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MORTALITY OUTCOMES OF DIFFERENT SULFONYLUREA DRUGS.**The results of a 14-year cohort study of type 2 diabetic patients**

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Abstract

Objective: Available data about mortality of type 2 diabetic patients treated with different sulfonylureas are scarce and contradictory. *Design:* We evaluated the associations between all-cause and cause-specific mortality and treatments with different sulfonylureas in a retrospective cohort of type 2 diabetic patients from a diabetes clinic. *Methods:* All 1277 patients treated with sulfonylureas during 1996-1997 were enrolled: 159 patients were treated with tolbutamide, 977 glibenclamide, and 141 gliclazide. The baseline data (centralised laboratory parameters, anthropometric data, presence of chronic complications) were abstracted from the clinical records. Information on vital status were collected from demographic files after 14-year-follow-up. Adjusted hazard ratios were estimated with Cox (all-cause mortality) or Fine and Gray models (cause-specific mortality), including several potential confounders. *Results:* 556 patients died during the follow-up: 262 from cardiovascular causes, 158 from cancer, and 136 from other causes. When compared to the glibenclamide-users, the gliclazide- and tolbutamide-users showed a significantly lower cancer mortality (HR=0.30;95%CI 0.16-0.55, and HR=0.48;95%CI 0.29-0.79, respectively). These results were strongly confirmed in the 555 patients on sulfonylurea-monotherapy. None of the patients who were treated with gliclazide monotherapy died from cancer during the follow-up, and the patients on tolbutamide exhibited a lower cancer mortality than the glibenclamide-users (HR=0.40;95%CI 0.22-0.71). Data did not change after stratification for the duration of sulfonylurea treatment from diabetes diagnosis to the study enrolment.

Conclusions: Cancer mortality was markedly reduced in the patients on gliclazide and tolbutamide. These results suggest additional benefits for these drugs beyond their blood glucose-lowering effect and strongly advocate for further investigation.

Introduction

The effects of sulfonylurea drugs on mortality in type 2 diabetes mellitus have not been conclusively established. The University Group Diabetes Program (UGDP) found increased mortality from cardiovascular (CV) disease with the use of the sulfonylurea tolbutamide [1]. However, subsequent analyses of the UGDP identified flaws in the patient selection and study design [2]. The United Kingdom Prospective Diabetes Study (UKPDS) reported no increase in adverse CV outcomes from the use of either first- or second-generation sulfonylurea therapy [3]. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN Modified Release Controlled Evaluation (ADVANCE) study revealed no deleterious effects of gliclazide MR on overall and CV mortality [4-5]. Therefore, sulfonylureas have remained a mainstay therapy for type 2 diabetes [6].

Metformin was associated with better outcomes in the UKPDS study [3]; both retrospective and prospective data suggested that the benefits of metformin were reduced when combined with sulfonylureas [7-8]. However, these results have not been confirmed by other studies [9-11], and either reduced [12-14] or increased all-cause or CV mortality have been reported in patients treated with sulfonylureas [15-16]. Furthermore, although metformin has been shown to consistently reduce the risks of cancer incidence and mortality [17], the data concerning sulfonylureas are controversial, because a neutral effect [14,18-19], an increased risk [20-23], and a reduced cancer-related mortality [24] have all been described in the literature.

The possibility that specific sulfonylurea drugs exert other than the hypoglycaemic role has been suggested for gliclazide, which reduces oxidative stress and produces beneficial effects on vessel wall biology and DNA damage protection [5]. A few epidemiologic studies have evaluated total and CV mortality according to the type of sulfonylurea drug used, with contrasting results [15, 25-29]. Only one study, to the best of our knowledge, has examined the association between sulfonylurea types and cancer-related mortality; this study revealed a protective effect of gliclazide [30]. In particular, the cumulative cancer-related mortality rates were 1.4% and 0.7% in glibenclamide- and

gliclazide-treated patients, respectively (OR=3.6;95%CI 1.1-11.9); pancreatic and pulmonary cancers were the most frequent malignancies in patients with cancer-related mortality [30]. Two studies have reported a reduced cancer incidence with gliclazide use (OR=0.40;95%CI 0.21-0.57 [31] and OR=0.62;95%CI 0.47-0.81 [24]); however, definitive conclusions about site-specific cancer types and hypoglycaemic drugs could not be drawn from these studies.

The aim of the present study was to evaluate the associations between all-cause and cause-specific mortality and treatment with three types of sulfonylurea drugs (tolbutamide, glibenclamide, and gliclazide) in a retrospective cohort of 1277 patients with type 2 diabetes mellitus after a 14-year follow-up period.

