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# No differences in mortality between users of pancreatic-specific and non-pancreatic-specific sulphonylureas: a cohort analysis

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## Abstract

To assess whether users of pancreatic-specific sulphonylureas are at reduced risk of mortality and cardiovascular mortality compared with users of non-specific sulphonylureas, we conducted a cohort study in the population of Tayside, Scotland. We identified 3331 patients with type 2 diabetes who were newly treated with sulphonylureas between 1994 and 2001 and categorized them into those treated with only pancreatic-specific sulphonylureas and those treated with only non-specific sulphonylureas. The risks of mortality and cardiovascular mortality were com-pared in a survival analysis. There were 2914 patients treated with pancreatic-specific sulphonylureas only, of which 683 (23.4%) died. Of 186 patients treated with non-specific drugs only, 40 (21.5%) died. After adjusting for con-founding factors, the adjusted risk ratios (with 95% CI) for mortality and cardiovascular mortality were 0.84 (0.61 to 1.17) and 0.81 (0.59 to 1.11) among the non-specific users compared with the pancreatic-specific users. This provides no evidence that there are differences between the two sulphonylureas types.

### Keywords

cardiovascular risk; metformin; sulphonylureas

We have carried out a study to examine whether there are differences in mortality between users of different sul-phonylureas in type 2 diabetes. Several recent observational studies have suggested that use of sulphonylureas is associated with increased mortality and cardiovascular mortality [1,2] when compared with metformin use. If this is a real effect (over which there remains some debate [3]), it could either be because of cardiovascular toxicity of sulphonylureas or improved insulin sensitivity in metformin users leading to

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**Conflicts of Interest**

F. M. G. and F. R. have received fees from Servier Inter-national for speaking at symposia.

**Ethical Approval**

This study received ethical approval from the Tayside Committee for Medical Research Ethics.


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reduced mortality. If it is because of cardiovascular toxicity of sulphonylureas, we might expect to observe mortality differences between users of pancreatic-specific and non-pancreatic-specific sulphonylureas.

We tested this hypothesis in a cohort of over 3000 sulphonylureas users resident in Tayside, Scotland. Sulphonylureas were classified according to whether they were pancreatic sulphonyl urea receptor (SUR)1 specific (tolbutamide, chlorpropamide, gliclazide and glipizide) or non-specific with affinity for both SUR1 and -2 subunits (glibenclamide and glimepiride) [4]. SUR specificity of glipizide was experimentally determined [5].

We used the data resources of the Health Informatics Centre, University of Dundee, for the population of Tayside (as previously described) [2,6,7]. From these databases, we identified a group of 3331 patients with type 2 diabetes who had no prescriptions in 1993 for oral hypoglycaemic agents but were commenced onsulphonylureas between 1994 and 2001. There were 2914 (87.5%) patients prescribed pancreatic-specific sulphonylureas only, and 186 (5.6%) who were pre-scribed non-specific drugs only. The remaining 231 patients who were prescribed both types were excluded from the study.

Survival analysis was used to compare mortality and cardiovascular mortality by sulphonylurea specificity (pancreatic specific vs. non-specific). Information on mortality was taken from death certification records from the Registrar General with International Classification of Diseases (ICD)9/10 coded cause of death. Patients were followed prospectively from their date of first sulphonylurea prescription until censoring, death or the end of the study period (January 2003). They were censored at the date they commenced another treatment.

The results are summarised in Table 1. Mean length of follow-up was 1061 days (2.9 years), during which 723 patients died: 683 (23.4%) in the pancreatic-specific cohort and 40 (21.5%) in the non-specific cohort. A Cox regression analysis suggested that there were no statistically significant differences in mortality and cardiovascular mortality between patients treated with pancreatic-specific and non-specific drugs, with adjusted risk ratios (and 95% confidence intervals) of 0.84 (0.61–1.17) and 1.06 (0.66–1.70) respectively. Risk ratios were adjusted for covariates that were either known risk factors for cardiovascular events or were significantly and individually associated with the out-come as previously described [2], (specifically sex, any use of cardiovascular drugs, duration of diabetes and age at index date, whether patients had a previous cardiovascular admission between 1980 and their index date, smoking status at index date and mean BMI, blood pressure, HbA1c and cholesterol levels during the study period).

