Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality

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ABSTRACT

Aims: There are safety concerns related to sulphonylurea treatment. The objective of this nationwide study was to compare the risk of cardiovascular disease (CVD), all-cause mortality and severe hypoglycemia in patients with type 2 diabetes (T2D) starting second-line treatment with either metformin + sulphonylurea or metformin + dipeptidyl peptidase-4 inhibitor (DPP-4i).

Methods: All patients with T2D in Sweden who initiated second-line treatment with metformin + sulphonylurea or metformin + DPP-4i during 2006–2013 (n = 40,736 and 12,024, respectively) were identified in this nationwide study. The Swedish Prescribed Drug Register and the Cause of Death and National Patient Registers were used, and Cox survival models adjusted for age, sex, fragility, prior CVD, and CVD-preventing drugs were applied to estimate risks of events. Propensity score adjustments and matching methods were used to test the results.

Results: Of 52,760 patients; 77% started metformin + SU and 23% metformin + DPP-4i. Crude incidences for severe hypoglycemia, CVD, and all-cause mortality in the SU cohort were 2.0, 19.6, and 24.6 per 1000 patient-years and in the DPP-4i cohort were 0.8, 7.6, and 14.9 per 1000 patient-years, respectively. Sulphonylurea compared with DPP-4i was associated with higher risk of subsequent severe hypoglycemia, fatal and nonfatal CVD, and all-cause mortality; adjusted HR (95% CI): 2.07 (1.11–3.86); 1.17 (1.01–1.37); and 1.25 (1.02–1.54), respectively. Results were confirmed by additional propensity-adjusted and matched
analyses. Among the SU drugs, glibenclamide had the highest risks.
Conclusions: Metformin + SU treatment was associated with an increased risk of subsequent severe hypoglycemia, cardiovascular events, and all-cause mortality compared with metformin + DPP4i. Results from randomized trials will be important to elucidate causal relationships.

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1. Introduction
The prevalence of type 2 diabetes treated with glucose-lowering drugs is increasing, and has now been estimated at 4.4% in Sweden [1]. It is recommended in the 2015 guidelines from the American Diabetes Association that glucose-lowering drug (GLD) therapy should be initiated as metformin monotherapy. When this fails, sulphonylurea or a dipeptidyl peptidase (DPP)-4 inhibitor is frequently added. Sulphonylurea, which has been available for 50 years, is still primarily used because of its efficacy and low cost, but it has known side effects such as hypoglycemia and weight gain [2]. DPP-4 inhibitors have demonstrated a lower risk of hypoglycemia and weight gain than sulphonylurea [3–5], and is therefore recommended for patients at increased risk of hypoglycemia and with established obesity [6,7]. In addition, DPP-4 inhibitor shows a neutral effect on risk of cardiovascular death and myocardial infarction compared with placebo [3–5,8–10] although there have been reports of increased numbers of non-fatal heart failure events [8].

Results from observational studies have raised safety concerns regarding increased risk of cardiovascular disease (CVD) and all-cause mortality in patients treated with sulphonylurea [11–18]. Hypoglycemia shows a strong association with cardiovascular events, and this could partially explain the reported increased risk of CVD and mortality with sulphonylurea [10,19]. Currently, no randomized trials have directly compared metformin combinations with sulphonylurea and DPP-4 inhibitor using CVD and mortality outcomes, but a larger randomized study is currently ongoing (Cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes [CAROLINA]), which is expected to be completed in late 2018 [20,21]. Meanwhile, observational studies may add to our knowledge of the association between sulphonylurea use and cardiovascular events in patients with type 2 diabetes.

The aim of this observational, full-population study was to investigate the risk of severe hypoglycemia, fatal and nonfatal CVD (unstable angina, myocardial infarction, or stroke), and all-cause mortality associated with combination treatment with either sulphonylurea or DPP-4 inhibitor added to metformin, using national healthcare registries in Sweden.

2. Material and methods

2.1. Data sources

This observational registry study utilized data from Swedish national registries: the Prescribed Drug Register covering all drug prescriptions filled since 2005 using Anatomical Therapeutic Chemical (ATC) codes; the Cause of Death Register (established 1961); the National Patient Register covering all hospitalisations and discharge diagnoses since 1987 and all out-patient hospital visits since 2001. All three registers are held by the Swedish National Board of Health and Welfare (NBHW).