Subjects and Methods

Patients

All 2113 patients with type 2 diabetes attending the diabetes clinic in Asti (northern Italy) in 1996-1997 were evaluated [32-34]. These patients represented 1.6% of the reference population ($n=134,646$) and, because the prevalence of known type 2 diabetes was 2% in northern Italy, we estimated that our cohort included approximately 80% of the known diabetes cases in the study area [32,34]. For the present analyses, we considered patients who were treated with sulfonylureas (1277/2113; 60.4%) during the enrolment period (1996-1997) either as a monotherapy or in combination with metformin and/or insulin.

Outcomes

Information on the vital status of each patient and the causes of death of those who were deceased were updated to 2010 from the demographic files in their towns of residence or death. The underlying causes of death were derived from death certificates and were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). The causes of death were coded by a single trained researcher who was blinded to the patients' characteristics and therapies. All of the procedures were in accordance with the Helsinki Declaration, as revised in 2000. Informed

consent was obtained from all of the patients at baseline, and the local ethics committee approved the study protocol.

Methods

At the diabetes clinic, all of the patients were examined every 4 months: their body weight, glycated haemoglobin (HbA1c) levels, and blood pressure values were measured at each visit, whereas lipid measurements and screening for chronic complications were performed annually. Centralised laboratory measurements were performed in the clinic.

The baseline data were abstracted from the clinical records during the enrolment period (1996-1997). When multiple measurements were available, the averages of the last three values found in the clinical records were reported.

Arterial blood pressure was measured in the morning after an overnight fast by the same nurse using a mercury sphygmomanometer with the appropriate cuff size, after a 5-minute rest in the sitting position, with the arm being supported at heart level. The reported value was the average of the three most recent measurements reported in the clinical records. The laboratory methods have been previously described [30]. HbA1c was measured using HPLC (Bracco, Italy; reference range 2.4-4.7%); the value reported was the mean of the three most recent determinations.

Retinopathy was diagnosed via an ophthalmoscopic examination and/or retinal photography [32].

Nephropathy was defined as an albumin excretion rate (AER) of more than 20 μ g/min in at least 2 of 3 urine collections within a 6 month period (immunoturbidimetric method), or the presence of gross proteinuria or elevated serum creatinine levels. Distal symmetric polyneuropathy was diagnosed by the presence of neuropathic symptoms, an abnormal vibration perception threshold, the absence of ≥ 2 ankle or knee reflexes, and/or an abnormal electromyographic test. Autonomic neuropathy was diagnosed by a loss of heart rate variability or by the presence of postural hypotension. The diagnosis of CV disease was based on documented events recorded by a physician (angina, myocardial infarction, a coronary artery by-pass graft or other invasive procedures to treat coronary artery disease, transient ischaemic attack, stroke, gangrene, amputation, vascular surgery,

intermittent claudication, absent foot pulses or abnormal brachial and posterior tibial blood pressures, as determined by Doppler techniques).

Statistical analyses

Both all-cause mortality and cause-specific mortality were considered as outcomes. The causes of death were grouped into three broad categories: CV diseases (ICD 410-414, 430-438, 440), cancer (140-239) and all other causes.

In 1996-1997, metformin was prescribed at our diabetes clinic as the first-line drug in obese patients, whereas sulfonylureas were administered to normal weight/overweight patients and to patients who did not reach their glycaemic goals or who were intolerant to metformin. Only three types of sulfonylureas were used: tolbutamide, glibenclamide and gliclazide. Other sulfonylureas or other hypoglycaemic drugs, such as metiglitinides and thiazolidinediones, were not used. The patients were analysed according to the type of sulfonylurea that was used at enrolment (tolbutamide, glibenclamide, or gliclazide), taking into account whether metformin or insulin were used in combination. All the analyses were also performed in the subgroup of patients who were treated with sulfonylureas alone ($n=555/2113$, 26.3%) and for those treated with glibenclamide ($n=977/2113$, 46.2%) to explore possible interactions with metformin or insulin. The duration of sulfonylurea treatment from diabetes diagnosis to the enrolment period was considered as a stratification variable. Furthermore, in the subgroup of patients treated with sulfonylureas alone at enrolment, the data relative to hypoglycemic treatment from enrolment to the end of follow-up were retrieved in 458/555 (82.5%) patients. Causes of death did not differ in those patients with respect to the 555 patients.

