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All-cause mortality in patients on sulphonylurea monotherapy compared to metformin monotherapy in a nation-wide cohort

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ABSTRACT

Background: Type 2 diabetes is associated with increased mortality. There is some data that sulphonylurea therapy may contribute to this.
Aims: To compare all-cause 3-year mortality of patients on sulphonylurea monotherapy to that of patients on metformin monotherapy after adjusting for potential confounders.
Methods: We searched the Maltese national electronic database for diabetes treatment in April 2014. This is an electronic database of all treatment that patients are prescribed through the local National Health Service. We identified patients on metformin or sulphonylurea monotherapy and linked this to the national mortality database and the laboratory information system.
Results: There were 25,792 persons who were on treatment for diabetes in April 2014. Of these, 9977 were on metformin monotherapy and 1717 on sulphonylurea monotherapy. This cohort was followed up until April 2017. There were 2518 deaths (9.76%) during this period, giving an average of 32.5 deaths per 1000 persons with diabetes. Logistic regression showed that persons on sulphonylurea monotherapy were 2.03 (95% CI 1.68–2.44, $p < .001$) times more likely to die within 3 years than persons on metformin monotherapy, after adjusting for age, eGFR and HbA1c. The logistic regression model was statistically significant, $p < .001$. Additional adjustment for LDL-cholesterol, HDL-cholesterol and urinary albumin-creatinine ratio did not alter the results.
Conclusion: Our data shows that sulphonylurea monotherapy is associated with higher all-cause mortality when compared to metformin monotherapy after adjusting for potential confounders.

1. Introduction

Diabetes is known to be associated with increased cardiovascular risk [1,2]. Diabetes results in a loss of 7.5 years of life in men and 8.2 years in women at 50 years of age [2]. Vascular conditions constitute the major single factor contributing to the increased mortality and reduction in life expectancy, but non-vascular conditions also result in substantial numbers

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premature deaths [3]. In fact, diabetes is associated with increased mortality from various types of cancer, infections, renal disease, liver disease, mental disorders, degenerative disorders and falls; these also contribute to reduced life expectancy in patients with diabetes [3].

There is growing evidence that sulphonylurea therapy in type 2 diabetes may contribute to decreased survival in persons with type 2 diabetes. Data from the UK Clinical Practice Research Datalink show that survival in patients on sulphonylurea monotherapy was worse than in those on metformin monotherapy [4]; however authors of this study did not have data on renal function. One of the main indications of using sulphonylurea monotherapy rather than metformin monotherapy is chronic kidney disease, which is known to be associated with reduced survival [5]. Therefore the fact that the authors of the above study were unable to adjust for renal function is a serious limitation. Using National Veterans Administration databases, Roumie et al. reported that the occurrence of the composite outcome of acute myocardial infarction, stroke or death was higher in those on sulphonylurea monotherapy compared to those on metformin monotherapy in a predominantly male population [6]. Amongst the co-variates that they adjusted for was renal function, but they used creatinine rather than glomerular filtration rate as a marker of renal function. Furthermore, they do not provide data on all-cause mortality and the population that they studied may not be representative. In a meta-analysis of observational studies, Phung et al. reported that sulphonylurea therapy was associated with more cardiovascular events when compared with other oral anti-hyperglycaemic agents [7], but again no data is provided on all-cause mortality; it is also limited by the quality of the included studies. Finally in a meta-analysis of randomised controlled studies, sulphonylurea therapy was reported to be associated with increased cardiovascular all-cause mortality when compared to other active comparators [8], but this meta-analysis drew on old, small studies of short duration where first-generation sulphonylureas were largely used.

