PATIENTS TREATED WITH INSULIN AND SULPHONYLUREA ARE AT INCREASED MORTALITY RISK AS COMPARED WITH THOSE TREATED WITH INSULIN PLUS METFORMIN

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Abstract

Aims. To investigate the effect of sulphonylurea (SU) treatment on all-cause and cardiovascular mortality as compared with metformin (MET), when used in combination with insulin (INS) in type 2 diabetes.

Methods. All type 2 diabetes patients aged ≥ 40 years were included at their first prescription of INS+MET or INS+SU, during 2001-2008. They were considered at risk until death or December 31st, 2011. Mortality rates were calculated per 1000 person-years. Crude and adjusted rate ratios (RR) were calculated using time dependent analysis with INS+MET as reference.

Results. There were 7122 patients (60.8% women) included in the analysis, with a mean age at baseline of 62.0 ± 9.9 years. During the 11 years of study, patients on INS+MET contributed 13620 person-years and 330 deaths (mortality rate 24, CI95% 22-27), while those on INS+SU contributed 8720 person-years and 393 deaths (mortality rate 45, CI95% 41-50). Adjusted all-cause mortality RR were: SU 1.6 (CI95% 1.21-2.11, $p < 0.001$), glimepiride 1.18 (CI95% 0.73-1.91, $p = 0.51$), gliclazide 1.78 (CI95% 1.07-2.95, $p = 0.024$), glibenclamide 1.66 (CI95% 0.71-3.88, $p = 0.23$), glipizide 1.24 (CI95% 0.68-2.27, $p = 0.49$), and gliquidone 2.32 (CI95% 1.54-3.50, $p = 0.001$).

Conclusions. When combined with insulin as dual therapy, patients treated with SU were at increased mortality risk as compared with insulin + MET.

Key words: metformin, sulphonylurea, mortality.

INTRODUCTION

Type 2 diabetes is a progressive disease, with the decline of beta cell function requiring periodic intensification of treatment regimen to reach glycemic targets (1). As life expectancy in type 2 diabetes patients is constantly growing, most patients will eventually require insulin added to their treatment regime (2). While the dual combination metformin (MET) plus

insulin (INS) is supported by the current guidelines, the dual treatment with sulphonylurea (SU) plus INS is not, particularly due to the high risk of hypoglycemia (3). However, in current clinical practice many patients are still treated with a combination of INS+SU, for various reasons like MET intolerance or clinical inertia. While MET+INS treatment is generally considered safe, INS+SU combination was shown to be associated with increased mortality, with variable risks among specific SU (4). Increased SU associated hypoglycaemia was the main culprit here, but differences between patients receiving SU or MET following a usual diabetes consultation as opposed to randomization in a clinical trial might have an even greater impact (5).

The current study aims to investigate all cause and cardiovascular mortality risk associated with exposure to combined treatment with INS plus either SU or MET, in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

All patients receiving a prescription for diabetes during 2001-2008 in two major centres from Bucharest were included, as previously described elsewhere (6). This retrospective, observational study was based on an anonymized version of a mortality database. Date of first prescription for INS and MET or INS and SU combined therapy was considered as baseline. Patients aged < 40 years at baseline ($n = 251$), or never receiving a prescription of INS+MET/INS+SU ($n = 72461$) were excluded from the analysis. Final cohort retained 7122 cases of type 2 diabetes patients receiving at least one prescription of the investigated treatment options. Inclusion of some type 1 diabetes patients cannot be completely overruled, especially of some patients with latent autoimmune diabetes in adults. The study was

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approved by the local ethic committee, without the need of informed consent to be obtained from each participant due to its database driven design.

Exposure and outcomes

The time between screening (first diabetes prescription) and baseline was used to create binary variables for ever exposed to INS, MET and each of the specific SU, irrespective of mono, dual or multitherapy prescription. Although unusual, there was one patient receiving glibenclamide and gliclazide (plus insulin) at baseline and therefore contributed to both categories (Table 1). In addition, variables storing time (in

years) of exposure to those treatment options up until baseline were created. All treatment related data was used as time-dependent variables. After baseline, time spent and outcomes appearing while on other options besides INS+MET / INS+SU were excluded from analysis. Follow-up time was split at any change in diabetes treatment. All subjects were followed-up until December 31st, 2011 for all-cause and cardiovascular mortality by cross-linking with the National Mortality Database. Mortality data was based on the death certificates, with causes of death encoded in the International Statistical Classification of Diseases and Related Health Problems 10th Revision system (ICD-10; www.who.int/classifications/icd/en/). Diabetes treatment data was available until December 31st, 2008, with last observation carried forward until the end of follow-up. Possible treatment misclassification during 2009-2011 might reduce the capacity for discrimination between risks associated with the investigated treatment options. This is partially offset by a reduced reverse causation bias, which might appear due to a change in diabetes treatment associated with the onset of a serious comorbidity around the end of follow-up.

