Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with…

Article *in* Diabetes Obesity and Metabolism · November 2014

DOI: 10.1111/dom.12354

CITATIONS
62

READS
1,330

8 authors, including:

Sara Jenkins-Jones
Pharmatelligence, Cardiff
41 PUBLICATIONS **697** CITATIONS
SEE PROFILE

Julian P Halcox
Swansea University
152 PUBLICATIONS **11,748** CITATIONS
SEE PROFILE

Guntram Schernthaner
Rudolfstifung Vienna, Austria
638 PUBLICATIONS **17,005** CITATIONS
SEE PROFILE

Jayanti Mukherjee
Bristol-Myers Squibb
47 PUBLICATIONS **1,281** CITATIONS
SEE PROFILE

Diabetes, Obesity and Metabolism 2014.

ORIGINAL ARTICLE

Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls

C. A. Bannister[1,2], S. E. Holden[1,3], S. Jenkins-Jones[3], C. Ll. Morgan[3], J. P. Halcox[4], G. Schernthaner[5], J. Mukherjee[6] & C. J. Currie[1,3]

[1] *The Cochrane Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, UK*
[2] *Cardiff School of Computer Science and Informatics, Cardiff University, Cardiff, UK*
[3] *Global Epidemiology, Pharmatelligence, Cardiff Medicentre, Cardiff, UK*
[4] *Department of Cardiology, School of Medicine, Swansea University, Swansea, UK*
[5] *Department of Medicine, Rudolfstiftung Hospital Vienna, Vienna, Austria*
[6] *Global Health Economics and Outcomes Research, Bristol-Myers Squibb, Wallingford, CT, USA*

Aims: Clinical and observational studies have shown an increased risk of cardiovascular events and death associated with sulphonylureas versus metformin. However, it has never been determined whether this was due to the beneficial effects of metformin or detrimental effects of sulphonylureas. The objective of this study was therefore to compare all-cause mortality in diabetic patients treated first-line with either sulphonylurea or metformin monotherapy with that in matched individuals without diabetes.

Methods: We used retrospective observational data from the UK Clinical Practice Research Datalink (CPRD) from 2000. Subjects with type 2 diabetes who progressed to first-line treatment with metformin or sulphonylurea monotherapy were selected and matched to people without diabetes. Progression to all-cause mortality was compared using parametric survival models that included a range of relevant co-variables.

Results: We identified 78 241 subjects treated with metformin, 12 222 treated with sulphonylurea, and 90 463 matched subjects without diabetes. This resulted in a total, censored follow-up period of 503 384 years. There were 7498 deaths in total, representing unadjusted mortality rates of 14.4 and 15.2, and 50.9 and 28.7 deaths per 1000 person-years for metformin monotherapy and their matched controls, and sulphonylurea monotherapy and their matched controls, respectively. With reference to observed survival in diabetic patients initiated with metformin monotherapy [survival time ratio (STR) = 1.0], adjusted median survival time was 15% lower (STR = 0.85, 95% CI 0.81–0.90) in matched individuals without diabetes and 38% lower (0.62, 0.58–0.66) in diabetic patients treated with sulphonylurea monotherapy.

Conclusions: Patients with type 2 diabetes initiated with metformin monotherapy had longer survival than did matched, non-diabetic controls. Those treated with sulphonylurea had markedly reduced survival compared with both matched controls and those receiving metformin monotherapy. This supports the position of metformin as first-line therapy and implies that metformin may confer benefit in non-diabetes. Sulphonylurea remains a concern.

Keywords: all-cause mortality, metformin, sulphonylurea, type 2 diabetes

Date submitted 2 May 2014; date of first decision 20 May 2014; date of final acceptance 30 June 2014

Introduction

Type 2 diabetes is a condition that affects 8% of the US population [1] and 4% of the UK population [2]. Good glucose control is important to reduce the risk of developing microvascular complications. This is initially achieved through diet and exercise, but glucose-lowering medication is required in most patients with progressing diabetes. Metformin is recommended as first-line therapy for type 2 diabetes in the current American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines [3].

In the UK, the proportion of people with type 2 diabetes treated with sulphonylureas decreased from 45% in 1996 to 33% in 2005 [4], and the number of people using metformin increased from 30% to 57% over the same period [5]. In the USA, the percentage of patients initially treated with sulphonylureas decreased from 61% in 1997 to 22% in 2012, whereas the proportion of patients initiating therapy with metformin increased from 23% in 1997 to 53% in 2012 [6] (although metformin was not approved by the Food and Drug Administration (FDA) until 1995 [7]). However, sulphonylureas are still commonly prescribed, especially when metformin is contraindicated, and it is relatively common to use sulphonylurea subsequent to metformin monotherapy [8]. By far the most common second-line glucose-lowering therapy is a combination of metformin and sulphonylurea [8].

Unlike metformin, sulphonylureas can cause weight gain and hypoglycaemia, and are thought to have a detrimental impact on cardiovascular risk [9–12]. It has been hypothesized that sulphonylureas may cause cardiovascular side effects by inhibiting K_{ATP} channels in cardiac muscle, thereby blocking ischaemic preconditioning (a cardioprotective mechanism)

Correspondence to: Craig J. Currie, Professor of Applied Pharmacoepidemiology, The Cochrane Institute of Primary Care and Public Health, Cardiff University, The Pharma Research Centre, Cardiff Medicentre, Cardiff CF14 4UJ, UK.
E-mail: currie@cardiff.ac.uk

[13,14]. However, metformin has been associated with beneficial effects, which include a cardioprotective effect that cannot be solely explained by its antihyperglycaemic effect [15–17]. Furthermore, metformin is believed to have anticancer properties, which would also impact on mortality risk [18,19]. A discussion of the relative merits of these two glucose-lowering drugs was published recently in *Diabetes, Obesity and Metabolism* [4].

