CLINICAL STUDY

Mortality outcomes of different sulphonylurea 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 sulphonylureas are scarce and contradictory.

Design: We evaluated the associations between all-cause and cause-specific mortality and treatments with different sulphonylureas in a retrospective cohort of type 2 diabetic patients from a diabetes clinic.

Methods: All 1277 patients treated with sulphonylureas during 1996–1997 were enrolled: 159 patients were treated with tolbutamide, 977 glibenclamide and 141 gliclazide. The baseline data (centralised laboratory parameters, anthropometric data and presence of chronic complications) were abstracted from the clinical records. Information on vital status was collected from demographic files after 14-year follow-up. Adjusted hazard ratios (HR) were estimated with Cox (all-cause mortality) or Fine and Gray models (cause-specific mortality), including several potential confounders.

Results: Five hundred and fifty-six patients died during the follow-up: 262 from cardiovascular causes, 158 from cancer and 136 from other causes. When compared with 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 sulphonylurea monotherapy. None of the patients who were treated with gliclazide monotherapy died from cancer during the follow-up, and the patients on tolbutamide treatment 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 sulphonylurea treatment from diabetes diagnosis to the study enrolment.

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

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Introduction

The effects of sulphonylurea 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 sulphonylurea 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 sulphonylurea 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, sulphonylureas 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 sulphonylureas (7, 8). However, these results have not been confirmed by other studies (9, 10, 11), and either reduced (12, 13, 14) or increased all-cause or CV mortality has been reported in patients treated with sulphonylureas (15, 16). Furthermore, although metformin has been shown to consistently reduce the risks of cancer incidence and mortality (17), the data concerning sulphonylureas are controversial because a neutral effect (14, 18, 19), an increased risk (20, 21, 22, 23) and a reduced cancer-related mortality (24) have been described in the literature.

The possibility that specific sulphonylurea 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 epidemiological studies have evaluated total and CV mortality according to the type of sulphonylurea drug used, with contrasting results (15, 25, 26, 27, 28, 29). Only one study, to the best of our knowledge, has examined the association between sulphonylurea 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 (odds ratio (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 this study was to evaluate the associations between all-cause and cause-specific mortality and treatment with three types of sulphonylurea 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, 33, 34). These patients represented 1.6% of the reference population ($n=134646$) and, because the prevalence of known type 2 diabetes was 2% in northern Italy, we estimated that our cohort included ~80% of the known diabetes cases in the study area (32, 34). For the present analyses, we considered patients who were treated with sulphonylureas (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 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 the patients were examined every 4 months: their body weight, 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-min 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, Milan, 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 of more than 20 µg/min in at least two of three 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 sulphonylureas 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 sulphonylureas were used: tolbutamide, glibenclamide and gliclazide. Other sulphonylureas or other hypoglycaemic drugs, such as meglitinides and thiazolidinediones, were not used. The patients were analysed according to the type of sulphonylurea that was used at enrolment (tolbutamide, glibenclamide or gliclazide), taking into account whether metformin or insulin was used in combination. All the analyses were also performed in the subgroup of patients who were treated with sulphonylureas 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 sulphonylurea treatment from diabetes diagnosis to the enrolment period was considered as a stratification variable. Furthermore, in the subgroup of patients treated with sulphonylureas alone at enrolment, the data relative to hypoglycaemic 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 s.d. or medians and inter-quartile ranges for the continuous variables. Percentage frequencies were used for the categorical variables. ANOVA, χ^2 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% CIs for all-cause mortality. The HRs for each type of sulphonylureas (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 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 sulphonylurea and either metformin or insulin was tested by introducing specific interaction terms into the models and by replicating all 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 sulphonylurea treatment before enrolment, as a

sensitivity analysis. As a further sensitivity analysis, in the group of patients on sulphonylureas alone at enrolment, the same models were replicated considering the hypoglycaemic treatment until the end of follow-up (metformin, insulin and sulphonylureas) as time varying variables. Statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX, USA) and R (2.15.0).