Statistical analysis

All mortality rates were calculated per 1000 person-years. Crude and adjusted rate ratios (RR) and 95% CI were calculated using the Mantel-Cox method (and log-rank test). Insulin + MET was used as reference. Adjustment was performed for age, gender, calendar year at baseline, ever exposed to and time spent up until the baseline on any of the following: INS,

Figure 1. Use of individual SU / MET plus insulin at baseline according to year of inclusion. GLIB glibenclamide (solid grey line); GLIC gliclazide (solid black line); GLIM glimepiride (round dotted grey line); GLIP glipizide (dash black line); GLIQ gliquidoneum (dash grey line); MET metformin (round dotted black line).

Table 1. Baseline characteristics of study subjects

Variable	Insulin + GLIB [#]	GLIC [#]	GLIM	GLIP	GLIQ	MET	All
n	245	611	754	815	1324	3374	7122
Women n (%)	145 (59.2)	352 (57.6)	459 (60.9)	459 (56.3)	743 (56.1)	2175 (64.5)	4333 (60.8)
Age (yrs)	65.6±10.6	63.6±10.6	62.7±10.1	63.2±9.5	64.9±9.9	59.8±9.3	62.0±9.9
Inclusion year n							
2001/2002	77	185	167	425	477	973	2304
2003/2004	61	207	187	294	467	732	1948
2005/2006	75	85	168	49	260	600	1236
2007/2008	32	134	232	47	120	1069	1634
Prior use of							
MET n (yrs)	84 (1.6)	161 (1.5)	296 (1.6)	268 (1.2)	313 (1.6)	1641 (2.3)	2763 (2.0)
SU n (yrs)	168 (2.2)	341 (2.2)	514 (2.3)	472 (1.8)	619 (2.1)	1603 (2.5)	3716 (2.3)
GLIB n (yrs)	149 (1.5)	126 (1.3)	235 (1.4)	203 (0.9)	234 (1.3)	1004 (1.6)	1950 (1.5)
GLIC n (yrs)	56 (0.9)	264 (1.4)	192 (1.1)	142 (0.6)	199 (0.9)	719 (1.2)	1572 (1.1)
GLIM n (yrs)	35 (0.7)	72 (0.9)	324 (1.1)	73 (0.7)	109 (0.8)	520 (1.1)	1133 (1.1)
GLIP n (yrs)	46 (1.2)	90 (1.1)	181 (1.1)	373 (1.2)	208 (1.2)	575 (1.2)	1473 (1.2)
GLIQ n (yrs)	14 (0.9)	37 (1.0)	80 (1.1)	70 (1.1)	362 (1.2)	210 (0.9)	773 (1.1)
INS n (yrs)	97 (1.1)	303 (1.2)	432 (1.3)	387 (1.0)	745 (1.3)	2020 (1.6)	3984 (1.4)

MET metformin, SU sulphonylurea, GLIB glibenclamide, GLIC gliclazide, GLIM glimepiride, GLIP glipizide, GLIQ gliquidoneum.

[#]one patient received glibenclamide and gliclazide (plus insulin) at baseline and therefore contributed to both categories.

MET, glimepiride, gliclazide, glibenclamide, glipizide and gliquidonium. Time bands used for adjusting were 20 years for age, and 2 years for cumulative exposure time on glucose lowering therapy (until baseline). All specific SU (in association with insulin) were supplementary tested against the SU molecule with the lowest found mortality relative risk (here glimepiride). Parametric and nonparametric tests were used as required, with chi square test evaluating frequencies. A p value <0.05 was considered as statistically significant. All calculations were performed using STATA 13 (www.stata.com). Sensitivity analysis was performed using six SU categories: glimepiride, gliclazide,

glibenclamide, glipizide and gliquidonium.