Demonstration of the efficacy and safety of glucose-lowering drugs with regard to hard clinical endpoints – especially cardiovascular outcomes – is important and now a regulatory requirement for new glucose-lowering medicines. This is no less important for long-established treatments. In the absence of adequately powered prospective trials, retrospective data are essential to help address continuing uncertainty.

Previous clinical and observational studies comparing metformin and sulphonylureas have shown an increased risk of cardiovascular events and death associated with the use of sulphonylureas compared with metformin [20,21]. However, it is difficult to determine whether this is due to the beneficial effects of metformin or due to detrimental effects associated with sulphonylureas.

The primary aim of this study was to compare the risk of all-cause mortality associated with first-line sulphonylurea monotherapy or first-line metformin monotherapy with that of matched non-diabetic controls.

Materials and Methods

Data Source

The data source was the Clinical Practice Research Datalink (CPRD) [22]. CPRD contains clinically rich, pseudonymized data collected from primary-care general practitioners (GPs) in the UK. The following data were available: demographics, symptoms and diagnoses, prescriptions, immunizations, results of investigations, referrals to specialists and secondary care, feedback from other care settings, and lifestyle information such as body mass index (BMI), smoking, and exercise. CPRD is broadly representative [23] and contains data from over 13 million research-quality patients. Details of hospital admissions are also provided for the majority of patients. Data were available till July 2013. Approval for this study was granted by the CPRD Independent Scientific Advisory Committee (reference 12_151RAR).

Patient Selection

Patients classed by CPRD as being of acceptable research quality were selected if diagnosed with type 2 diabetes and exposed to glucose-lowering therapy. Patients were excluded if they had any record of secondary diabetes.

Patients were defined as incident diabetes cases based on a wash-in period of at least 180 days from registration to diagnosis. Patients subsequently initiated with sulphonylurea or metformin from 2000 were selected, provided they received treatment for a minimum of 180 days. The index date was defined as that of the first sulphonylurea or metformin prescription. Patients were followed to death or censorship.

Cases were matched to people without diabetes using the following criteria: age at baseline (±2 years), gender, same general practice, prior cancer status and smoking status. The index date for the controls was the same as that of their corresponding case. Only individuals with ≥180 days' survival following index date were included as controls.

Study Endpoint

The study endpoint was all-cause mortality. For diabetic patients who died, the event date was defined as the patient's date of death provided that this occurred before the censor date, defined as the earliest of (i) the end of the recorded data, (ii) 90 days from regimen change or (iii) 5 years plus 180 days from the index date.

For controls who died, the event date was defined as the patient's recorded date of death provided that this was prior to the end of the recorded data, the censor date for the corresponding case or the 5½ year follow-up period. Otherwise cases were censored. The censor date here was defined as the earliest of the end of a patient's recorded data, the censor date of their corresponding case or the end of the 5½ year follow-up period.

Statistical Methods

Continuous baseline characteristics were compared using the independent *t*-test or Mann–Whitney *U* test depending on their distribution. Categorical variables were compared using the chi-squared test. Differences in survival in Kaplan–Meier (KM) analysis were compared using the log-rank test.

Candidate covariates for modelling survival comprised age, Charlson co-morbidity index [24], gender, smoking status, prior antiplatelet therapy, prior lipid-lowering therapy, prior antihypertensive therapy, index year, and study arm. Glycated haemoglobin (HbA1c), systolic blood pressure, total cholesterol, creatinine and BMI were not considered because of large proportions of missing data in controls. Prior major adverse cardiac events (MACEs) are components of the Charlson index. All categorical variables were treated as discrete and converted to binary variables with the exception of index year and Charlson index.

People with type 2 diabetes have a minimum Charlson index of 1 or 2 units, depending on whether they do or do not have complications, respectively. Here, group status indicated diabetes status. The Charlson index was therefore modified to subtract 1 unit from all patients with diabetes so that uncomplicated diabetes contributed nothing to the index, and diabetes with complications contributed 1 unit. Other co-morbidities contributed to the index conventionally.

Continuous variables (age and modified Charlson index) were modelled using restricted cubic splines to allow for non-linear effects. The start date for the survival analysis was defined as the index date + 180 days' treatment exposure. The survival analysis was truncated at 5½ years as the average duration of first-line monotherapy was 3 years.

Modelling of survival was not performed with a Cox proportional hazards model because the proportional hazards assumption was violated. We therefore fitted a parametric accelerated failure time (AFT) survival model. Weibull, log-normal and log-logistic models were assessed

for goodness-of-fit using the Akaike information criterion (AIC) [25]. The log-logistic model resulted in the best fit in terms of AIC, and the adequacy of this distribution was further assessed by plotting appropriately transformed non-parametric estimates against time. The log-logistic survival model provides beta coefficients that equal the difference in log survival time between groups or for continuous predictors. Exponentiation of the beta coefficient gives the ratio between median survival times, known as the survival time ratio (STR), or acceleration factor. STRs less than 1 represent a decrease in survival time; values greater than 1 represent prolonged survival.

All candidate covariates were included in the final model with no variable selection performed, as it has been shown that excluding statistically insignificant variables does not improve predictive accuracy and makes accurate confidence intervals (CIs) hard to obtain [26].

Extensive subgroup analyses are reported using the final model. To enable the impact of concomitant cardioprotective medications to be evaluated over time, three variants of the final model were developed: model variants 1 – 3 replaced baseline values for antihypertensive, lipid-lowering and antiplatelet therapy with values for the first 1, 2 or 3 years of study, respectively. Patients were excluded if they were censored within the relevant years and had received a different combination of antihypertensive, antiplatelet and lipid-lowering therapy in those years. All statistical analyses were performed using R software (version 3.0.1) [27].