The characteristics of the patients were described using means and standard deviations or medians and inter-quartile ranges for the continuous variables. Percentage frequencies were used for the categorical variables. ANOVA, chi-square and Kruskal-Wallis tests were used to compare the baseline characteristics of the patients among the three treatment groups.

The overall survival, estimated with the Kaplan-Meier method, was defined as the time from enrolment until the date of death or the end of the observation. A Cox proportional hazard model was employed to estimate the crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. The HRs for each type of sulfonylureas (introduced into the model as dummy variables, considering the glibenclamide-treated patients as the reference group) were adjusted for metformin and insulin use, as well as other baseline characteristics (age, sex, BMI, smoking, the time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, and CV diseases). We validated the proportional hazards assumption by using the scaled Schoenfeld residual tests. To analyse the effects of all these variables on the three groups of cause-specific mortality, a Fine and Gray model was used to consider deaths from alternative causes as competing events. The presence of an effect modification between each sulfonylurea and either metformin or insulin was tested by introducing specific interaction terms into the models and by replicating all of the analyses after excluding patients who were treated with drug combinations. To account for exposure duration, treatment effects were also estimated using Cox and Fine and Gray models stratified by the duration of the sulfonylurea treatment prior to enrolment, as a sensitivity analysis. As a further sensitivity analysis, in the group of patients on sulfonylureas alone at enrolment, the same models were replicated considering the hypoglycemic treatment until the end of follow-up (metformin, insulin, and sulfonylureas) as time varying variables.

Statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, Texas) and R (2.15.0).

Results

The patient characteristics according to the type of sulfonylurea used at enrolment are reported in Table 1. Glibenclamide was frequently used in association with metformin in complicated patients with higher HbA1c levels. Gliclazide and tolbutamide were more frequently administrated as monotherapies to patients with shorter diabetes durations.

Overall, 556 patients died during the follow-up: 262 from CV diseases, 158 from cancer, and 136 from all other causes. The cumulative incidence of all-cause (panel A) and cause-specific mortality (panels B, C, and D) according to sulfonylurea type is shown in Figure 1.

Both the gliclazide and tolbutamide-users showed a trend towards a lower risk of all-cause mortality and significantly lower cancer mortality than the glibenclamide-users (Table 3). Notably, the 10 cancer deaths among the gliclazide-users occurred in those patients who had also been treated with insulin in association. The data did not change after stratifying for the duration of sulfonylurea exposure.

Intriguingly, when the analyses were limited to the patients who took glibenclamide ($n=977$), those whose treatment included insulin exhibited increased all-cause mortality (HR=1.48; 95%CI 1.06-2.07), and increased cancer mortality (HR=1.45; 95%CI 0.80-2.62), whereas those whose treatment included metformin exhibited significantly lower all-cause mortality (HR=0.70; 95%CI 0.56-0.87), and strongly reduced cancer mortality (HR=0.33; 95%CI 0.22-0.50). The protective effect of metformin on cancer mortality was also evident in the patients who were treated with the combination of glibenclamide, insulin, and metformin compared to those treated with glibenclamide alone (HR=0.22; 95%CI 0.08-0.65) (data not shown).

In our patients, metformin used either alone or in any combination was associated with lower risks of all-cause mortality (HR=0.67; 95%CI 0.55-0.82) and cancer mortality (HR=0.32; 95%CI 0.21-0.47) (data not shown). Conversely, the insulin-users experienced higher risks of both all-cause mortality (HR=1.47; 95%CI 1.17-.84) and cancer mortality (HR=1.81; 95%CI 1.15-2.86) (data not shown).

Although no statistically significant interactions between the sulfonylureas and metformin or insulin were detected, all of the analyses were performed in patients undergoing monotherapy with sulfonylureas ($n=555$), whose characteristics are reported in Table 2. The associations between the individual sulfonylureas and all-cause and cancer mortality were confirmed in this group (Table 4). None of the patients who were treated with gliclazide died from cancer during the follow-up period.

The cancer mortality rates were significantly lower among the patients who were treated with tolbutamide, compared to those who were administered glibenclamide. During the follow-up, most patients of this group did not change glibenclamide or gliclazide while most on tolbutamide did, because this drug was withdrawn from the market at the end of nineties in Italy (Supplementary Table 1). The associations between sulphonylurea types and all-cause and cancer mortality were confirmed in the sensitivity analysis that considered the changes in the hypoglycaemic treatment during the follow-up period (Supplementary Table 2).