Results

The patient characteristics according to the type of sulphonylurea 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 administered 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 (Fig. 1A) and cause-specific mortality (Fig. 1B, C and D) according to sulphonylurea type is shown in Fig. 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 2). Notably, the ten 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 sulphonylurea 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 with 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 1.17–0.84) and cancer mortality (HR = 1.81; 95% CI 1.15–2.86) (data not shown).

Although no statistically significant interactions between the sulphonylureas and metformin or insulin were detected, all the analyses were performed in patients undergoing monotherapy with sulphonylureas

Table 1 Baseline clinical characteristics of the patients according to the type of sulphonylurea 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 (s.d.) ^a	65.3 (10.1)	66.4 (9.1)	67.7 (10.7)	0.02	65.7 (10.1)
Males, number (%) ^b	412 (42.2)	63 (44.7)	73 (45.9)	0.61	548 (42.9)
Time since diagnosis (years), median (IQR) ^c	10 (11)	8 (10)	7 (10)	<0.001	9 (11)
BMI (kg/m ²), number (%) ^b				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 (s.d.) ^a	29.4 (5.2)	28.1 (5.0)	28.1 (5.0)	0.007	28.6 (5.4)
Smokers, number (%) ^b	157 (16.1)	20 (14.2)	19 (12.0)	0.38	196 (15.4)
HbA1c (%), mean (s.d.) ^a	6.8 (1.3)	6.6 (1.3)	6.1 (1.0)	<0.001	6.7 (1.2)
Systolic blood pressure (mmHg), mean (s.d.) ^a	144.6 (10.5)	143.1 (11.9)	144.7 (9.6)	0.30	144.4 (10.6)
Diastolic blood pressure (mmHg), mean (s.d.) ^a	83.6 (4.2)	83.3 (4.4)	83.3 (4.1)	0.60	83.5 (4.2)
Total cholesterol (mg/dl), mean (s.d.) ^a	209.4 (40.1)	216.8 (42.4)	205.2 (38.5)	0.04	209.7 (40.2)
HDL cholesterol (mg/dl), mean (s.d.) ^a	46.0 (12.6)	49.1 (12.8)	46.4 (13.5)	0.03	46.4 (12.8)
Triglycerides (mg/dl), median (IQR) ^c	126 (77)	117 (70)	113 (66)	0.03	124 (76)
Retinopathy, number (%) ^b	213 (21.8)	17 (12.1)	19 (12.0)	0.001	249 (19.5)
Nephropathy, number (%) ^b	199 (20.4)	30 (21.3)	27 (17.0)	0.57	256 (20.1)
Neuropathy, number (%) ^b	94 (9.6)	13 (9.2)	10 (6.3)	0.40	117 (9.2)
Cardiovascular diseases, number (%) ^b	280 (28.7)	41 (29.1)	45 (28.3)	0.99	366 (28.7)
Anti-hypertensive drugs, number (%) ^b	513 (52.5)	74 (52.5)	94 (59.1)	0.29	681 (53.3)
Treatment, number (%) ^b				<0.001	
Only sulphonylureas	310 (31.7)	105 (74.5)	140 (88.1)		555 (43.5)
Sulphonylureas + insulin	72 (7.4)	28 (19.9)	17 (10.7)		117 (9.2)
Sulphonylureas + metformin	508 (52.0)	7 (5.0)	2 (1.3)		517 (40.5)
Sulphonylureas + insulin + metformin	87 (8.9)	1 (0.7)	0 (0)		88 (6.9)

IQR, inter-quartile range.

^aANOVA *F*-test.^b χ^2 test.^cKruskal–Wallis test.