RESULTS

A total of 7122 patients (60.8% women) contributed 22340 person-years of follow-up on either INS+MET or INS+SU, during 10.9 years of study. Mean age at baseline was 62.0 ± 9.9 years, slightly higher in women (62.7 ± 9.8 years) as compared with men (60.9 ± 10.1 years, $p < 0.001$). There were 3899 patients exposed to INS+MET during 13620 person-years and 4028 patients exposed to INS+SU during 8720 person-years. The number of patients exposed to INS+MET added to that exposed to INS+SU is higher than the total number of study cases because a patient can be temporarily exposed to INS+MET and later to INS+SU or the other way around. Baseline characteristics are available in Table 1.

Compared with INS+MET, subjects treated with INS+SU were more likely to be older, with a higher percentage of men, recruited earlier during the inclusion period, with a higher exposure to SU prior to baseline. Baseline prescriptions for individual SU and MET combined with insulin changed over the inclusion time (Fig. 1).

Crude all-cause and cardiovascular mortality rates are presented in Table 2. Crude mortality rates for INS+SU category were almost double as compared with INS+MET. All specific SU had higher mortality rates as compared with MET (added to INS). Adjusted relative risks using INS+MET as reference are presented in Figure 2. INS+SU was associated with a significantly higher risk for all-cause (RR 1.6 CI95% 1.21-2.11, $p < 0.001$) and cardiovascular mortality (RR 1.65 CI95% 1.14-2.37, $p < 0.01$) comparing with INS+MET. When looking at individual SU, exposure to gliclazide and gliquidonium was associated with a significant higher risk for all-cause and cardiovascular mortality, and no significant impact was found for glibenclamide, glimepiride and glipizide, when used in association with

Figure 2. Adjusted relative risks using INS+MET as reference for (a) all-cause mortality and (b) cardiovascular mortality.

Table 2. Crude all-cause and cardiovascular mortality rates per 1000 person-years

Variable	Insulin + MET	All SU	GLIB	GLIC	GLIM	GLIP	GLIQ
All-cause mortality							
Events	330	393	41	79	96	53	124
Person-years	13620	8720	605	1543	2487	1519	2572
Crude rates	24 (22-27)	45 (41-50)	68 (50-92)	51 (41-64)	39 (32-47)	35 (27-46)	48 (40-57)
Cardiovascular death							
Events	207	228	21	49	58	35	65
Person-years	13620	8720	605	1543	2487	1519	2572
Crude rates	15 (13-17)	26 (23-30)	35 (23-53)	32 (24-42)	23 (18-30)	23 (17-32)	25 (20-32)

MET metformin, SU sulphonylurea, GLIB glibenclamide, GLIC gliclazide, GLIM glimepiride, GLIP glipizide, GLIQ gliquidonium.

INS (Fig. 2). All-cause mortality restricted to women showed similar results, with gliclazide RR 2.17 (CI95% 1.22-3.86, $p=0.007$), gliquidonium RR 2.61 (CI95% 1.49-4.56, $p<0.01$), glibenclamide RR 3.34 (CI95% 0.81-13.69, $p=0.076$), glimepiride RR 1.08 (CI95% 0.54-2.18, $p=0.83$) and glipizide RR 1.66 (CI95% 0.77-3.57, $p=0.19$). Results in men were gliclazide RR 1.05 (CI95% 0.36-3.09, $p=0.92$), gliquidonium RR 2.0 (CI95% 1.09-3.69, $p=0.023$), glibenclamide RR 1.1 (CI95% 0.36-3.36, $p=0.87$), glimepiride RR 1.27 (CI95% 0.65-2.48, $p=0.48$) and glipizide RR 0.8 (CI95% 0.29-2.24, $p=0.67$).

There was no significant increase in all-cause mortality risk associated with exposure to INS plus glibenclamide 3.02 (CI95 0.86-10.57, $p=0.069$), gliclazide 1.38 (CI95% 0.67-2.87, $p=0.38$), glipizide 1.08 (CI95 0.40-2.87, $p=0.88$), or gliquidonium 1.71 (CI95% 0.94-3.13, $p=0.075$), as compared with INS plus glimepiride. Similar results were obtained for cardiovascular mortality: glibenclamide 1.57 (CI95 0.33-7.38, $p=0.56$), gliclazide 1.98 (CI95% 0.75-5.22, $p=0.16$), glipizide 1.33 (CI95 0.36-4.92, $p=0.66$), gliquidonium 2.03 (CI95% 0.88-4.70, $p=0.09$), as compared with INS plus glimepiride.