Discussion

Individual sulphonylureas may influence the risk of mortality, particularly cancer mortality. Gliclazide and tolbutamide, administered either as monotherapies and in combination with metformin or insulin, demonstrated a protective effect on cancer mortality when compared to glibenclamide. The beneficial effects of metformin against cancer mortality, both alone and in combination with other drugs, were confirmed.

Glibenclamide

The literature evaluating the association between all-cause and cause-specific mortality and sulphonylurea drugs is highly discordant. Furthermore, not all studies evaluated glibenclamide separately from other sulphonylureas, but considered “second-generation” sulphonylureas, [13], or “old sulphonylureas” [35], or “sulphonylureas” alone [7-11,14,20]. The possibility that the sulphonylureas are not equal in terms of all-cause mortality risk or CV risk had already been raised [1-5,12-13,15,25-29]. Sulphonylureas act on beta cells by blocking ATP-dependent potassium channels; sulphonylurea receptors and functional potassium ATP channels have been identified as ubiquitous [36]. Opening these channels in the heart appeared to be cardioprotective, and this effect was blocked by sulphonylureas [36]. Indeed, sulphonylureas with a greater selectivity for beta-cell receptors, such as glimepiride and gliclazide, have been associated with a lower CV risk [25,37], whereas glibenclamide has been associated with an excess all-cause and CV mortality [15,25-27]. The adverse effects reported for glibenclamide include: increased peripheral vascular tone, reduced

diazoxide-induced vasodilatation, the inhibition of preconditioning, increased infarct size, the inhibition of the fibrinolytic system, and increased QT interval dispersion [2,36,38].

Accordingly, we found an excess of mortality among the glibenclamide-treated patients in our study: 45.5% of the glibenclamide-treated survived *versus* 72.4% of the gliclazide-treated in monotherapy. However, these differences were mainly caused by increases in cancer mortality, but not CV mortality. Other cohorts have been followed for shorter time periods and cancer deaths have not been considered [15, 25-28]. Thus, it is possible that the differences in CV mortality were evident in the short-term, but progressively diminished or, more likely, that the gliclazide-treated patients survived cancer and had time to develop CV diseases. Similarly, in the UKPDS and in other population-based cohorts, the use of glibenclamide produced no adverse effects on CV outcomes [1,13,28-29].

The differences in cancer deaths between sulfonylurea types are impressive in our cohort (Tables 2 and 4). Studies evaluating the association between cancer and the use of sulfonylureas have provided conflicting evidence [14,18-23,39]. A few studies of individual sulfonylureas have revealed an increased cancer incidence and mortality with glibenclamide use [30-31], but a protective effect of glibenclamide on cancer incidence has also been reported [24]. In the latter study there were interactions between metformin and glibenclamide use towards lower cancer risk; after adjusting for the interaction terms, the use of glibenclamide provided no protective effect (HR=1.27; 95%CI 0.76-2.11) [24]. Some studies have not found an imbalance in cancer types among glibenclamide-users [40], but others have found increased risks of pancreatic or hepatocellular carcinoma among sulfonylurea-users [22,41-42]. A recent meta-analysis, however, found no evidence that sulfonylureas affected the risk of cancer at any site [43].

The possibility of a drug-specific effect of glibenclamide on carcinogenesis is worthy of further investigation.

Gliclazide

No cancer deaths occurred among our patients who were treated with gliclazide as monotherapy, and the risk of cancer was significantly reduced among the patients using other hypoglycaemic drugs in combination with gliclazide. A few studies have reported significantly reduced cancer incidence [24,31] and mortality rates [30] among gliclazide-treated patients. In addition to its hypoglycaemic effect, gliclazide was found to exert extra-pancreatic and anti-oxidant actions [44]. Its unique molecular structure contains an azabicyclo-octyl ring grafted onto a hydrazide group, which may explain some of these specific effects [45]. In particular, gliclazide possesses free radical scavenging activity and may up-regulate the expression of antioxidant enzymes, enhance NO-mediated vasodilatation, reduce glucose-induced apoptosis and mitochondrial alterations, increase nitrotyrosine concentration [5,44-46], inhibit some key biologic events associated with the processes of monocyte differentiation, endothelium adhesion and atherosclerotic plaque formation and rupture [47-48], and exert anti-inflammatory effects [49].