(*n* = 555), whose characteristics are reported in Table 3. The associations between the individual sulphonylureas 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 with 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, see section on supplementary data given at the end of this article). 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 with 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, 8, 9, 10, 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, 2, 3, 4, 5, 12, 13, 15, 25, 26, 27, 28, 29). Sulphonylureas act on β 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 β -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, 26, 27). The adverse effects reported for glibenclamide include increased peripheral vascular tone, reduced diazoxide-induced

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

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 vs 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, 26, 27, 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 sulphonylurea types are impressive in our cohort (Tables 3 and 4). Studies evaluating the association between cancer and the use of sulphonylureas have provided conflicting evidence (14, 18, 19, 20, 21, 22, 23, 39). A few studies of individual sulphonylureas 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 sulphonylurea users (22, 41, 42). A recent meta-analysis, however, found no evidence that sulphonylureas 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 antioxidant 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

Table 2 Crude and adjusted hazard ratios (HR) for all-cause and cause-specific mortality, by the type of sulphonylurea 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) ^a	1	0.76 (0.56–1.02)	0.79 (0.60–1.03)
Adjusted HR (95% CI) ^b	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) ^a	1	0.30 (0.16–0.55)	0.48 (0.29–0.79)
Adjusted HR (95% CI) ^b	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) ^a	1	1.28 (0.84–1.95)	1.20 (0.79–1.84)
Adjusted HR (95% CI) ^b	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) ^a	1	0.81 (0.44–1.51)	0.62 (0.34–1.15)
Adjusted HR (95% CI) ^b	1	0.87 (0.19–4.03)	0.62 (0.29–1.33)

^aHR 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.

^bHR 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 sulphonylurea exposure.

antioxidant enzymes, enhance NO-mediated vasodilatation, reduce glucose-induced apoptosis and mitochondrial alterations, increase nitrotyrosine concentration (5, 44, 45, 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 endpoints 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 sulphonylureas 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. Our cohort included

Table 3 Baseline clinical characteristics of the patients according to the type of sulphonylurea used at enrolment in the type 2 diabetic patients in monotherapy with sulphonylurea drugs.

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

IQR, inter-quartile range.

^aANOVA *F*-test.^b χ^2 test.^cKruskal–Wallis test.

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

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

	Glibenclamide (<i>n</i> =310)	Gliclazide (<i>n</i> =105)	Tolbutamide (<i>n</i> =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) ^a	1	0.52 (0.35–0.77)	0.72 (0.53–0.98)
Adjusted HR (95% CI) ^b	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) ^a	1	0.00 (0.00–0.00)	0.40 (0.22–0.71)
Adjusted HR (95% CI) ^b	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) ^a	1	1.39 (0.84–2.29)	1.22 (0.75–1.99)
Adjusted HR (95% CI) ^b	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) ^a	1	0.89 (0.50–1.61)	0.67 (0.37–1.22)
Adjusted HR (95% CI) ^b	1	0.79 (0.07–8.42)	0.57 (0.21–1.53)

^aHR adjusted by age, sex, BMI, smoking, time since diagnosis, anti-hypertensive therapy, HbA1c values, presence of retinopathy, nephropathy, neuropathy, and CV diseases.^bHR 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 sulphonylurea exposure.

large expected proportion of treatment crossover needed to treat hyperglycaemia.

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

We are confident in our data sources, as 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 sulphonylureas 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.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-13-0299>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

S Bo was involved in the conception and design of the study, supervision of data collection, interpretation of findings and manuscript writing; A Castiglione was involved in data analysis; E Ghigo was involved in manuscript writing; L Gentile, and M Durazzo were involved in data collection; P Cavallo-Perin was involved in the interpretation of the findings and manuscript writing; G Ciccone was involved in the design of the study and data analysis. All authors were involved in manuscript revision.