Because of these limitations, the association between sulphonylurea therapy and mortality is still not generally accepted. Sulphonylureas remain a viable option in current guidelines [9,10] and are still widely used in the treatment of type 2 diabetes [11]. The aim of the present study was to compare the all-cause mortality in patients with type 2 diabetes on sulphonylurea monotherapy to that of patients on metformin monotherapy in a contemporary real world scenario. We feel that this is important since all-cause mortality is the hardest outcome and because diabetes is associated with increased mortality not only from vascular causes but also from non-vascular ones [3]. Furthermore confirmatory data on the effect of sulphonylurea therapy on outcomes are required.

2. Methods

We searched the national electronic database for diabetes treatment in April 2014. This is an electronic database of all treatments that patients are prescribed through the local National Health Service. We selected those on metformin or sulphonylurea monotherapy and linked this to other databases, namely the laboratory information system for investigations performed between 1st January 2014 and 30th June 2017 and the national mortality register. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation [12].

2.1. Statistical methods

Normality of distribution of data was assessed using the Kolmogorov-Smirnov test. Since all parameters were non-normally distributed, we used the Mann-Whitney test to assess the statistical significance of differences in baseline characteristics between those on metformin monotherapy and those on sulphonylurea monotherapy. Logistic regression was performed to assess the independent contribution of type of monotherapy on all-cause mortality after adjusting for co-variates.

2.2. Ethics statement

The Mater Dei Hospital Data Protection Officer and the respective Data Controllers approved the study. We had full access to the data. Identity card numbers were used to link the various electronic databases. Once linking was done, all cases were given a code and all ID card numbers were erased irretrievably to ensure anonymity, leaving no way to trace back any data to individuals. There was no patient contact.

3. Results

There were 25,792 persons who were on treatment for diabetes in April 2014. This cohort was followed up until April 2017. Linkage with the other databases was complete. There were 2518 deaths (9.76%) during this period, giving an average of 32.5 deaths per 1000 persons with diabetes. Of the 25,792 patients on some form of diabetes treatment, 9977 were on metformin monotherapy and 1717 on sulphonylurea monotherapy. Table 1 shows the baseline characteristics of the two groups.

Logistic regression was performed to ascertain the effects of treatment type, age, eGFR and HbA1c on the likelihood of passing away within 3 years. The logistic regression model was statistically significant, $p < .001$. The model explained 22.2% (Nagelkerke R^2) of the variance in mortality rate. Persons on sulphonylurea monotherapy were 2.03 (95% CI 1.68–2.44, $p < .001$) times more likely to die than persons on metformin monotherapy (Fig. 1). Increasing age (odds ratio (OR) = 1.09 (95% CI 1.08–1.11), $p < .001$), a higher HbA_{1c} (OR = 1.07 (95% CI 1.01–1.14), $p = .023$), and a lower eGFR (OR = 1.02 (95% CI 1.01–1.02), $p < .001$) were also associated with a slightly increased likelihood of death within 3 years. Adding LDL and HDL cholesterol levels to the model resulted in a statistically significant model as well ($p < .001$). In this second model additionally adjusted for LDL-cholesterol and HDL-cholesterol, persons on sulphonylurea monotherapy were 2.11 (95% CI 1.66–2.69, $p < .001$) times more likely to pass away than persons on metformin monotherapy. ACR was not found to be a significant factor, and so was not added to the model.

Table 1 – Baseline characteristics of patients on sulphonylurea and on metformin monotherapy. Data are median (interquartile range); ACR = urinary albumin-creatinine ratio. HDL = high-density lipoprotein; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; LDL = low-density lipoprotein.

	On metformin monotherapy	On sulphonylurea monotherapy	Mann-Whitney test (*p* value)
Age (yrs)	69.7 (62.8–75.8)	75.7 (69.2–82.2)	<.001
Total cholesterol (mmol/L)	4.30 (3.74–4.93)	4.15 (3.53–4.90)	<.001
LDL-cholesterol (mmol/L)	2.18 (1.73–2.73)	2.14 (1.71–2.75)	>.05
HDL-cholesterol (mmol/L)	1.35 (1.11–1.62)	1.23 (1.00–1.49)	<.001
HbA_{1c}	6.6 (6.1–7.3)% [49 (43–56) mmol/mol]	7.0 (6.3–8.1)% [53 (45–65) mmol/mol]	<.001
eGFR (ml/min/1.73m^2)	86 (68–102)	51 (34–83)	<.001
ACR (mg/g)	13.55 (6.30–31.92)	25.04 (9.40–89.52)	<.001
FPG (mmol/L)	7.35 (6.43–8.61)	8.07 (6.16–10.03)	<.001
Triglycerides (mmol/L)	1.38 (1.00–1.86)	1.34 (1.01–1.87)	>.05