2.2. Study population

All patients with a filled prescription for an incident combination treatment of either a sulphonylurea or a DPP-4 inhibitor together with metformin during the period July 1 2006 to end of 2013 were identified. Patients had to be receiving monotherapy with one non-insulin antidiabetic drug (NIAD) prior to the start of combination treatment, and the index date was defined as the date of combination treatment initiation (sulphonylurea or metformin or DPP-4 inhibitor). Second-line treatment was defined as concomitant use of two or more NIADs, or as initiation of insulin treatment. Switching from NIAD to another was not considered as second-line treatment, unless a new prescription of the first-line drug was filled within 1 year after the switch, in which case the starting date of the second antidiabetic drug was the index date. Patients with a diagnosis of gestational diabetes (International Classification of Diseases [ICD] code 10: O24.4) within 1 year of the index date and patients with type 1 diabetes were excluded. (See Online-Only Supplementary Table 1 for ICD diagnoses and ATC codes.) Patients with type 1 diabetes were arbitrarily defined as those with a registered type 1 diabetes diagnosis (ICD-10 E10) and treated with insulin during their first year of GLD treatment, or aged under 30 years at the start of insulin medication, or aged under 15 years at the start of any diabetes medication. The main analyses were done according to an on-treatment approach, and patients were observed from the index date until: a gap of at least 6 months in filled prescription of metformin and sulphonylurea or DPP-4 inhibitor; death; or December 31, 2013. In addition, ITT (intention-to-treat) analyses were performed as above, but also including those with interrupted or changed treatment. The study cohort was formed among patients with type 2 diabetes moving from treatment with one NIAD to dual NIAD, as outlined in Fig. 1.

Individual patient-level data from the national registers were linked using personal identification numbers, which are assigned at birth and whose use is mandatory in dealing with the public healthcare system. Data linkage was performed by the NBHW and the linked database was managed at Statisticon AB, Stockholm, Sweden. The study protocol
was approved by the Stockholm regional ethics committee (registration number 2013/2206-31). Baseline treatments, defined by ATC codes, were defined as any identified filled prescription of the treatment of interest during the year prior to the index date.

Three endpoints were defined as follows: (1) Severe hypoglycemia a main or secondary diagnosis in the inpatient register of hypoglycemia (E16.0, E16.1, or E16.2) or diabetes with coma (ICD-10 E10.0, E11.0, E12.0, E13.0, or E14.0), as these codes are typically used for hypoglycemia requiring third party assistance. (2) Fatal and nonfatal CVD – a main diagnosis in the inpatient register of myocardial infarction (I21), ischemic stroke (I63–I64), unstable angina pectoris (I20.0), or cardiovascular death (death with an ICD-10 code I diagnosis as primary cause of death). (3) Death of any cause.

2.3. Statistical analyses

The time from initiation of second-line treatment to a clinical event (severe hypoglycemia, fatal or nonfatal CVD, or all-cause mortality) was visualized using Kaplan–Meier graphs. Patients were censored at treatment discontinuation, death, or study period end.

Statistical analyses comparing treatments (metformin + DPP-4 inhibitor vs. metformin + sulphonylurea) was performed using Cox proportional hazards models. Two separate adjustment models were determined for risk of severe hypoglycemia and for fatal and nonfatal CVD and all-cause mortality. Directed acyclic graphs [22] were used to minimize the risk of bias and identify the two primary adjustment models (Online-Only Supplementary Figs. 1 and 2).

The model for estimating the risk of severe hypoglycemia was adjusted for age and fragility (defined as at least 3 days of hospitalization during the year prior to the index date). The model for fatal and nonfatal CVD was adjusted for age, sex, fragility, prior CVD, and use of statins, low-dose aspirin, and antihypertensives. Prior history of CVD was assessed in the National Patient Register from 1987 until index date.