Results

A total of 78 241 subjects treated with metformin and 12 222 treated with sulphonylurea were identified; 78 241 and 12 222 non-diabetic patients were matched to their respective cases. Subjects were followed from their index date for an average of 2.8 (median 2.4) years, representing a censored total follow-up period of 503 384 years.

Baseline Characteristics

Metformin Monotherapy Compared With Sulphonylurea Monotherapy. Patients in the sulphonylurea group were older than those treated with metformin (mean age of 67.8 vs. 61.2 years, respectively; $p < 0.001$). Patients in the sulphonylurea group had higher baseline HbA1c values (9.2% vs. 8.6%; $p < 0.001$) and serum creatinine (97.9 vs. 84.2 µmol/l; $p < 0.001$). Baseline, unmodified Charlson index was higher in the sulphonylurea group than in the metformin group (2.3 vs. 1.9; $p < 0.001$). There was also a higher percentage of people who had previously had cancer (14% vs. 10%; $p < 0.001$) and/or MACE (16% vs. 10%; $p < 0.001$) in the sulphonylurea group. Conversely, a higher percentage of people in the metformin group had previously been prescribed lipid-lowering therapy (50% vs. 35%; $p < 0.001$). Baseline characteristics are detailed in Table 1.

Relative morbidity between these two groups at baseline was difficult to gauge because of differing mean age.

Metformin Monotherapy Compared With Matched Control Group. BMI was higher for those treated with metformin (32.4 vs. 27.4 kg/m^2; $p < 0.001$; Table 1), and people in the metformin group also had more GP consultations in the year prior to treatment initiation (11.3 vs. 6; $p < 0.001$). In addition, people in the metformin group were more likely to have had a previous MACE (10% vs. 6%; $p < 0.001$) and to have previously received prescriptions for lipid-lowering (50% vs. 20%; $p < 0.001$), antihypertensive (66% vs. 39%; $p < 0.001$) and/or

Table 1. Baseline characteristics.

Parameter	Metformin	Sulphonylurea	Control (matched with metformin)	Control (matched with sulphonylurea)
Number of people, n (%)	78 241 (43)	12 222 (7)	78 241 (43)	12 222 (7)
Age at index, mean (s.d.)	61.2 (12.7)	67.8 (12.8)	61.2 (12.7)	67.8 (12.8)
Males, n (%)	44 286 (57)	7100 (58)	44 286 (57)	7100 (58)
Smoking status				
Non-smoker, n (%)	36 781 (47)	6002 (49)	36 781 (47)	6002 (49)
Ex-smoker, n (%)	27 662 (35)	3879 (32)	27 662 (35)	3879 (32)
Current smoker, n (%)	13 798 (18)	2341 (19)	13 798 (18)	2341 (19)
HbA1c, mean (s.d.), %	8.6 (1.8)	9.2 (2.1)	—	—
Systolic BP, mean (s.d.), mmHg	138.5 (16.8)	139.7 (19.5)	136.2 (16.6)	140.7 (18.2)
Total cholesterol, mean (s.d.), µmol/l	5.0 (1.2)	5.1 (1.3)	5.1 (1.1)	5.1 (1.1)
Serum creatinine, mean (s.d.), µmol/l	84.2 (18.9)	97.9 (33.8)	89.1 (25.8)	95.5 (29.6)
BMI, mean (s.d.), kg/m^2	32.4 (5.9)	27.1 (4.9)	27.4 (5.0)	26.7 (4.6)
Charlson index*, mean (s.d.)	1.9 (1.3)	2.3 (1.7)	0.7 (1.2)	0.8 (1.3)
GP contacts in the year prior, mean (s.d.)	11.3 (9.9)	11.7 (10.6)	6.0 (7.8)	6.5 (8.1)
Prior cancer, n (%)	7553 (10)	1698 (14)	7550 (10)	1695 (14)
Prior MACE, n (%)	8162 (10)	1995 (16)	5058 (6)	1119 (9)
Prior lipid-lowering therapy, n (%)	39 407 (50)	4303 (35)	15 913 (20)	2112 (17)
Prior antihypertensive therapy, n (%)	52 016 (66)	7779 (64)	30 585 (39)	5474 (45)
Prior antiplatelet therapy, n (%)	28 285 (36)	4656 (38)	14 619 (19)	3017 (25)

BMI, body mass index; BP, blood pressure; GP, general practitioner; HbA1c, glycated haemoglobin; MACE, major adverse cardiac event; s.d., standard deviation. *Unmodified Charlson co-morbidity index.

antiplatelet medications (36% vs. 19%; $p < 0.001$) (Figure 1). Non-diabetic controls had less morbidity than cases.

Sulphonylurea Monotherapy Compared With Matched Control Group. The Charlson index was higher for patients in the sulphonylurea group than for those in the control group (2.3 vs. 0.8; $p < 0.001$) as was the number of GP contacts in the year prior to index date (11.7 vs. 6.5; $p < 0.001$) (Table 1). In addition, people in the sulphonylurea group were more probable to have had a MACE (16% vs. 9%; $p < 0.001$) and to have previously received prescriptions for lipid-lowering (35% vs. 17%; $p < 0.001$), antihypertensive (64% vs. 45%; $p < 0.001$) and/or antiplatelet therapies (38% vs. 25%; $p < 0.001$) (Figure 1). Controls had far less morbidity than the diabetic subjects.