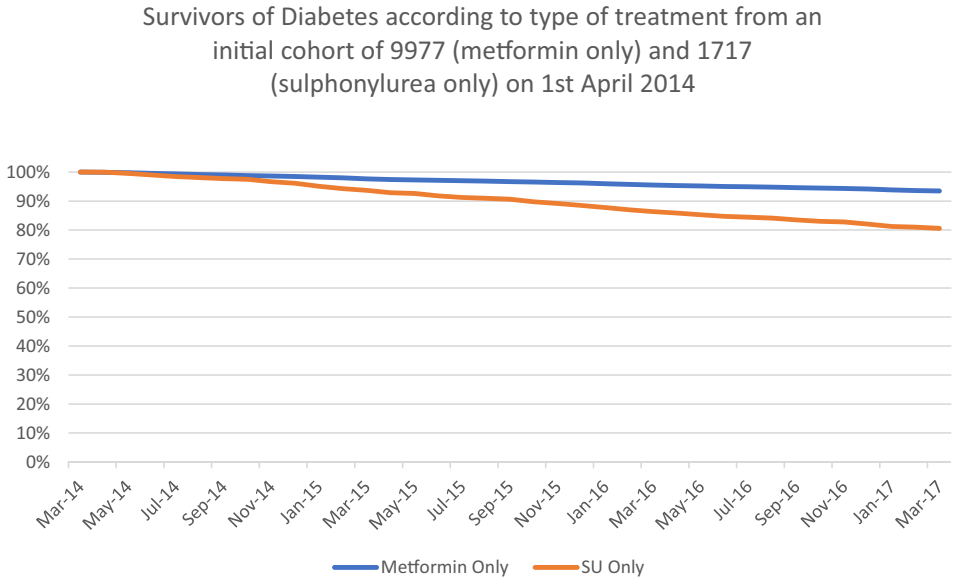

Fig. 1 – Survival of subjects on sulphonylurea monotherapy compared to those metformin monotherapy.

4. Discussion

Our data provide further evidence that sulphonylurea treatment is associated with adverse outcomes in a real world setting. The results of our study are consistent with those of other studies, but we are first to report on all-cause mortality. Unlike many previous studies comparing metformin to sulphonylurea monotherapy, we were also able to adjust for important potential confounders, including age, eGFR, HbA_{1c}, serum lipids and ACR. Furthermore patients on metformin-sulphonylurea combination have been reported to have worse outcomes than those on metformin-pioglitazone [11] or metformin-gliptin [13] combinations.

There are various possible mechanisms which might mediate increased mortality associated with sulphonylurea therapy. Sulphonylureas have a high hypoglycaemia risk [14], since they stimulate the secretion of insulin in a glucose-independent manner. There is a considerable amount of data linking hypoglycaemia to increased adverse cardiovascular events and mortality [15–17]. Although the myocardium can utilise energy substrates other than glucose, these may also be unavailable during hypoglycaemia because of inappropriate hyperinsulinaemia. At the same time, hypoglycaemia-induced sympatho-adrenergic activation increases myocardial energy requirements. These factors may explain why hypoglycaemia is an ischaemia equivalent [18,19]. Hypoglycaemia may also induce serious arrhythmias as a result of sympatho-adrenergic activation and QTc prolongation [20,21]. Severe bradycardia may occur, probably as a result of excessive compensatory vagal activation after the counterregulatory phase [20].