The main analysis was performed using an on-treatment approach, in which a treatment chain was regarded as uninterrupted if a medication of interest had a prescription filled within 6 months of the prior time of a filled prescription. As a sensitivity analysis, an intention-to-treat (ITT) approach was adopted, in which patients were analyzed according to their index medication combination (with at least two dispenses) irrespective of subsequent switches or treatment interruption or discontinuation.

A separate analysis, irrespective of treatment combination, was performed to compare two patient groups, those with or without any event of severe hypoglycemia, and examine the association with fatal and nonfatal CVD using a Cox proportional hazard model adjusted for age, sex, fragility, and prior CVD. This analysis is based on the same cohort used in the main analysis, and follow-up started at the date of initiation of metformin + sulphonylurea or metformin + DPP-4 inhibitor. The proportional hazard assumptions were assessed by examining Schoenfeld residuals.

Since this is a clinical effectiveness study to assess two different treatment strategies a propensity score adjusted and a propensity score match model were additional used to test the results from the adjusted Cox proportional hazard model. Propensity scores were calculated using age, sex, fragility, prior CVD, and use of statins, low-dose aspirin, and antihypertensives. They were used in propensity score adjusted survival models and in propensity score matching of SU and DPP-4 inhibitor treatment groups (2:1 using a caliper of 0.2 when identifying matches). The matching was performed using the Match function in the R package Matchit [23].

A P value below 0.05 was considered significant, but because no adjustment for multiplicity was performed, P values should be interpreted with caution. All analyses were conducted using R statistical software (R version 3.2.3) [24].

3. Results

3.1. Patient characteristics and treatments

A total of 52,760 patients with type 2 diabetes initiated second-line treatment with metformin + sulphonylurea or metformin + DPP-4 inhibitor during 2006–2013. Of these, 77.2% initiated metformin + sulphonylurea and 22.8% metformin + DPP-4 inhibitor. These regimens were the two most commonly seen second-line dual NIAD treatments, followed by a number of less frequently seen dual NIAD combinations (Fig. 1).

The patients in the metformin + sulphonylurea group were slightly older than those in the metformin + DPP-4 inhibitor group, were less frequently men, had slightly more frequent history of cardiovascular- and microvascular disease (Table 1). Antihypertensive and low-dose aspirin treatments differed
<table>
<thead>
<tr>
<th>Table 1 – Baseline characteristics of patients initiated on either sulphonylurea (SU) or DPP-4 inhibitor (DPP-4i) in combination with metformin.</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
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<tr>
<td>Number of patients, N</td>
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<tr>
<td>Age, years, mean (SD)</td>
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<td>Sex, male, n (%)</td>
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<tr>
<td><strong>Comorbidities, n (%)</strong></td>
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<tr>
<td>CVD</td>
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<td>Myocardial infarction</td>
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<td>STEMI</td>
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<td>NSTEMI</td>
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<td>Severe hypoglycemia</td>
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<td>Cancer</td>
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<td>Chronic obstructive pulmonary disease</td>
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**Treatments, n (%)**

| CVD risk treatment | 33,758 (82.9) | 10,269 (85.4) | 44,027 (83.4) | 20,220 (84.8) | 10,169 (85.3) | 30,389 (85.0) |
| Antihypertensives | 29,064 (71.3) | 8833 (73.5) | 37,897 (71.8) | 17,398 (73.0) | 8746 (73.4) | 26,144 (73.1) |
| Statins | 21,591 (53.0) | 7269 (60.5) | 28,860 (54.7) | 14,308 (60.0) | 7189 (60.3) | 21,497 (60.1) |
| Low-dose aspirin | 14,645 (36.0) | 4063 (33.8) | 18,708 (35.5) | 8005 (33.6) | 4036 (33.9) | 12,041 (33.7) |
| Beta blockers | 15,966 (39.2) | 4654 (38.7) | 20,620 (39.1) | 9178 (38.5) | 4618 (38.7) | 13,796 (38.6) |
| Lower limb amputations | 89 (0.2) | 13 (0.1) | 102 (0.2) | 43 (0.2) | 13 (0.1) | 56 (0.2) |

CVD, cardiovascular disease (unstable angina, myocardial infarction, or stroke); DPP, dipeptidyl peptidase; NSTEMI, non-ST-segment-elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment-elevation myocardial infarction.
marginally between the two patient groups, while statins were substantially more often prescribed in the metformin + DPP-4 inhibitor group (Table 1).