The following mechanisms have been proposed to explain the increased cancer risk among type 2 diabetic patients: insulin-resistance, hyperinsulinaemia, oxidative stress, advanced glycation end products, and chronic low-grade inflammation [50]. Therefore, it is possible that by reducing the susceptibility of cells to oxidative stress and inflammation, gliclazide may exert a protective effect on carcinogenesis. These retrospective data require replication in larger prospective cohorts and experimental confirmation. Nevertheless, these findings are worthy of consideration, particularly the suggestion that the “old” hypoglycaemic drugs, gliclazide and metformin, should not be considered “outmoded”, if major end-points in the efficacy and safety of the therapeutic interventions for diabetes mellitus are considered, instead of surrogate endpoints, which are much more frequently evaluated, unfortunately [51].

Tolbutamide

The tolbutamide-treated patients exhibited lower all-cause and cancer-mortality rates than the glibenclamide-treated individuals, both when tolbutamide was used in combination with other drugs and as monotherapy. Few reports are available on this topic. Increased all-cause and CV mortality

rates have been reported for tolbutamide [1,15,28], but reduced all-cause mortality has also been reported [12]. We did not find any published data concerning cancer mortality in tolbutamide-treated patients. Therefore, evaluating a possible drug-specific effect of this drug on carcinogenesis is highly complex. Tolbutamide has been shown to inhibit fatty acid oxidation by inhibiting mitochondrial carnitine palmitoyltransferase, the key regulator enzyme in fatty acid oxidation [52], and to up-regulate several antioxidant enzymes, by suppressing the ATP-dependent potassium channel, which is a target for oxidants. These data suggest an antioxidant effect of tolbutamide. These results strongly support additional randomised trials to compare the effects of different sulfonylureas in reducing the risk of cancer, which should be considered an important endpoint in type 2 diabetes.

Limitations and strengths

This was an observational study and neither the differences between the study groups nor the time sequence criterion for causality could be controlled. Even if we controlled for multiple confounders, the possibility of residual or unknown confounders cannot be excluded. Nevertheless, it is quite unlikely that this limitation accounts for the entire reduction in the risk of cancer death that was observed. ~~The diabetic patients could have modified their hypoglycaemic treatment during the follow-up and this information was not available. This type of misclassification, however, could have biased the association found in any direction.~~ Our cohort included patients with different diabetes duration; therefore, a selection effect of patients with longer diabetes duration at inception was unavoidable. Nevertheless, the duration of diabetes and the presence of chronic diabetes complications were carefully considered in the analyses. A randomised, controlled clinical trial could definitively establish whether hypoglycaemic drugs confer protection against cancer incidence or death. However, such a trial should be large and pragmatic, with a follow-up that is sufficiently long to analyse the large expected proportion of treatment crossover needed to treat hyperglycaemia.

The number of cases in the present study was insufficient to perform separate analyses of other causes of deaths and neoplasm types. Our study had a statistical power of approximately 85% for detecting statistically significant (at the 0.05 level) HRs of 0.65 or lower for the best treatment *versus* the worst treatment in terms of all-cause mortality.

We are confident in our data sources, since the clinical records and data that were obtained from the demographic files were independent of one another and provided objective measurements of exposures and outcomes. Furthermore, after considering the changes in hypoglycaemic treatment during follow-up in the subgroup of patients on sulfonylureas alone at enrolment, the inverse associations between gliclazide and tolbutamide and cancer mortality were confirmed. Other strengths of the study include: the length (14 years) and completeness (100%) of the follow-up, the simultaneous analysis of cause-specific mortality with a competing-risk model, with consideration of the effects of multiple potential confounders, the fact that the studied cohort was representative of the diabetic patients from the study area, and that all the laboratory measurements were centralised.

Conclusion

Our “real world” data offer evidence of a protective effect of gliclazide and tolbutamide on cancer mortality. These findings deserve further research and the cancer risk of the patient should be considered when the type of hypoglycaemic treatment is chosen. Randomised trials are warranted to establish whether these drugs truly confer protection in type 2 diabetic patients.

Declaration of interest: There is no conflict of interests.

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Table 1. Baseline clinical characteristics of the patients according to the type of sulfonylurea used at enrolment (years 1996-1997).