Acute hypoglycaemia has been reported to decrease nitric oxide bioavailability and to increase oxidative stress [22], platelet activation [23] and release of pro-inflammatory [23–25], pro-atherogenic and pro-thrombotic cytokines [24,25]. Many of these effects may extend to beyond the hypoglycaemic per-

iod [23]. Furthermore, Fadini and colleagues have recently reported that hypoglycaemia may impair endothelial progenitor cells response [26].

Sulphonylureas may also cause adverse cardiovascular outcomes through hypoglycaemia-independent mechanisms. Sulphonylureas stimulate the release of insulin by opening the ATP-sensitive potassium channel [27]. However this action on potassium channel is not specific to the pancreatic β-cells, as other cell types are affected, including myocardial cells [28]. This may result in inhibition of pre-conditioning [29], a cardioprotective mechanism in recurrent myocardial ischaemia [30]. Furthermore, being insulin secretagogues, sulphonylureas stimulate the co-secretion of C-peptide which has been reported to be atherogenic in both animal [31] and human [32] studies.

It is also possible that sulphonylureas increase non-vascular deaths. There is some data linking hyperinsulinaemia with various types of cancers [33,34]. This is biologically plausible since insulin stimulates mitogenesis [35] and hyperinsulinaemia probably mediates the link between obesity and cancer [36]. Sulphonylureas are insulin secretagogues and so it is possible that they might increase malignancy through this mechanism. There is some data to support this [37,38], but this is far from conclusive. Sulphonylureas may also increase risk of falls and injury through hypoglycaemia [39,40].

4.1. *Strengths and limitations*

One major strength of the study is that we studied all patients receiving anti-diabetes treatment in the National Health Service irrespective of whether they were being cared for in primary care, secondary care or both. Access to diabetes treatment through the National Health Service is universal with no barriers such as by social class or income. Therefore, we are confident that there are no biases in patient selection. Another strength of our study is the robustness of all the databases we used (treatment, laboratory and mortality databases). We were also in a position to adjust for important potential confounders such as eGFR, urine ACR, HbA_{1c} and serum lipids. Adjustment for eGFR is particularly important since as outlined above, patients on sulphonylurea monotherapy are more highly to have renal impairment as was in fact confirmed by our results.

However since our study was an observational one, we cannot exclude the possibility of the presence of residual confounders or of bias by drug indication. An important limitation is that results could not be adjusted for prior cardiovascular events, prior heart failure or prior cancer morbidity. Patients with liver disease or heart failure may be more likely to be prescribed sulphonylurea monotherapy rather than metformin monotherapy. On the other hand frail patients may be more likely to be prescribed metformin monotherapy.

Nonetheless, since it is unlikely that data from good-quality randomised studies will be available in the near future, data from observational studies such as ours are important. Furthermore, patients in randomised controlled studies and the standard of care that they receive might not be representative of the real world. We pooled all patients on any type of sulphonylurea; we cannot exclude the possibility that some sulphonylureas might be less dangerous than others. Another limitation of the study is that we cannot be sure that patients were actually taking the prescribed medications, or that they were not taking other diabetic medications in addition to the metformin/sulphonylurea from outside the National Health Service. However, the vast majority of patients obtain all their medications through the National Health Service.

In conclusion, we provide evidence that sulphonylurea monotherapy is associated with higher all-cause mortality when compared to metformin monotherapy after adjusting for potential confounders. Although the limitations of the observational nature of our study should be kept in mind, the consistency of the data from several similar studies linking sulphonylurea therapy with adverse outcomes increases the likelihood that the observed results reflect a true association. This is biologically plausible as there are various mechanisms through which sulphonylureas may increase mortality.

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SR is the guarantor of the data. SF conceived the study; SR collected & analysed the data; both authors were involved in writing of the manuscript and in its final approval. The authors have no potential dualities of interest to declare. There was no external funding.

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