Patients were followed from initiation of dual NIAD treatment (occurring during the period July 1, 2006 to December 31, 2013) until death or end of the study period (December 31, 2013). Thus, the follow-up time ranged up to 7.5 years. The median follow-up time for the metformin + sulphonylurea and metformin + DPP-4 inhibitor groups was 3.4 and 2.5 years, respectively, and the number of patient-years was 143,344 and 32,133, respectively. The most frequently filled prescriptions for sulphonylureas were glibenclamide (41.7%), glipizide (34.9%), and glimepiride (23.4%), while among the DPP-4 inhibitors, prescriptions for sitagliptin, saxagliptin, and vildagliptin were filled for 80.3%, 5.4%, and 2.1% of patients with type 2 diabetes, respectively (Online-Only Supplementary Table 2a). The metformin dose at index was 21% higher in the metformin + DPP-4 inhibitor group than in the metformin + sulphonylurea group (Online-Only Supplementary Table 2a).

3.2. Risk of events in the two treatment groups

The main results were obtained by on-treatment analyses. In the metformin + sulphonylurea group, the crude numbers (incidence per 1000 patient-years) of severe hypoglycemia, fatal and nonfatal CVD, and all-cause death were 120 (2.0), 1153 (19.6), and 1420 (24.6), respectively. The corresponding results for the metformin + DPP-4 inhibitor group were 11 (0.8), 105 (7.6), and 204 (14.9). As illustrated by the Kaplan–Meier curves (Fig. 2A–C), the increased incidence in the metformin + sulphonylurea group of all types of events can be observed already in the first 6 months, with a continued increase in separation between the curves with follow-up time.

3.3. Adjusted analyses

In analyses adjusting for known risk factors, metformin + sulphonylurea compared with metformin + DPP-4 inhibitor as second-line treatment was associated with a higher risk of severe hypoglycemia, fatal and nonfatal CVD, and all-cause mortality. Adjusted hazard ratios (95% CI) in on-treatment analyses were as follows: 2.07 (1.11–3.86), 1.17 (1.01–1.37), and 1.25 (1.02–1.54), respectively (Fig. 2 and Table 2). The ITT analyses yielded similar results with hazard ratios (95% CI) of 2.08 (1.11–3.89), 1.21 (1.04–1.40) and 1.35 (1.10–1.65), respectively (Table 2).

3.4. Propensity score adjusted analyses

Propensity score adjustments survival analyses resulted in slightly greater differences between SU and DPP4 inhibitor treatment for severe hypoglycemia, CVD and all-cause mortality compared to the adjusted survival analyses, 2.08 (1.11–3.89), 1.21 (1.04–1.40) and 1.35 (1.10–1.65), respectively (Table 2).

3.5. Propensity matched analyses

Propensity matching decreased the total number of patients from 52,760 to 35,769, i.e. 16,991 (32%) patients could not be matched. The resulting groups were very similar in essentially all baseline parameters (Table 1). Hazard ratios were 1.88 (0.98–3.62), 1.23 (1.05–1.44) and 1.43 (1.55–1.77) for severe hypoglycemia, CVD and all-cause mortality, respectively (Table 2). This was very similar to the primary adjusted survival analysis.
In this nationwide register-based study metformin + sulphonylurea + DPP-4 inhibitor all sulpho-
nylurea compared to DPP-4 inhibitors, in combination with metformin, was associated with a 88–107%, 17–
23%, and 25–43% increased risk of severe hypoglycemia, fatal and nonfatal CVD, and all-cause mortality, respectively. This
was seen after adjustment for comorbidities and other risk factors. Propensity score adjusted and matched analyses
yielded similar results compared with the primary adjusted survival analyses, and this consistency supports the robust-
ness of the findings. The increased risk associated with SU can be observed early after initiation of second-line treatment and continues to increase with follow-up time. We also found a strong association between severe hypoglycemia and CVD, in support of the above-reported findings. These results sup-
port the association of increased CVD risk with metformin + sulphonylurea treatment described in previous reports
[16,25].