References

- 1 Meinert CL, Knatterud GL, Prout TE & Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II Mortality results. *Diabetes* 1970 **19** S789–S830.
- 2 Feinglos MN & Bethel MA. Therapy of type 2 diabetes, cardiovascular death, and the UGDP. *American Heart Journal* 1999 **138** S346–S352.
- 3 Holman RR, Sanjoy PK, Bethel A, Matthews DR & Neil AW. 10-Year follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine* 2008 **359** 1577–1589. (doi:10.1056/NEJMoa0806470)
- 4 The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine* 2008 **235** 2560–2572. (doi:10.1056/NEJMoa0802987)
- 5 Avogaro A. Treating diabetes today with gliclazide MR: a matter of numbers. *Diabetes, Obesity and Metabolism* 2012 **14** S14–S19. (doi:10.1111/j.1463-1326.2011.01508.x)
- 6 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferranini E, Nauck M, Peters AL, Tsapas A, Wender R & Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. *Diabetes Care* 2012 **35** 1364–1379. (doi:10.2337/dc12-0413)
- 7 Olsson J, Lindberg G, Gottsäter M, Lindwall K, Sjöstrand Å, Tisell A & Melander A. Increased mortality in type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. *Diabetologia* 2000 **43** 558–560. (doi:10.1007/s001250051343)
- 8 Mannucci E, Monami M, Masotti G & Marchionni N. All-cause mortality in diabetic patients treated with combinations of sulphonylureas and biguanides. *Diabetes/Metabolism Research and Reviews* 2004 **20** 44–47. (doi:10.1002/dmrr.411)
- 9 Johnson JA, Majumdar SR, Simpson SH & Toth EL. Decreased mortality associated with the use of metformin compared with sulphonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002 **25** 2244–2248. (doi:10.2337/diacare.25.12.2244)
- 10 Gulliford M & Latinovic R. Mortality in type 2 diabetic subjects prescribed metformin and sulphonylurea drugs in combination: cohort study. *Diabetes/Metabolism Research and Reviews* 2004 **20** 239–245. (doi:10.1002/dmrr.457)
- 11 Sillars B, Davis WA, Hirsch IB & Davis TME. Sulphonylurea–metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. *Diabetes, Obesity and Metabolism* 2010 **12** 757–765. (doi:10.1111/j.1463-1326.2010.01230.x)
- 12 Knowler WC, Sartor G, Melander A & Scherstén B. Glucose tolerance and mortality, including a substudy of tolbutamide treatment. *Diabetologia* 1997 **40** 680–686. (doi:10.1007/s001250050734)
- 13 Arruda-Olson AM, Patch RK III, Leibson CL, Vella A, Frye RL, Weston SA, Killian JM & Roger VL. Effect of second-generation sulphonylureas on survival in patients with diabetes mellitus after myocardial infarction. *Mayo Clinic Proceedings* 2009 **84** 28–33. (doi:10.4065/84.1.28)
- 14 Bo S, Ciccone G, Rosato R, Villosio P, Appendino G, Ghigo E & Grassi G. Cancer mortality and metformin: a retrospective cohort study in type 2 diabetic patients. *Diabetes, Obesity and Metabolism* 2011 **14** 23–29. (doi:10.1111/j.1463-1326.2011.01480.x)
- 15 Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT & Johnson JA. Dose–response relation between sulphonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *Canadian Medical Association Journal* 2006 **74** 169–174. (doi:10.1503/cmaj.050748)
- 16 Corrao G, Romio SA, Zambon A, Merlino L, Bosi E & Scavini M. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. *European Journal of Clinical Pharmacology* 2011 **67** 289–299. (doi:10.1007/s00228-010-0939-6)