| | Glibenclamide | | Gliclazide | | Tolbutamide | | P | Total | |
|---|---------------|--------|------------|--------|-------------|--------|--------|-------|--------|
| Total, number [prevalence %] | 977 | [76.5] | 141 | [11.0] | 159 | [12.5] | | 1277 | [100] |
| Age (years), mean [SD] ¹ | 65.3 | [10.1] | 66.4 | [9.1] | 67.7 | [10.7] | 0.02 | 65.7 | [10.1] |
| Males, number [%] ² | 412 | [42.2] | 63 | [44.7] | 73 | [45.9] | 0.61 | 548 | [42.9] |
| Time since diagnosis (years), median [IQR] ³ | 10 | [11] | 8 | [10] | 7 | [10] | <0.001 | 9 | [11] |
| BMI (kg/m ²), number [%] ² | | | | | | | 0.006 | | |
| ≤25 | 177 | [18.1] | 41 | [29.1] | 41 | [25.8] | | 259 | [20.3] |
| 25-30 | 423 | [43.3] | 60 | [42.5] | 66 | [41.5] | | 549 | [43.0] |
| >30 | 377 | [38.6] | 40 | [28.4] | 52 | [32.7] | | 469 | [36.7] |
| BMI (kg/m ²), mean [SD] ¹ | 29.4 | [5.2] | 28.1 | [5.0] | 28.1 | [5.0] | 0.007 | 28.6 | [5.4] |
| Smokers, number [%] ² | 157 | [16.1] | 20 | [14.2] | 19 | [12.0] | 0.38 | 196 | [15.4] |
| HbA1c (%), mean [SD] ¹ | 6.8 | [1.3] | 6.6 | [1.3] | 6.1 | [1.0] | <0.001 | 6.7 | [1.2] |
| Systolic blood pressure (mmHg), mean [SD] ¹ | 144.6 | [10.5] | 143.1 | [11.9] | 144.7 | [9.6] | 0.30 | 144.4 | [10.6] |
| Diastolic blood pressure (mmHg), mean [SD] ¹ | 83.6 | [4.2] | 83.3 | [4.4] | 83.3 | [4.1] | 0.60 | 83.5 | [4.2] |
| Total cholesterol (mg/dl), mean [SD] ¹ | 209.4 | [40.1] | 216.8 | [42.4] | 205.2 | [38.5] | 0.04 | 209.7 | [40.2] |
| HDL cholesterol (mg/dl), mean [SD] ¹ | 46.0 | [12.6] | 49.1 | [12.8] | 46.4 | [13.5] | 0.03 | 46.4 | [12.8] |
| Triglycerides (mg/dl), median [IQR] ³ | 126 | [77] | 117 | [70] | 113 | [66] | 0.03 | 124 | [76] |
| Retinopathy, number [%] ² | 213 | [21.8] | 17 | [12.1] | 19 | [12.0] | 0.001 | 249 | [19.5] |
| Nephropathy, number [%] ² | 199 | [20.4] | 30 | [21.3] | 27 | [17.0] | 0.57 | 256 | [20.1] |
| Neuropathy, number [%] ² | 94 | [9.6] | 13 | [9.2] | 10 | [6.3] | 0.40 | 117 | [9.2] |
| Cardiovascular diseases, number [%] ² | 280 | [28.7] | 41 | [29.1] | 45 | [28.3] | 0.99 | 366 | [28.7] |
| Antihypertensive drugs, number [%] ² | 513 | [52.5] | 74 | [52.5] | 94 | [59.1] | 0.29 | 681 | [53.3] |
| Treatment, number [%] ² | | | | | | | <0.001 | | |
| Only sulfonylureas | 310 | [31.7] | 105 | [74.5] | 140 | [88.1] | | 555 | [43.5] |

| | | | | | | | | |
|-------------------------------------|-----|--------|----|--------|----|--------|-----|--------|
| Sulfonylureas + insulin | 72 | [7.4] | 28 | [19.9] | 17 | [10.7] | 117 | [9.2] |
| Sulfonylureas + metformin | 508 | [52.0] | 7 | [5.0] | 2 | [1.3] | 517 | [40.5] |
| Sulfonylureas + insulin + metformin | 87 | [8.9] | 1 | [0.7] | 0 | [0] | 88 | [6.9] |

SD=standard deviations; IQR=inter-quartile range

¹ Anova F-test ² Chi-square test ³ Kruscal-Wallis test

Table 2. Baseline clinical characteristics of the patients according to the type of sulfonylurea used at enrolment in the type 2 diabetic patients in monotherapy with sulfonylurea drugs.