In a Danish nationwide study of patients with type 2 dia-
betes without a prior history of CVD, Mogensen et al. found that metformin + sulphonylurea was associated with increased risk of cardiovascular and all-cause mortality compared with DPP-4 inhibitor: 1.8-fold and 1.5-fold, respectively
[25]. Their use of a different statistical method, Poisson regression, allowed patients to switch groups and contribute risk time on the new treatment, whereas we used an on-
treatment approach with censoring at treatment discontinu-
ation. The consequences of these different statistical approaches are difficult to assess, but it may be speculated
that the increased on-treatment time in the Danish study increased the number of registered events, thereby resulting in a numerically increased risk estimation. Still, the numeric direction for CVD mortality related to metformin + sulphonylurea treatment was similar to our fatal and nonfatal CVD rate, and estimated risks of all-cause mortality were also sim-
ilar in both studies.

Using data from the Clinical Practice Research Datalink in the UK [26], Morgan et al. found similar associated risks of CVD and all-cause mortality with metformin + sulphonylurea versus metformin + DPP-4 inhibitor: 1.4-fold and 1.7-fold, when using a similar statistical method (adjusted Cox regres-
sion) (15). To compare statistical methods, they used three dif-
ferent statistical methods: full- (adjusted Cox regression),
direct-, and propensity-matched cohorts. Small numerical differences were found between the methods, but the two lat-
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their full population design, they used only laboratory mea-

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<th>Severe hypoglycemia</th>
<th>Fatal and nonfatal CVD</th>
<th>All-cause mortality</th>
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<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>2.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.11–3.86</td>
<td>0.022</td>
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<tr>
<td>1.17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.01–1.37</td>
<td>0.035</td>
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<tr>
<td>1.25&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.02–1.54</td>
<td>0.030</td>
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</table>

<sup>a</sup> Adjusted for age and fragility.
<sup>b</sup> Adjusted for age and sex, frailty, prior CVD, and use of statins, low-dose aspirin, and antihypertensives.
<sup>c</sup> Matched by age, sex, frailty, prior CVD, and use of statins, low-dose aspirin, and antihypertensives. Other HRs for single variables are unadjusted.

### 3.6. Severe hypoglycemia and CVD

In patients with type 2 diabetes, regardless of treatment group, who had an episode of severe hypoglycemia during follow-up compared with those who did not, the risk of fatal and nonfatal CVD was increased 1.5-fold (adjusted hazard ratio 1.51, 95% CI 1.21–1.88, P < 0.001).

### 3.7. Risk of events within sulphonylurea class

In comparison with metformin + DPP-4 inhibitor all sulphon-
ylurea agents in combination with metformin had numerically increased risk of fatal-/nonfatal CVD and all-cause mortality, i.e. glibenclamide (25% and 37% respectively), glip-
zide (11% and 17%) and glimepiride (11% and 11%), however only glibenclamide use reached statistical significance (Online-Only Supplementary Table 2b). Based on the limited number of events (81, 19 and 20 for the glibenclamide, glip-
zide and glimepiride groups, respectively), risk of severe hypoglycemia was numerically increased with glibenclamide and glimepiride, where the former reached statistical signifi-
cance (Online-Only Supplementary Table 2b).

### 4. Discussion

In this nationwide register-based study metformin + sulphonylurea and metformin + DPP-4 inhibitor were the most common non-insulin second-line treatment strategies in patients with type 2 diabetes. Using three different statistical meth-
ods, sulphonylurea compared to DPP-4 inhibitors, in combi-
nation with metformin, was associated with a 88–107%, 17–
23%, and 25–43% increased risk of severe hypoglycemia, fatal and nonfatal CVD, and all-cause mortality, respectively. This
was seen after adjustment for comorbidities and other risk factors. Propensity score adjusted and matched analyses
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ter methods seemed to generate higher risk estimates. In
their full population design, they used only laboratory mea-
measurements to adjust for cardiovascular risk at baseline, whereas we used only history of CVD and cardiovascular preventive treatment. When comparing metformin in combination with sulphonylurea versus DPP-4 inhibitor, irrespective of statistical method, all their results were of the same direction and magnitude as those in our study. Recently Seong et al. published results from the Korean National Health Insurance claims database, also showing that metformin + sulphonylurea was associated with a 1.2-fold higher risk of nonfatal CVD compared with metformin + DPP-4 inhibitor (17). They used an on-treatment approach and their risk estimates are similar to our results. A nationwide study from the Taiwan National Health Insurance database by Chang et al. reported numerically increased 1.1-fold (1.11 [95% CI 0.98–1.27]) risk of nonfatal CVD with metformin + sulphonylurea versus metformin + DPP-4 inhibitor (16). This study used an intention-to-treat approach, and their nonsignificant finding is identical with our significant intention-to-treat result of 1.11 (95% CI 1.01–1.21). The low number of patients treated with metformin + DPP-4 inhibitor (n = 2242) might very well have resulted in too low power for CVD risk estimations.