- 17 Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B & Gandini S. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prevention Research* 2010 **3** 1451–1461. (doi:10.1158/1940-6207.CAPR-10-0157)
- 18 Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD & Evans JMM. New users of metformin are at low risk of incident cancer. *Diabetes Care* 2009 **32** 1620–1625. (doi:10.2337/dc08-2175)
- 19 Bodmer M, Meier C, Krähenbühl S, Jick SS & Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 2010 **33** 1304–1308. (doi:10.2337/dc09-1791)
- 20 Currie CJ, Poole CD & Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009 **52** 1766–1777. (doi:10.1007/s00125-009-1440-6)
- 21 Bowker SL, Majumdar SR, Veugelers P & Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulphonylureas or insulin. *Diabetes Care* 2006 **29** 254–258. (doi:10.2337/diacare.29.02.06.dc05-1558)
- 22 Chang CH, Lin JW, Wu LC, Lai MS & Chuang LM. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1170–E1175. (doi:10.1210/jc.2012-1162)
- 23 Ruiter R, Visser LE, van Herk-Sukel MPP, Cobergh JWW, Haak HR, Geelhoed-Duijvestijn PH, Straus SMJM, Herings RMC & Stricker BHC. Lower risk of cancer in patients with metformin in comparison with those on sulphonylurea derivatives. *Diabetes Care* 2012 **35** 119–124. (doi:10.2337/dc11-0857)
- 24 Yang X, So WY, Ma RC, Yu LW, Ko GT, Kong AP, Ng VW, Luk AO, Ozaki R, Tong PC *et al.* Use of sulphonylurea and cancer in type 2 diabetes: the Hong Kong Diabetes Registry. *Diabetes Research and Clinical Practice* 2010 **90** 343–351. (doi:10.1016/j.diabres.2010.08.022)
- 25 Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, Masotti G, Marchionni N & Mannucci E. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. *Diabetes/Metabolism Research and Reviews* 2006 **22** 477–482. (doi:10.1002/dmrr.642)
- 26 Khalangot M, Tronko M, Kravchenko V & Kovtun V. Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. *Diabetes Research and Clinical Practice* 2009 **86** 247–253. (doi:10.1016/j.diabres.2009.09.008)
- 27 Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, Atreja A & Zimmerman RS. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy. *Diabetes Care* 2010 **33** 1224–1229. (doi:10.2337/dc10-0017)
- 28 Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, Fosbøl EL, Køber L, Norgaard ML, Madsen M *et al.* Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. *European Heart Journal* 2011 **32** 1900–1908. (doi:10.1093/eurheartj/ehr077)
- 29 Horsdal HT, Johnsen SP, Søndergaard F, Jacobsen J, Thomsen RW, Schmitz O, Sørensen HT & Rungby J. Sulphonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. *Diabetes/Metabolism Research and Reviews* 2009 **25** 515–522. (doi:10.1002/dmrr.971)
- 30 Monami M, Balzi D, Lamanna C, Barchielli A, Masotti G, Buiatti E, Marchionni N & Mannucci E. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. *Diabetes/Metabolism Research and Reviews* 2007 **23** 479–484. (doi:10.1002/dmrr.736)
- 31 Monami M, Lamanna C, Balzi D, Marchionni N & Mannucci E. Sulphonylureas and cancer: a case-control study. *Acta Diabetologica* 2009 **46** 279–284. (doi:10.1007/s00592-008-0083-2)
- 32 Bo S, Cavallo-Perin P, Gentile L, Repetti E & Pagano G. Relationship of residual β -cell function, metabolic control and chronic complications in type 2 diabetes mellitus. *Acta Diabetologica* 2000 **37** 125–129. (doi:10.1007/s005920070014)
- 33 Bo S, Cavallo-Perin P & Gentile L. Prevalence of patients reaching the targets of good control in normal clinical practice. A cohort-based study in type 2 diabetes. *Diabetes Care* 1999 **22** 2092. (doi:10.2337/diacare.22.12.2092b)
- 34 Bo S, Gentile L, Castiglione A, Prandi V, Canil S, Ghigo E & Ciccone G. C-peptide and the risk for incident complications and mortality in type 2 diabetic patients: a retrospective cohort study after a 14-year follow-up. *European Journal of Endocrinology* 2012 **167** 173–180. (doi:10.1530/EJE-12-0085)
- 35 Johnsen SP, Monster TBM, Olsen ML, Thisted H, McLaughlin JK, Sørensen HT, Lervang HH & Rungby J. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *American Journal of Therapy* 2006 **13** 134–140. (doi:10.1097/00045391-200603000-00009)
- 36 Schotborgh CE & Wilde AAM. Sulphonylurea derivatives in cardiovascular research and in cardiovascular patients. *Cardiovascular Research* 1997 **34** 73–80. (doi:10.1016/S0008-6363(97)00036-9)
- 37 Gribble FM & Ashcroft FM. Differential sensitivity of β -cell and extrapancreatic K(ATP) channels to gliclazide. *Diabetologia* 1999 **42** 845–848. (doi:10.1007/s001250051236)
- 38 Smits P, Bijlstra PJ, Russel FG, Lutterman JA & Thien T. Cardiovascular effects of sulphonylurea derivatives. *Diabetes Research and Clinical Practice* 1996 **31** S55–S59. (doi:10.1016/0168-8227(96)01230-2)
- 39 Baur DM, Klotzsch J, Hamnvik OPR, Sievers C, Pieper L, Wittchen HU, Stalla GK, Schmid RM, Kales SN & Mantzoros CS. Type 2 diabetes mellitus and medications for type 2 diabetes mellitus are associated with risk for and mortality from cancer in a German primary care cohort. *Metabolism* 2011 **60** 1363–1371. (doi:10.1016/j.metabol.2010.09.012)
- 40 Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H & Viberti G. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes) clinical trials. *Diabetologia* 2010 **53** 1838–1845. (doi:10.1007/s00125-010-1804-y)
- 41 Donadon V, Balbi M, Ghersesti M, Grazioli S, Perciaccante A, Della Valentina G, Gardenal R, Dal Mas M, Casarin P, Zanette G *et al.* Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. *World Journal of Gastroenterology* 2009 **15** 2506–2511. (doi:10.3748/wjg.15.2506)
- 42 Bodmer M, Becker C, Meier C, Jick SS & Meier CR. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. *American Journal of Gastroenterology* 2012 **107** 620–626. (doi:10.1038/ajg.2011.483)
- 43 Soranna D, Scotti L, Zambon A, Bosetti C, Grassi G, Catapano A, La Vecchia C, Mancina G & Corrao G. Cancer risk associated with use of metformin and sulphonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012 **17** 813–822. (doi:10.1634/theoncologist.2011-0462)
- 44 Sliwinska A, Rogalska A, Szwed M, Kasznicki J, Jozwiak Z & Drzewoski J. Gliclazide may have an antiapoptotic effect related to its antioxidant properties in human normal and cancer cells. *Molecular Biology Reports* 2012 **39** 5253–5267. (doi:10.1007/s11033-011-1323-z)
- 45 O'Brien RC, Luo M, Balazs N & Mercuri J. *In vitro* and *in vivo* anti-oxidant properties of gliclazide. *Journal of Diabetes and its Complications* 2000 **14** 201–206. (doi:10.1016/S1056-8727(00)00084-2)
- 46 Gier B, Krippeit-Dreus P, Sheiko T, Aguilar-Bryan L, Bryan J, Düfer M & Dreus G. Suppression of K_{ATP} channel activity protects murine pancreatic β cells against oxidative stress. *Journal of Clinical Investigation* 2009 **119** 3246–3256. (doi:10.1172/JCI38817)

