironolactone and statins.

<sup>b</sup> SU subgroup comparison (Wald test) showed no statistical significant differences.

**TABLE 2** Risk of all-cause mortality in patients using sulphonylureas or metformin

| Non-insulin glucose-lowering agent exposure | Risk of all-cause mortality |                      |                               |   |
|---|-----------------------------|----------------------|-------------------------------|---|
|   | Events                      | IR/1000 person-years | Age-/sex-adjusted HR (95% CI) | Fully adjusted HR (95% CI) <sup>a</sup> |
| <b>Sulphonylurea use</b>                    |                             |                      |                               |   |
| Current use                                 |                             |                      |                               |   |
| Gliclazide                                  | 684                         | 24.1                 | Reference                     | Reference                               |
| Non-gliclazide                              | 118                         | 23.0                 | 0.97 (0.80-1.18)              | 0.97 (0.80-1.17)                        |
| Glimepiride                                 | 69                          | 24.9                 | 1.04 (0.82-1.34)              | 1.05 (0.82-1.34) <sup>b</sup>           |
| Glibenclamide                               | 10                          | 16.4                 | 0.70 (0.37-1.30)              | 0.70 (0.37-1.30) <sup>b</sup>           |
| Glipizide                                   | 31                          | 23.6                 | 0.99 (0.69-1.42)              | 0.99 (0.69-1.42) <sup>b</sup>           |
| Tolbutamide                                 | 8                           | 18.5                 | 0.78 (0.39-1.56)              | 0.78 (0.39-1.56) <sup>b</sup>           |
| Recent use                                  | 46                          | 16.9                 | 0.71 (0.53-0.95)              | 0.71 (0.52-0.95)                        |
| Past use                                    | 345                         | 24.4                 | 1.01 (0.89-1.15)              | 0.99 (0.87-1.13)                        |
| <b>Metformin use</b>                        |                             |                      |                               |   |
| Current use                                 | 4746                        | 23.7                 | 0.99 (0.92-1.07)              | 0.98 (0.91-1.06)                        |
| Recent use                                  | 317                         | 24.3                 | 1.01 (0.89-1.15)              | 1.00 (0.88-1.15)                        |
| Past use                                    | 1331                        | 22.3                 | 0.93 (0.85-1.02)              | 0.92 (0.84-1.01)                        |

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; NIAA, non-insulin antidiabetic agent; SU, sulphonylurea. All analyses adjusted for current, recent, past use of all exposure groups (metformin only, SU only, metformin + SU, metformin + other NIAA, SU + other NIAA, and other NIAA). Current use (1-90 days), recent use (91-180 days), or past use (>180 days) defined by time since most recent prescription.

<sup>a</sup> Statistically adjusted for age, sex, body mass index, alcohol use, smoking status, acute coronary syndrome, atrial fibrillation, cancer, cerebrovascular disease, chronic heart failure, chronic kidney disease, hypertension, ischaemic heart disease, myocardial infarction, peripheral vascular disease, stroke, and use of oral anticoagulants and insulin.

<sup>b</sup> Sulphonylurea subgroup comparison (Wald test) showed no statistical significant differences.

evidence that gliclazide, the current first-choice sulphonylurea, is not associated with a lower risk of several clinically relevant outcomes, when compared with other sulphonylureas.

There is great discrepancy in the current literature with regard to the preferred sulphonylurea. This probably results from different study designs, study populations, duration of follow-up and choice of

variables for which statistical adjustments were made. Results of the largest population-based study thus far, are not in line with our study. Schramm et al.<sup>7</sup> showed that treatment with gliclazide might be associated with improved cardiovascular outcomes, compared with other sulphonylureas; however, their results may have been influenced by residual confounding and bias since the database used did not contain information on important confounders, including body mass index, smoking status and plasma lipids. Our analyses show that correcting for all selected confounders with regard to risk of a first-ever AMI in metformin users is important, as the final adjusted HR (0.72) differed substantially from the age-/sex-adjusted HR (0.50). Moreover, as the database used by Schramm et al.<sup>7</sup> was not linked to general practitioner files, more under-reporting of underlying diseases can be expected. Given these limitations, the present study provides important additional information regarding the (cardiovascular) safety profile of sulphonylureas, and suggests that there are minimal differences between the individual sulphonylureas with regard to the risk of a first-ever AMI and all-cause mortality. These findings, combined with our previous study demonstrating no difference in hypoglycaemia rate between gliclazide and non-gliclazide sulphonylurea users,<sup>1</sup> call into question whether gliclazide is still justified as the first-choice sulphonylurea.