In this study, we have demonstrated a markedly increased risk of severe hypoglycemia associated with sulphonylurea, compared with DPP-4 inhibitors. It is also already well known that sulphonylurea in comparison with DPP-4 inhibitor treatment is associated with increased risk of hypoglycemia, which in turn has been reported to be strongly associated with CVD and mortality (3–5,10,19,27–29). Hypoglycemic responses, such as sympathoadrenergic activation, have been suspected to trigger CVD and might act as a causal pathway between sulphonylurea treatment and risk of CVD and mortality, and may contribute to serious cardiac arrhythmias (19). We also found an association between occurrence of severe hypoglycemia and CVD events, similar to another study (19), in support of this suggested causal mechanism. In addition, the early separation of event curves for CVD and all-cause death, between the two treatment groups, is compatible with hypoglycemia being a contributing factor. The hypoglycemia risk is known to be increased, very early after the start of sulphonylurea medication (30), as noticed in our study.

Myocardial ischemic preconditioning has also been discussed as a potential explanation for the harmful CVD effects observed with sulphonylurea. Sulphonylurea promotes the release of insulin from beta cells by binding to the sulphonylurea receptor, inhibiting the ATP-sensitive potassium channels (31). However, sulphonylurea receptors are also present in cardiac muscle cells, and inhibition of ATP-sensitive potassium channels impairs ischemic preconditioning (32,33). Consequently, the mechanism for cardiac muscle cells to survive brief ischemic events is disturbed, which may translate to increased CVD risk (34).

Numerically increased risk of fatal-/nonfatal CVD and all-cause mortality was observed with all sulphonylureas + metformin, compared to DPP-4 inhibitors + metformin. In the current study, treatment with glibenclamide was associated with the highest mortality-, and CVD risks compared to the other sulphonylureas. This finding might be explained by its higher unselective binding to cardiac muscle cells (34), leading to impaired cardiac preconditioning (32,33), and also by its higher risk of hypoglycemia (35) compared to other sulphonylureas. The increased all-cause mortality associated with glibenclamide is supported by a recently published meta-analysis by Simpson et al. (36), demonstrating variations in all-cause mortality risks within the sulphonylurea class. Notably, gliclazide, which never was introduced on the Swedish market, has been reported to have the lowest cardiovascular risk in mono- or combination therapy compared to other sulphonylureas (14,37). In our study, severe hypoglycemia risk was increased with glibenclamide and glimepiride compared to DPP-4 inhibitors in combination with metformin. Glipizide, on the other hand, did not display any significant increase of risk, albeit this has been reported in randomized controlled trials (4,5). Taken together, current and previous results suggest that short-acting glipizide might carry less risk of severe hypoglycemia when compared to long-acting sulphonylureas. Importantly, interpretation of severe hypoglycemia risk for the different sulphonylureas should be made with caution because of the very limited number of events in our study.

Another partial explanation for the increased CVD risk shown with sulphonylurea could be that treatment with DPP-4 inhibitor is not associated with any weight gain, in contrast to the association of sulphonylurea treatment with moderate weight gain. Moderate weight gain has been strongly associated with increased risk of cardiovascular death and all-cause mortality (38,39). Furthermore, in subgroup analyses of the Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS), a positive CVD-preventive effect of DPP-4 inhibitor was reported in obese patients, suggesting that body mass index might be an important clinical measurement when considering blood glucose-lowering drug treatment (9). This reasoning is obviously speculative, and further studies are needed to explore such associations.