Numbers of Deaths and Crude Event Rates

In total, there were 7498 deaths, corresponding to an unadjusted event rate of 18.1 deaths per 1000 person-years. Unadjusted event rates were highest in the sulphonylurea group and lowest in the metformin group (50.9 vs. 14.4 per 1000 person-years, respectively; $p < 0.001$; Table 2). Unadjusted event rates were higher in sulphonylurea-treated patients than in their matched, non-diabetic controls (50.9 vs. 28.7 per 1000 person-years, respectively; $p < 0.001$) but, surprisingly, were lower in those treated with metformin than in their matched controls (14.4 vs. 15.2 per 1000 person-years, respectively; $p = 0.054$). Unadjusted event rates were lowest in people aged <60 years at index date and highest for people aged >70 years for both diabetic and control subjects.

Unadjusted Survival Patterns

KM survival curves, stratified by treatment arm and diabetes status, are illustrated in Figure 2. Favouring metformin, these survival curves show that overall there was a small yet statistically significant difference between metformin cases and their non-diabetic controls ($p = 0.037$; Figure 2a). However those treated with sulphonylureas had markedly reduced survival ($p < 0.001$; Figure 2b) compared with their controls. KM curves are also presented for patients aged 71–75 years: the most frequent age group for incident sulphonylurea initiation

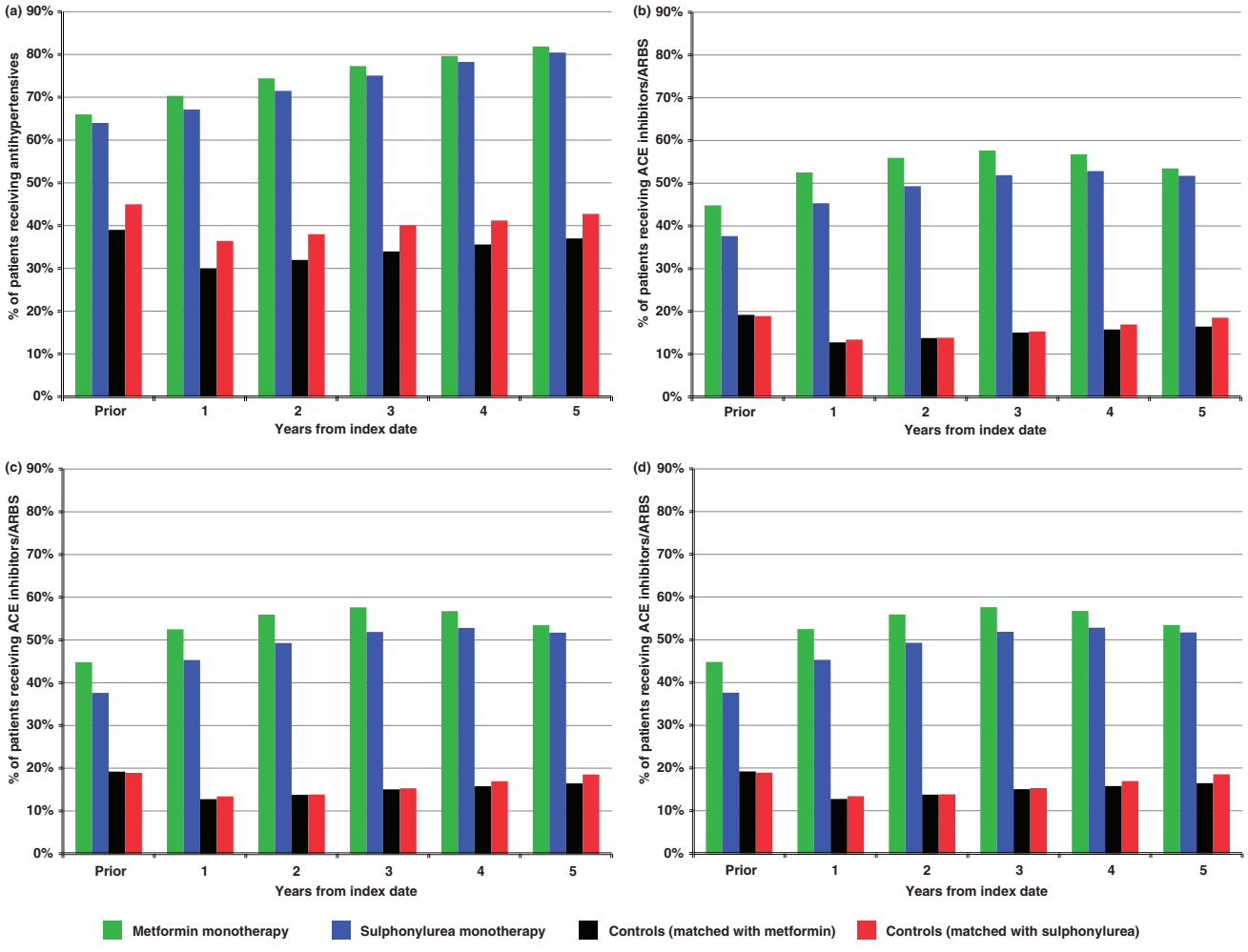

Figure 1. Use of cardiovascular prophylactic medications during the study follow-up: (a) all antihypertensives, (b) ACE inhibitors/angiotensin II antagonists, (c) statins and (d) antiplatelets. Numbers of subjects per year following index date were: 157 862 for year 1; 106 406 for year 2; 71 461 for year 3; 46 682 for year 4 and 30 550 for year 5.

Table 2. Crude event rate per 1000 person-years for all-cause mortality for patients with type 2 diabetes treated with first-line sulphonylurea monotherapy, metformin monotherapy or their respective matched, non-diabetic controls.