| | Glibenclamide | | Gliclazide | | Tolbutamide | | P | Total |
|---|---------------|--------|------------|--------|-------------|--------|-------|--------------|
| Total, number [prevalence %] | 310 | [55.9] | 105 | [18.9] | 140 | [25.2] | | 555 [100.0] |
| Age (years), mean [SD] ¹ | 67.1 | [10.4] | 65.0 | [9.1] | 66.9 | [10.8] | 0.20 | 66.6 [10.3] |
| Males, number [%] ² | 153 | [49.4] | 44 | [41.9] | 68 | [48.6] | 0.41 | 265 [47.8] |
| Time since diagnosis (years), median [IQR] ³ | 8 | [12] | 6 | [10] | 6 | [9] | 0.01 | 7 [10] |
| BMI (kg/m ²), number [%] ² | | | | | | | 0.32 | |
| ≤25 | 76 | [24.5] | 34 | [32.4] | 38 | [27.1] | | 148 [26.7] |
| 25-30 | 156 | [50.3] | 43 | [41.0] | 60 | [42.9] | | 259 [46.7] |
| >30 | 78 | [25.2] | 28 | [26.7] | 42 | [30] | | 148 [26.7] |
| BMI (kg/m ²), mean [SD] ¹ | 27.9 | [4.5] | 28.0 | [5.2] | 28.3 | [5.3] | 0.74 | 28.0 [4.9] |
| Smokers, number [%] ² | 56 | [18.1] | 14 | [13.3] | 18 | [12.9] | 0.28 | 88 [15.9] |
| HbA1c (%), mean [SD] ¹ | 6.4 | [1.0] | 6.3 | [1.1] | 6.0 | [0.9] | 0.001 | 6.3 [1.0] |
| Systolic blood pressure (mmHg), mean [SD] ¹ | 143.6 | [10.5] | 142.1 | [12.5] | 144.3 | [9.7] | 0.27 | 143.5 [10.7] |
| Diastolic blood pressure (mmHg), mean [SD] ¹ | 83.2 | [3.9] | 83.0 | [4.4] | 83.2 | [4.2] | 0.85 | 83.2 [4.1] |
| Total cholesterol (mg/dl), mean [SD] ¹ | 209.5 | [40.9] | 218.1 | [41.0] | 203.5 | [39.0] | 0.02 | 209.6 [40.6] |
| HDL cholesterol (mg/dl), mean [SD] ¹ | 46.7 | [13.8] | 48.5 | [11.9] | 46.6 | [13.7] | 0.44 | 47.0 [13.4] |
| Triglycerides (mg/dl), median [IQR] ³ | 142.2 | [90.6] | 128.4 | [72.3] | 125.3 | [61.0] | 0.37 | 135.3 [81.0] |
| Retinopathy, number [%] ² | 44 | [14.2] | 7 | [6.7] | 13 | [9.3] | 0.07 | 64 [11.5] |
| Nephropathy, number [%] ² | 62 | [20.0] | 15 | [14.3] | 22 | [15.7] | 0.31 | 99 [17.8] |
| Neuropathy, number [%] ² | 30 | [9.7] | 9 | [8.6] | 8 | [5.7] | 0.38 | 47 [8.5] |
| Cardiovascular diseases, number [%] ² | 98 | [31.6] | 29 | [27.6] | 39 | [27.9] | 0.62 | 166 [29.9] |
| Antihypertensive drugs, number [%] ² | 163 | [52.6] | 52 | [49.5] | 80 | [57.1] | 0.47 | 295 [53.2] |

SD=standard deviations; IQR=inter-quartile range

¹ Anova F-test ² Chi-square test ³ Kruscal-Wallis test

Table 3. Crude and adjusted hazard ratios (HR) for all-cause and cause-specific mortality, by the type of sulfonylurea used at enrolment.