A strength of the present work is the population-based, nationwide and unselected real-world study design, which provides a high external validity. In addition, this is a study with full (100%) register coverage for hospitalizations, filled drug prescriptions, and cause of death in a country with an established and complete public healthcare system. Diagnoses in the Swedish Patient Registry have been reported to have high validity (40), and few patients are lost to follow-up. Moreover, the directed acyclic graphs used to create the optimal adjustments of hazard models should provide minimal bias (22).

Observational studies such as this obviously have limitations. The present study has no information on laboratory measurements, lifestyle parameters, primary healthcare data, or socioeconomic data, and consequently there may be remaining confounding factors. Moreover, glucose-lowering drugs such as metformin could potentially have been used for reasons other than type 2 diabetes treatment (such as polycystic ovarian syndrome or prediabetes), which could influence the results. However, such usage should be very small compared with the type 2 diabetes indication. Specifically, the combination treatments addressed in this study (i.e. metformin together with either a DPP4 inhibitor or a sulphonylurea) would have been used to a negligible extent for conditions other than type 2 diabetes. In the propensity score -matched analyses, the numerical risk of severe hypoglycemia reflected the unmatched analyses, but
without showing statistically significant differences. This was likely due to lack of power, with low number of events and a substantially reduced study cohort (by 32%). We have no information on emigration, which could result in loss to follow-up. However, the on-treatment analyses used in this study should minimize the effects of patients moving out of Sweden. Furthermore, our assessment of severe hypoglycemia is crude, including only events leading to hospital admission. It was not possible to evaluate other hypoglycemic events in this register-based study. Another limitation is that patients with a recorded hypoglycemia had to survive until this occasion and, if anything, this would underestimate the total mortality rate in these patients compared to those without a hypoglycemic event.

Although a major concern with the present analyses is the non-randomized approach with risk for confounding by indication, the data are an in agreement with several other observational studies reporting data raising concerns about the use of sulphonylureas compared with DPP-4 inhibitor, both as monotherapy and in combinations with metformin [13,14,16,18,25]. Of these studies, four papers from Denmark, South Korea, Sweden, and the UK have compared metformin combinations with sulphonylurea versus DPP-4 inhibitor using different analytic approaches and data sources. In spite of this, the resulting risk estimates are similar and show increased clinical risks for metformin + sulphonylurea compared with metformin + DPP-4 inhibitor [16,25]. These concordant study results may thus demonstrate the robustness of epidemiological methods using large register datasets to assess specific research questions. Despite unknown factors potentially confounding the results, the results may raise concerns regarding the cardiovascular safety of sulphonylurea while awaiting results from the CAROLINA study [21].

5. Conclusion

This nationwide register-based study shows that type 2 diabetes patients that received a combination of metformin and sulphonylurea as second-line treatment had an increased risk of subsequent severe hypoglycemia, cardiovascular events and all-cause mortality compared with those receiving metformin in combination with a DPP-4 inhibitor. The causal relationships remain to be further elucidated, but results from this and other observational studies should be considered in the choice of treatment for patients with type 2 diabetes, until results from future randomized trials are available.

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Conflicts of interest statement

JWE was previously employed by AstraZeneca R&D and has received honoraria or research grants from AstraZeneca, NovoNordisk, Bristol-Myers-Squibb and MSD. JB holds a full-time position at AstraZeneca as epidemiologist. DN has received consultancy fees from Novo Nordisk, Astra Zeneca and Eli Lilly. MT is employed by an independent statistical consultant company, Statisticom AB, Uppsala, Sweden, for which AstraZeneca Nordic-Baltic is a client. TN is on the national board of Novo Nordisk, Sanofi-Aventis and Eli Lilly. AN has honoraria from expert group participation (MSD, Astra Zeneca, Eli Lilly). Editorial support funded by AstraZeneca was provided by Oxford PharmaGenesis.

Author contributions

All authors participated in the study design. MT performed the data collection and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing the manuscript. All authors took final responsibility in the decision to submit for publication.

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Appendix A. Supplementary data

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