	Parameter	Metformin	Sulphonylurea	Controls (matched with metformin)	Controls (matched with sulphonylurea)
Overall	Number of deaths	2663	1418	2669	748
	Follow-up period (years)*	184 708	27 879	175 614	26 020
	Crude event rate	14.4	50.9	15.2	28.7
Age <60 years	Number of deaths	249	75	223	27
	Follow-up period (years)*	74 986	6236	72 560	6050
	Crude event rate	3.3	12.0	3.1	4.5
Age 60–70 years	Number of deaths	654	235	713	125
	Follow-up period (years)*	62 034	8252	59 365	7853
	Crude event rate	10.5	28.5	12.0	15.9
Age >70 years	Number of deaths	1760	1108	1733	596
	Follow-up period (years)*	47 689	13 391	43 689	12 117
	Crude event rate	36.9	82.7	39.7	49.2

*Excluding the first 180 days following the index date.

(Figure 2c). Reassuringly, the two groups of non-diabetic controls resulted in the same pattern of survival ($p = 0.879$); however, there was improved survival in people exposed to metformin versus controls ($p < 0.001$) and reduced survival in the sulphonylurea group versus controls ($p < 0.001$).

Adjusted Survival Patterns

With reference to the observed survival in the group initiated with metformin, the median survival time was 15% lower in controls (STR = 0.85, 95% CI 0.81–0.90) and 38% lower (0.62, 0.58–0.66) in patients with type 2 diabetes treated with sulphonylurea (Figure 3: final model).

These patterns remained generally consistent across a wide range of clinically relevant subgroups (Figure 3). The central points of the STRs did not cross unity in a discordant way in analysis of any subgroup. However, a number of interesting patterns emerged. When compared with matched, non-diabetic controls, diabetic patients with high co-morbidity who were treated with metformin had particularly improved survival (Charlson index ≥3: STR = 0.67, 0.59–0.77), and this pattern increased with increasing morbidity (Figure 3). Importantly, survival was better with metformin even in those people who had not received cardiac prophylactic medications at baseline, but consistent survival benefits were observed with metformin when used in people with a prior history of each prophylactic treatment subgroup.

With regard to decreased survival in subjects with diabetes treated with sulphonylurea compared with metformin, those initiated at a younger age were at a particularly increased relative risk (≤53 years: STR = 0.34, 0.22–0.53). Furthermore, the difference appeared to increase over calendar time: the STR was 0.62 (0.56–0.68) in those initiating treatment between 2000 and 2004, and 0.46 (0.33–0.64) in those initiating between 2011 and 2012 (Figure 3). Adjustment for up to 3 years' continuous exposure to concomitant cardioprotective prophylaxis had no notable impact on relative STRs for metformin and sulphonylureas (Figure 3: model variants 1–3).

Discussion

We have shown that in a contemporary UK population use of metformin as first-line, glucose-lowering treatment was associated with survival that was at least as good as that of matched, non-diabetic controls. Treatment with first-line sulphonylurea monotherapy was associated with increased mortality.

There remains considerable conjecture about the relative merits of metformin versus sulphonylureas [4]. Reported differences in safety generally favour metformin. If one accepts that there exists a difference in outcome favouring metformin, it has not yet been established whether this is due to the beneficial impact of metformin or a detrimental impact of sulphonylureas. Here we uniquely introduced non-diabetic controls into an evaluation of these treatments, and the findings were illuminating. Patients treated with metformin had a small but statistically significant improvement in survival compared with matched, non-diabetic controls, whereas those treated with sulphonylureas had consistently reduced survival versus non-diabetic controls. There also remained a difference in outcome between those taking metformin and sulphonylurea, although this needs to be interpreted with caution because we did not adjust for important covariates because they were unavailable in the non-diabetic subjects. This was carried out in separate but related studies in this journal, and showed worse outcome with metformin [8,12,28], Importantly, these data not only show once again a better outcome with metformin relatively to sulphonylurea but also suggest that this is due to a beneficial effect of metformin on all-cause mortality.

Surprisingly, patients treated with metformin had a slightly longer adjusted survival than matched, non-diabetic controls, despite greater morbidity. This was independent of cardiovascular disease prophylaxis.

Evidence in support of the use of metformin as first-line, glucose-lowering therapy originated largely from the UK Prospective Diabetes Study (UKPDS) group, where obese patients receiving metformin had lower incidence of diabetes-related endpoints, including all-cause mortality