| | Glibenclamide (n=977) | | Gliclazide (n=141) | | Tolbutamide (n=159) | |
|-----------------------------------|-----------------------|--------|--------------------|-------------|---------------------|-------------|
| All-cause mortality | | | | | | |
| Number of deaths [%] | 429 | [43.9] | 55 | [39.0] | 72 | [45.3] |
| Crude HR [95% CI] | 1 | - | 0.89 | [0.67-1.17] | 1.08 | [0.84-1.39] |
| Adjusted HR [95% CI]* | 1 | - | 0.76 | [0.56-1.02] | 0.79 | [0.60-1.03] |
| Adjusted HR [95% CI]** | 1 | - | 0.66 | [0.49-0.89] | 0.76 | [0.58-1.01] |
| Cancer mortality | | | | | | |
| Number of deaths [%] | 128 | [13.1] | 10 | [7.1] | 20 | [12.6] |
| Crude HR [95% CI] | 1 | - | 0.52 | [0.27-0.99] | 0.96 | [0.60-1.53] |
| Adjusted HR [95% CI]* | 1 | - | 0.30 | [0.16-0.55] | 0.48 | [0.29-0.79] |
| Adjusted HR [95% CI]** | 1 | - | 0.30 | [0.12-0.75] | 0.50 | [0.33-0.77] |
| Cardiovascular mortality | | | | | | |
| Number of deaths [%] | 194 | [19.9] | 30 | [21.3] | 38 | [23.9] |
| Crude HR [95% CI] | 1 | - | 1.10 | [0.75-1.62] | 1.26 | [0.88-1.79] |
| Adjusted HR [95% CI]* | 1 | - | 1.28 | [0.84-1.95] | 1.20 | [0.79-1.84] |
| Adjusted HR [95% CI]** | 1 | - | 1.41 | [0.54-3.68] | 1.25 | [1.15-1.35] |
| Mortality for other causes | | | | | | |
| Number of deaths [%] | 107 | [11.0] | 15 | [10.6] | 14 | [8.8] |
| Crude HR [95% CI] | 1 | - | 0.99 | [0.57-1.71] | 0.80 | [0.46-1.41] |
| Adjusted HR [95% CI]* | 1 | - | 0.81 | [0.44-1.51] | 0.62 | [0.34-1.15] |
| Adjusted HR [95% CI]** | 1 | - | 0.87 | [0.19-4.03] | 0.62 | [0.29-1.33] |

*HR adjusted by age, sex, BMI, smoking, time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, CV diseases and metformin or insulin use.

**HR adjusted by age, sex, BMI, smoking, time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, CV diseases and metformin or insulin use; model stratified by the duration of sulfonylurea exposure

Table 4. Crude and adjusted hazard ratios for all-cause and for cause-specific mortality in the type 2 diabetic patients in monotherapy with sulfonylurea drugs at enrolment.

| | Glibenclamide (n=310) | | Gliclazide (n=105) | | Tolbutamide (n=140) | |
|-----------------------------------|-----------------------|--------|--------------------|--------------|---------------------|-------------|
| All cause mortality | | | | | | |
| Number of deaths [%] | 168 | [54.2] | 29 | [27.6] | 58 | [41.4] |
| Crude HR [95% CI] | 1 | - | 0.43 | [0.29-0.63] | 0.72 | [0.53-0.97] |
| Adjusted HR [95% CI]* | 1 | - | 0.52 | [0.35-0.77] | 0.72 | [0.53-0.98] |
| Adjusted HR [95% CI]** | 1 | - | 0.52 | [0.35,0.77] | 0.72 | [0.53,0.98] |
| Cancer mortality | | | | | | |
| Number of deaths [%] | 69 | [22.3] | 0 | [0.0] | 15 | [10.7] |
| Crude HR [95% CI] | 1 | - | 0.00 | [0.00-0.00]. | 0.45 | [0.26-0.79] |
| Adjusted HR [95% CI]* | 1 | - | 0.00 | [0.00-0.00] | 0.40 | [0.22-0.71] |
| Adjusted HR [95% CI]** | 1 | - | 0.00 | [0.00-0.00] | 0.40 | [0.19-0.84] |
| Cardiovascular mortality | | | | | | |
| Number of deaths [%] | 59 | [19.0] | 20 | [19.1] | 32 | [22.9] |
| Crude HR [95% CI] | 1 | - | 1 | [0.61-1.67] | 1.25 | [0.81-1.93] |
| Adjusted HR [95% CI]* | 1 | - | 1.39 | [0.84-2.29] | 1.22 | [0.75-1.99] |
| Adjusted HR [95% CI]** | 1 | - | 1.38 | [0.30-6.29] | 1.22 | [1.12-1.33] |
| Mortality for other causes | | | | | | |
| Number of deaths [%] | 40 | [12.9] | 9 | [8.6] | 11 | [7.9] |
| Crude HR [95% CI] | 1 | - | 0.65 | [0.32-1.35] | 0.60 | [0.31-1.17] |
| Adjusted HR [95% CI]* | 1 | - | 0.89 | [0.50-1.61] | 0.67 | [0.37-1.22] |
| Adjusted HR [95% CI]** | 1 | - | 0.79 | [0.07-8.42] | 0.57 | [0.21-1.53] |

*HR adjusted by age, sex, BMI, smoking, time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, and CV diseases.

**HR adjusted by age, sex, BMI, smoking, time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, CV diseases and metformin or insulin use; model stratified by the duration of sulfonylurea exposure.

Figure 1. Cumulative incidence of all-cause and cause-specific mortality in the cohort of 1277 type 2 diabetic patients, by the type of sulfonylurea used at enrolment.