In summary, we observed no differences in mortality and cardiovascular mortality between patients treated with different types of sulphonylureas. Sulphonylureas bind to the SUR moiety of the KATP channels to close the channel. There are two SUR isoforms (SUR1 and -2), with SUR1 isoforms present in the pancreatic beta cell, but SUR2 isoforms present in cardiac, skeletal and vascular smooth muscle. In cardiac muscle, KATP channel opening in the presence of ischaemia is implicated in the phenomenon of ischaemic pre-conditioning [8], and this effect has been shown to be blocked by glibenclamide [9]. In addition, vascular

smooth muscle KATP channels are thought to mediate vascular tone. Thus, sulphonylurea use could promote cardiovascular mortality through their action on cardiac and smooth muscle KATP channels containing SUR2. Pancreatic-specific sulphonylureas bind with high affinity only to the SUR1 subunit of the KATP channel, while non-specific sulphonylureas bind to both SUR1 and SUR2 subunits (non-specific sulphonylureas). If the increased cardio-vascular and all-cause mortality seen in users of sulphonylureas compared with metformin is because in part of the action of sulphonylureas at the cardiac- or vascular smooth muscle KATP channel, we would expect to see increased cardiovascular effects in users of non-specific sulphonylureas. We found no such effect therefore concerns over sulphonylureas reducing ischaemic pre-conditioning and thereby increasing cardiovascular mortality may be unfounded.

This is one of the few studies to stratify mortality from sulphonlyureas by sulphonylurea selectivity. The finding that the majority of the sulphonylureas used in our cohorts do not bind to cardiac- or vascular smooth muscle KATP channels; and the fact that we show that mortality and cardiovascular mortality is not increased in patients who take sulphonylureas that do bind to cardiac KATP channels, suggest that the observed mortality difference between sulphonylurea and metformin users [1,2] could be explained by improved insulin sensitivity in those taking metformin, rather than a direct toxic effect of sulphonylureas.

A limitation to this study was its observational design. While every effort was made to adjust for known confounders, it is possible that unmeasured factors could be influencing prescription choice. Also, it is more difficult to prove absence of an effect than to identify an effect, particularly with the small sample sizes giving relatively wide confidence intervals in this study. But as they stand, we consider that these findings do not support the concept that sulphonylureas increase mortality by direct cardiovascular toxicity and provide no evidence that a pancreatic-specific sulphonylurea should be chosen over a non-specific type.

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## Table 1

**Demographic characteristics and cardiovascular risk factors of patients treated with pancreatic-specific and non-specific sulphonylureas, with unadjusted and adjusted risk ratios for mortality and cardiovascular mortality**

| | | |
|---|---|---|
| % female | 44.0 | 40.9 |
| Mean age at index date | 66.3 | 64.0 |
| Carstairs postcode measure of material deprivation (% ranks 1,2/3,4/5,6,7) * | 25.4/44.9/29.7 | 25.2/45.5/29.5 |
| Mean diabetes duration at index date (years) | 4.4 | 7.4 |
| % previous hospital admission for cardiovascular event | 34.8 | 29.0 |
| Smoking (% never/current/ex) | 43.9/27.3/18.2 | 34.9/28.0/21.5 |
| Mean HbA1c in study period | 7.8 | 7.7 |
| Mean BMI in study period | 28.5 | 29.4 |
| Mean systolic blood pressure in study period | 142.2 | 143.8 |
| Mean diastolic blood pressure in study period | 78.9 | 80.4 |
| Mean cholesterol in study period | 5.2 | 5.4 |
| % any use of aspirin | 50.5 | 41.9 |
| % any use of statins | 38.3 | 38.7 |
| % any use of beta blockers | 27.9 | 21.5 |
| % any use of ACE inhibitors/AIIRA | 47.0 | 41.9 |
| Mortality | | |
| Total number of deaths | 683 (23.4%) | 40 (21.5%) |
| Unadjusted risk ratio (95% CI) | 1.00 | 0.87 (0.63, 1.21) |
| Adjusted risk ratio (95% CI) | 1.00 | 0.84 (0.61, 1.87) |
| CV mortality | | |
| Total number of CV deaths | 285 (9.8%) | 20 (10.8%) |
| Unadjusted risk ratio (95% CI) | 1.00 | 0.86 (0.63, 1.17) |
| Adjusted risk ratio (95% CI) | 1.00 | 0.81 (0.59, 1.11) |

ACE inhibitors, angiotensin-converting enzyme inhibitors; AIIRA, angiotensin-II receptor antagonists; CI, confidence intervals; CV, cardiovascular.

*Highest ranks denote least material deprivation.