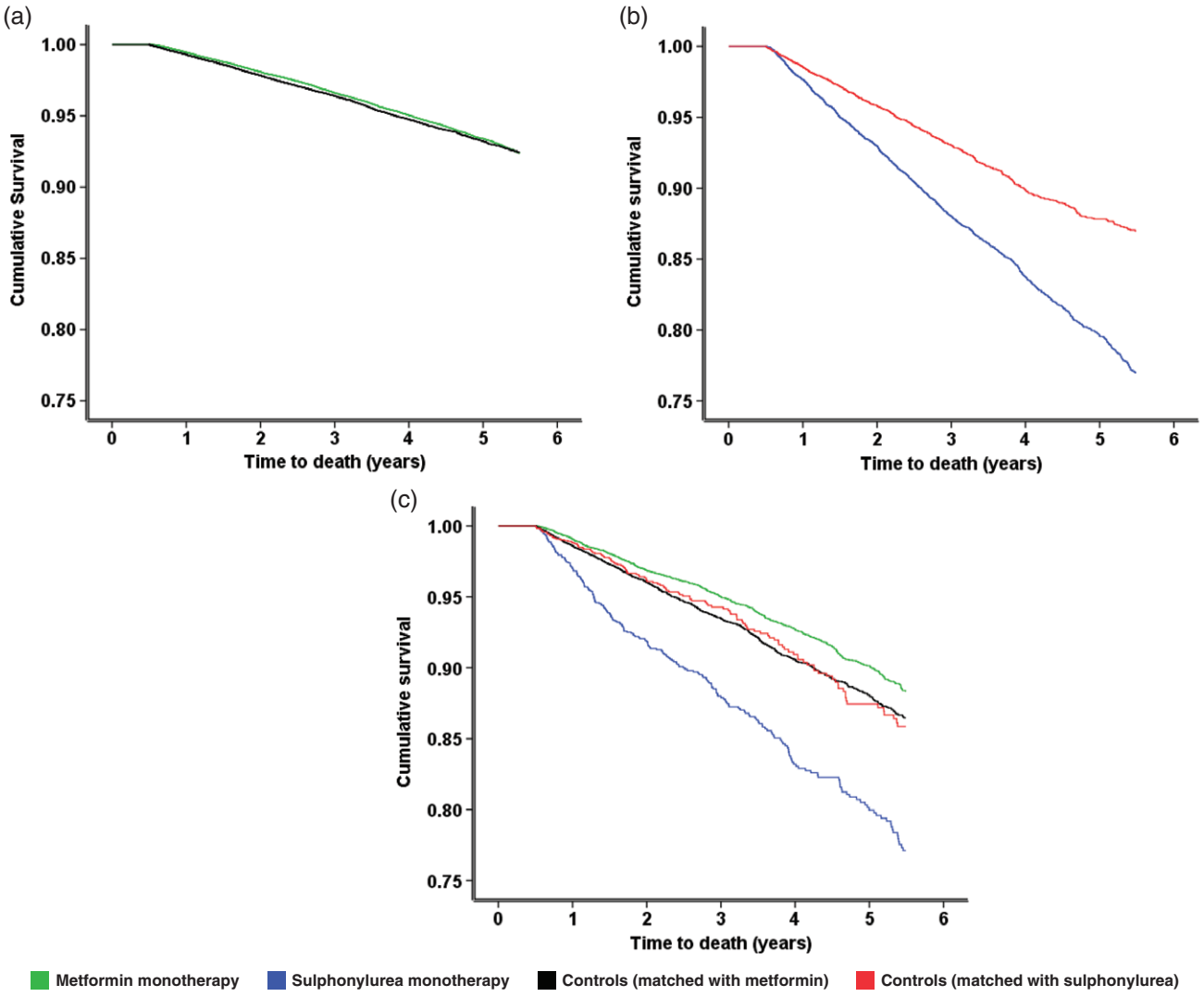

Figure 2. Kaplan–Meier curves comparing (a) metformin monotherapy with their matched control group without diabetes, (b) sulphonylurea monotherapy with their matched control group without diabetes and (c) patients aged 71–75 years at baseline for all four cohorts (reported because it is the most frequent 5-year age group in subjects initiating sulphonylurea monotherapy).

when compared with intensive treatment with sulphonylureas or insulin [20]. A relative benefit of metformin has also been reported in various observational studies [21,30–34], including decreased risk of cancer [35–38]. Mixed results have been observed, however, in meta-analyses of randomized controlled trials (RCTs) of metformin versus active comparators or placebo. A meta-analysis of trials, including UKPDS, investigating cardiovascular risk in metformin found significant cardiovascular benefit in metformin versus placebo/no therapy (odds ratio = 0.79, p = 0.031) but not in active comparator trials (1.03, p = 0.89) [39]. Another meta-analysis found no evidence to support its hypothesis that metformin lowers cancer risk by one third, nor did eligible trials show a significant effect on all-cause mortality [40]. However, the trials included were clinically heterogeneous and follow-up was short, especially for mortality.

Study Limitations

This study included a large number of patients, who were followed-up for a median of 2.4 years. Unlike RCTs, less strict inclusion and exclusion criteria are often used in observational studies. The data source used for this study, CPRD, contained data collected from routine practice; therefore, some data may be missing and coding imperfections may lead to diabetes misclassification. However, only those patient records meeting CPRD's quality criteria were included, and rules were applied to maintain consistency in the selection of patients with type 2 diabetes. Data quality in CPRD is considered to be good [41].

As this was an observational study, patients were not randomized to treatment, and uncharacterized confounders may account for some of the differences between groups. Although differences in baseline characteristics existed between the four groups, these were adjusted for as far as possible in the models. However, we could not adjust for some parameters due