Although there was no difference in risk of a first-ever AMI and all-cause mortality between individual sulphonylureas, the present results showed relevant differences between the different types of non-insulin glucose-lowering agents. In comparison with metformin, gliclazide users had a 1.4-fold increased risk of a first-ever AMI. This higher risk of AMI in sulphonylurea users is consistent with several studies.<sup>3,4,7,14</sup> Several mechanisms have been proposed to explain the higher risk of adverse cardiovascular effects associated with the use of sulphonylureas. One of the most plausible mechanisms is sulphonylurea-associated risk of hypoglycaemia.<sup>15</sup> Hypoglycaemic events are associated with cardiac ischaemia and can prolong the QT interval.<sup>16,17</sup> Unfortunately, because of the low number of hypoglycaemic events in our cohort we were not able to stratify patients by history of hypoglycaemia to examine whether hypoglycaemic events did indeed mediate the risk of AMI in sulphonylurea users.

The increased risk of a first-ever AMI in users of sulphonylureas did not result in a higher risk of all-cause mortality. These results are consistent with a recently published meta-analysis of randomized studies with a long duration.<sup>2</sup> A possible reason why the increased risk of a first-ever AMI in sulphonylurea users does not result in an increased risk of all-cause mortality could be the improvement in treatment options and significant decline of long-term mortality rates after AMI in the last decades.<sup>18</sup> Moreover, all-cause mortality is a more generic, or non-specific outcome.

In addition to those already mentioned, several limitations should be considered when interpreting the results of the present study. A recent study showed a 25% under-recording rate of AMI in the CPRD,<sup>19</sup> this may have resulted in more severe cases of AMI being reported in our database, and an underestimation of AMI. Although there is no evidence to suggest that there would be a difference in reporting between sulphonylurea exposure groups, several scenarios are possible and under-reporting can be differential or non-differential. Further investigation about reporting of AMI in users of different

sulphonylureas is warranted. It should also be noted that some exposure groups of individual sulphonylureas were underpowered when assessing AMI, which deserves additional studies to confirm these associations. Third, although the CPRD contains information on a wide range of confounding factors, the influence of possible important unmeasured confounders, e.g. socio-economic status, diet and exercise, cannot be discounted. Fourth, glibenclamide users were healthier and less likely to use cardiovascular medications. This is probably the result of confounding by indication and may mask a higher risk of a first-ever AMI and all-cause mortality in glibenclamide users.

A major strength of the present study is the comparable disease state of the patients. Many studies comparing metformin and sulphonylureas are limited by a potential time-lag bias, as metformin is a first-line treatment option while sulphonylureas are second-line. To overcome this common limitation, we compared different sulphonylurea users with each other. To our knowledge, this is the first study to look at the individual sulphonylureas, with the comparator being the preferred sulphonylurea, gliclazide. Another strength is the generalizability of the study results. Although an observational study has limitations inherent in its design, it tends to be more reflective of the general population compared with patients in randomized clinical trials. Additionally, our dynamic time-dependent analysis permits an assessment of real-world exposure patterns to non-insulin glucose-lowering medications. As a result, we were able to take into account switching between different sulphonylureas or other treatments and avoid exposure misclassification that often arises if an intention-to-treat approach is used.<sup>20</sup> Similarly, as detailed information was available on comorbidities and concomitant use of other drugs, we were able to classify disease and drug confounders in a time-dependent manner.

In conclusion, our results suggest that gliclazide is not superior to other sulphonylureas with regard to the risk of a first-ever AMI or all-cause mortality. These results provide additional evidence to the ongoing debate regarding the safety profile of sulphonylureas, and in particular the comparative profiles among the different sulphonylureas. Given the accumulating evidence suggesting gliclazide is not safer than other sulphonylureas, we believe the current guidelines recommending gliclazide as first-choice sulphonylurea should be carefully evaluated for revision.

## Conflict of interest

O. K. reports receiving funding from GSK, IMI PROTECT and IMI EU2P, in addition personal fees from educational lecture on methods to control for confounding for Roche. These sources are outside of the submitted work. Other authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

## Author contributions

J. D., M. B., F. V. and A. B. initiated the study and were responsible for the study concept and design. J. D. and A. B. analysed the data.

J. D. interpreted the data and drafted and revised the paper. All authors critically revised the paper for important intellectual content and approved the final version to be published.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

## ORCID

Judith van Dalem  <http://orcid.org/0000-0002-1904-2505>

Coen D. A. Stehouwer  <http://orcid.org/0000-0001-8752-3223>

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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