- 47 Renier G, Mamputu JC & Serri O. Benefits of gliclazide in the atherosclerotic process: decrease in monocyte adhesion to endothelial cells. *Metabolism* 2003 **52** 13–18. (doi:10.1016/S0026-0495(03)00212-9)
- 48 Li L & Renier G. The oral, anti-diabetic agent gliclazide inhibits oxidized LDL-mediated LOX-1 expression, metalloproteinase-9 secretion and apoptosis in human aortic endothelial cells. *Atherosclerosis* 2009 **204** 40–46. (doi:10.1016/j.atherosclerosis.2008.08.008)
- 49 Räkel A, Renier G, Roussin A, Buithieu J, Mamputu JC & Serri O. Beneficial effects of gliclazide modified release compared with glibenclamide on endothelial activation and low-grade inflammation in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 2007 **9** 127–129. (doi:10.1111/j.1463-1326.2006.00571.x)
- 50 Vigneri P, Frasca F, Sciacca L, Pandini G & Vigneri R. Diabetes and cancer. *Endocrine-Related Cancer* 2009 **16** 1103–1123. (doi:10.1677/ERC-09-0087)
- 51 Wiczorek A, Rys P, Skrzekowska-Baran I & Malecki M. The role of surrogate endpoints in the evaluation of efficacy and safety of therapeutic interventions in diabetes mellitus. *Review of Diabetic Studies* 2008 **5** 128–135. (doi:10.1900/RDS.2008.5.128)
- 52 Cook GA. The hypoglycemic sulfonylureas glyburide and tolbutamide inhibit fatty acid oxidation by inhibiting carnitine palmitoyl-transferase. *Journal of Biological Chemistry* 1987 **262** 4968–4972.

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