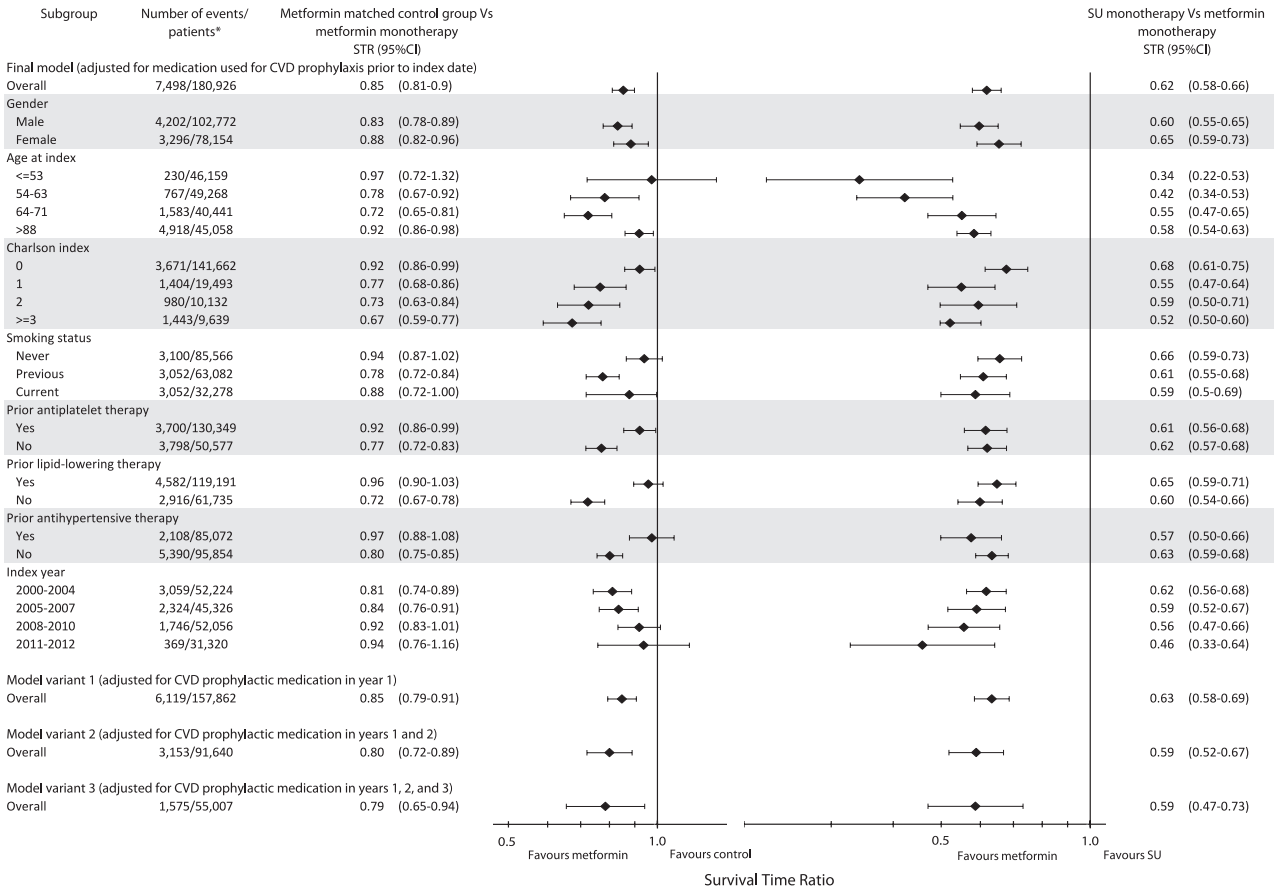

Figure 3. Forest plot showing adjusted survival time ratios (STR), overall and for relevant diabetes-related subgroups. Data are for those initiated with metformin monotherapy versus non-diabetic controls (left-hand panel), and metformin monotherapy versus sulphonylurea monotherapy. *Final model 1*: Covariates were age, modified Charlson index, gender, smoking status, prior antiplatelet therapy (yes/no), prior lipid-lowering therapy (yes/no), prior antihypertensive therapy (yes/no), year of study index date and study arm. *Model variant 1*: Covariates were age, modified Charlson index, gender, smoking status, a score based on whether the patient had received antihypertensive, lipid-lowering or antiplatelet therapy in the first year of study, year of study index date and study arm. Patients censored within the first year were excluded. *Model variant 2*: Covariates were age, modified Charlson index, gender, smoking status, a score based on whether the patient had received antihypertensive, lipid-lowering or antiplatelet therapy in the first 2 years of study, year of study index date and study arm. Patients were excluded if they were censored within the first 2 years and had received a different combination of antihypertensive, antiplatelet and lipid-lowering therapy in those years. *Model variant 3*: Covariates were age, modified Charlson index, gender, smoking status, a score based on whether the patient had received antihypertensive, lipid-lowering or antiplatelet therapy in the first 3 years of study, year of study index date and study arm. Patients were excluded if they were censored within the first 3 years and had received a different combination of antihypertensive, antiplatelet and lipid-lowering therapy in those years. *The total number of patients in the complete model includes patients in the control group matched with sulphonylureas (data not presented in this figure). CVD, cardiovascular disease.

to the understandably high percentage of missing data in controls. This may impact on the comparison between metformin monotherapy and sulphonylurea monotherapy particularly. We did not investigate for a dose–response association in this study; however, this would be interesting. We have detailed the profile of the specific types of sulphonylureas that are commonly used in these cohorts in another study, and this is 90% gliclazide [28].

Symptoms of type 2 diabetes can be mild and people with type 2 diabetes can remain undiagnosed for many years [42]. Therefore, it is probable that some controls had undiagnosed type 2 diabetes.

Due to the association between type 2 diabetes and increased cardiovascular risk, people with type 2 diabetes are more likely to be receiving exercise and lifestyle interventions and close monitoring and control of blood pressure and cholesterol levels. Hypertension and hypercholesterolaemia are risk factors for cardiovascular disease but are generally asymptomatic. Therefore, these conditions may be less well diagnosed in the control group.

Conclusion

Considered as a whole, our data suggest that patients with diabetes treated with metformin monotherapy can expect their survival to be at least as good as that of the non-diabetic population while on this specific regimen. We remain unsure about how survival changes relative to those without diabetes once glucose-lowering treatment is intensified, although

treatment with metformin plus sulphonylurea combination therapy remains concerning [8,28]. For people treated with sulphonylurea monotherapy, our findings further support the hypothesis that this drug class increases the risk of all-cause mortality. Intriguingly, these findings suggest that there may be a prognostic benefit of metformin prophylaxis in people without diabetes.

Acknowledgements

This article was reviewed for scientific content and supported by AstraZeneca/Bristol-Myers Squibb. The funding agencies had no other role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflict of Interest

C. A. B. and C. Ll. M. are contractors of, S. E. H. and S. J.-J. are employed by and C. J. C. is a director of Pharmatelligence, a research consultancy receiving funding from pharmaceutical companies. J. M. is an employee of Bristol-Myers Squibb. C. J. C. reports research grants from various health-related organizations, including Abbott, ALK, Astellas, AstraZeneca, Bristol-Myers Squibb, Diabetes UK, the Engineering and Physical Sciences Research Council, the EASD, Ferring, GSK, Jenson (Internis), Lilly, the Medical Research Council, Medtronic, MSD, the National Health Service, Norgine, Pfizer, Sanofi-Aventis, Shire and Wyeth, and consults for Amylin, Aryx, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Diabetes UK, Eisel, Ferring, GSK, Ipsen, Lilly, Medtronic, MSD, Pfizer, Sanofi-Aventis, Takeda and Wyeth. J. P. H. and G. S. report no conflicts of interest.