DISCUSSION

This observational study investigated the all-cause and cardiovascular mortality associated with exposure to INS plus either MET or SU in a mixed urban and rural population of Romania ($n=7122$) and established four major findings. First, patients exposed to INS+MET are significantly different from those exposed to INS+SU in terms of age, gender, calendar year at inclusion and previous exposure to SU/MET. Second, although not recommended by guidelines, the dual combination of INS+SU was still prescribed to a high number of patients. Third, MET identified a better mortality risk profile as compared with SU, when used in combination with INS. And fourth, no specific SU performed significantly different from glimepiride when used as a combined treatment with INS.

Higher age and male gender are strong predictors of all-cause and cardiovascular mortality in both general population and patients with diabetes (6). Although they were adjusted for, together with calendar year at inclusion and previous oral medication, there are several unmeasured confounders, that might explain at least partial if not all found differences in mortality between the two study groups. Therefore, clinicians are advised to place a special focus on cardiovascular risk

assessment and multifactorial intervention, allocating more time for those patients found in this study to be at particular high risk, i.e. INS+SU treatment group.

While clinical indication of INS+SU is clearly debatable, a study by Mogensen *et al.* showed a similar, unexpected high number of patients treated in this way in Denmark (4). In that study, patients included later were more likely to receive INS+MET comparing with early inclusion, showing increased MET preference over SU with every passing year (4). The same pattern was found in the current study, which may be interpreted as a steady increase in diabetes guideline recommendations penetrance in the medical field.

While SU were shown to be associated with higher mortality, some studies argued that not all SU are the same in this respect (5, 7-12). While this issue dates back from The University Group Diabetes Program, where tolbutamide was associated with a significant increase in all-cause and cardiovascular mortality, the more robustly conducted UK Prospective Diabetes Study showed no increased mortality in relation to sulphonylurea exposure (13,14). Many other treatment options for type 2 diabetes are now available, and all have their up- and downsides (15, 16).

Weight gain and increased risk of hypoglycaemia are class related perpetrators, but interference with ischaemic preconditioning due to increased SU receptor 2A affinity is worse with glibenclamide as compared with glimepiride or gliclazide (17). Using MET as reference, gliclazide and gliquidonium showed unexpected high mortality risks, even higher than that expected for glibenclamide, which is often considered the worse performer in this regard within the SU class. This finding is most likely due to a higher propensity for gliclazide to be prescribed in patients with heart disease and gliquidonium in patients with advanced renal disease, both recognized as strong predictors of future macrovascular events. Similar with results from the study performed by Mogensen *et al.* no significant differences among specific SU were found with a more appropriate and perhaps more objective approach, using glimepiride as reference (4).

As strength points, this study included all consecutive patients seeking diabetes related health care in a large urban city and its extended urban and rural surroundings, significantly reducing selection bias. In addition, during the first 6 years of inclusion period there were only two centres in Bucharest (included in the study) allowed to prescribe and dispense free diabetes medication, maximizing the probability to catch almost all diabetes patients. Treatment allocation

was carefully accounted for as time-dependent variables for a continuous and precise risk assessment.

As weak points, major risk factors like history of cardiovascular heart disease, smoking, body mass index, physical activity, blood pressure, lipid profile or HbA1c were not available in this observational study. Some important characteristics of the patients included in this study and known to influence mortality outcomes, among which history of cardiovascular disease, chronic kidney diseases and diabetes duration are missing, which is a major limitation. Also, the quality of treatment interventions for major cardiovascular risk factors most probable have changed during the relative large study inclusion period. This is the reason behind adjusting for calendar year of inclusion, but significant residual confounding more likely remained.

Important biological changes are already in place in the prediabetes state and future focus might shift into this period, as is currently happening for type 1 diabetes (18, 19).

In conclusion, this study showed that in clinical practice patients treated with a combination of INS+SU are at increased mortality risk as compared with those treated with INS+MET. MET is increasingly used instead of SU in this context, which agrees with the current guidelines. The findings of this study uphold the guidelines recommendation for combined treatment with insulin plus metformin in patients with type 2 diabetes, when clinically indicated.

Conflict of interest

The authors declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethic committee, without the need of informed consent to be obtained from each participant due to its retrospective database driven design. For this type of study formal consent is not required.

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