C. J. C. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C. J. C., C. A. B. and S. E. conceptualized the study and design. C. J. C. and S. J.-J. acquired the data for the study. C. J. C., C. A. B., S. E. H., C. Ll. M., J. P. H. and G. S. contributed to analysis and interpretation of data. C. J. C., C. A. B. and S. E. H. drafted the manuscript. All authors were involved in critical revision of the manuscript for important intellectual content. C. A. B. and S. E. H. performed statistical analysis. C. J. C. obtained funding. S. J.-J. provided administrative, technical and material support. C. J. C. supervised the study.

References

1. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet 2011. Available from URL: http://www.cdc.gov/diabetes/pubs/factsheet11.htm. Accessed 28 January 2014.
2. Diabetes UK. Diabetes in the UK 2012: Key statistics on diabetes 2012. Available from URL: http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf. Accessed 18 December 2013.
3. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; **35**: 1364–1379.
4. Holden SE, Currie CJ. Mortality risk with sulphonylureas compared to metformin. Diabetes Obes Metab 2014; DOI: 10.1111/dom.12280 [Epub ahead of print].
5. Massó González EL, Johansson S, Wallander MA, García Rodríguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996–2005. J Epidemiol Community Health 2009; **63**: 332–336.
6. Turner LW, Nartey D, Stafford RS, Singh S, Caleb Alexander G. Ambulatory treatment of type 2 diabetes mellitus in the United States, 1997–2012. Diabetes Care 2014; **37**: 985–992.
7. U.S. Food and Drug Administration. Drugs @FDA. Drug Details – Glucophage. Silver Spring: U.S. Food and Drug Administration 2014. Available from URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=GLUCOPHAGE. Accessed 8 March 2014.
8. Morgan CLI, Poole CD, Evans M, Barnett AH, Jenkins-Jones S, Currie CJ. What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab 2012; **97**: 4605–4612.
9. Pantalone KM, Kattan MW, Yu C et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab 2012; **14**: 803–809.
10. Forst T, Hanefeld M, Jacob S et al. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Diab Vasc Dis Res 2013; **10**: 302–314.
11. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. Diabetologia 2010; **53**: 1552–1561.
12. Morgan CLI, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. Diabetes Obes Metab 2014; DOI: 10.1111/dom.12302 [Epub ahead of print].
13. Sturgess NC. The sulfonylurea receptor may be an ATP-sensitive potassium channel. Lancet 1985; **326**: 474–475.
14. Terzic A, Jahangir A, Kurachi Y. Cardiac ATP-sensitive K+ channels: regulation by intracellular nucleotides and K+ channel-opening drugs. Am J Physiol 1995; **269**: C525–545.
15. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002; **137**: 25–33.
16. Beisswenger PJ, Howell SK, Touchette AD, Lal S, Szwergold BS. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. Diabetes 1999; **48**: 198–202.
17. Kooy A, de Jager J, Lehert P et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009; **169**: 616–625.
18. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; **52**: 1766–1777.
19. Franciosi M, Lucisano G, Lapice E, Strippoli GFM, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013; **8**: e71583.
20. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; **352**: 854–865.
21. Roumie CL, Hung AM, Greevy RA et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 2012; **157**: 601–610.
22. Clinical Practice Research Datalink (CPRD). Clinical Practice Research Datalink. 2013. Available from URL: http://www.cprd.com/intro.asp. Accessed 17 June 2013.
23. Hollowell J. The General Practice Research Database: quality of morbidity data. Popul Trends 1997; **87**: 36–40.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; **40**: 373–383.

25. Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. Appl Stat 1999; **48**: 313–329.
26. Harrell FE. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. 2nd edn. New York: Springer, 2006.
27. The R Project for Statistical Computing. Available from URL: http://www.r-project.org. Accessed 3 February 2014.
28. Morgan CLI, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. Diabetes Obes Metab 2014; DOI: 10.1111/dom.12306 [Epub ahead of print].
29. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med 2005; **22**: 497–502.
30. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006; **49**: 930–936.
31. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 2002; **25**: 2244–2248.
32. Azoulay L, Schneider-Lindner V, Dell'aniello S, Schiffrin A, Suissa S. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case–control study. Pharmacoepidemiol Drug Saf 2010; **19**: 335–342.
33. Schramm TK, Gislason GH, Vaag A et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin inx type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 2011; **32**: 1900–1908.
34. Hong J, Zhang Y, Lai S et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013; **36**: 1304–1311.
35. Qiu H, Rhoads GG, Berlin JA, Marcella SW, Demissie K. Initial metformin or sulphonylurea exposure and cancer occurrence among patients with type 2 diabetes mellitus. Diabetes Obes Metab 2013; **15**: 349–357.
36. Hsieh MC, Lee TC, Cheng SM, Tu ST, Yen MH, Tseng CH. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. Exp Diabetes Res 2012; **2012**: 413782.
37. Ruiter R, Visser LE, van Herk-Sukel MP et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. Diabetes Care 2012; **35**: 119–124.
38. Bowker SL, Yasui Y, Veugelers P, Johnson JA. Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure. Diabetologia 2010; **53**: 1631–1637.
39. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2011; **13**: 221–228.
40. Stevens RJ, Ali R, Bankhead CR et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. Diabetologia 2012; **55**: 2593–2603.
41. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010; **60**: e128–136.
42. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 1992; **15**: 815–819.