Can people with type 2 diabetes live longer than people without diabetes? A comparison of all-cause mortality in people initiated with metformin monotherapy or sulfonylurea monotherapy and matched controls without diabetes.

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Abstract

Aims

Clinical and observational studies have demonstrated increased risk of cardiovascular events and death associated with sulfonylureas versus metformin. However, it has never been determined whether this was due to the beneficial effects of metformin or detrimental effects of sulfonylureas. Our objective was therefore to compare all-cause mortality in diabetic patients treated first-line, glucose lowering therapy with either sulfonylurea or metformin monotherapy with that in matched individuals without diabetes.

Materials and 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 sulfonylurea 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 sulfonylurea, and matched 90,463 cases without diabetes. This resulted in a total, censored follow-up period of 503,384 years. There were 7,498 deaths in total, representing unadjusted mortality rates of 14.4 and 15.2, and 50.9 and 28.7 deaths per 1,000 person-years for metformin monotherapy and their matched controls, and sulfonylurea monotherapy and their matched controls, respectively. With reference to observed survival in diabetic patients initiated with metformin monotherapy, adjusted median survival time was 15% lower (survival time ratio=0.85, 95%CI 0.81–0.90) than in matched individuals without diabetes, and

adjusted median survival time was reduced by 38% (survival time ratio=0.62, 0.58–0.66) in diabetic patients treated with sulfonylurea monotherapy.

Conclusions

Patients with type 2 diabetes initiated with metformin monotherapy had longer survival than did matched, non-diabetic controls. Those treated with sulfonylurea had markedly reduced survival than 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. Sulfonylurea remains a continued concern.

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 the first-line therapy for type 2 diabetes in the current ADA/EASD guidelines.[3]

In the UK, the proportion of people with type 2 diabetes treated with sulfonylureas 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 sulfonylureas decreased from 61% in 1997 to 22% in 2012, while the proportion of patients initiating therapy with metformin increased from 23% in 1997 to 53% in 2012.[6] However, sulfonylureas are still commonly prescribed, especially when metformin is contraindicated, and it is relatively common to use sulfonylurea subsequent to metformin monotherapy.[7] By far the most common second-line glucose-lowering therapy is a combination of metformin and sulfonylurea[7], although metformin was not approved by the FDA until 1995.[8]

Unlike metformin, sulfonylureas can cause weight gain and hypoglycemia, thought to have a detrimental impact on cardiovascular risk.[9,10,11,12] In addition, it has been hypothesized that sulfonylureas may cause cardiovascular side-effects by inhibiting K_{ATP} channels in cardiac muscle, thereby blocking ischemic preconditioning (a cardioprotective mechanism).[13,14] On the other hand, metformin has been associated with beneficial effects, which include a cardioprotective effect that cannot be solely explained by its antihyperglycemic effect.[15,16,17] Furthermore, metformin is believed to have anti-cancer 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 sulfonylureas have demonstrated an increased risk of cardiovascular events and death associated with the use of sulfonylureas compared with metformin.[20,21] However, it is difficult to determine whether this is due to the beneficial effects of metformin or to detrimental effects associated with sulfonylureas.

The primary aim of this study was to compare the risk of all-cause mortality associated with first-line sulfonylurea 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 physicians 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 to 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 sulfonylurea or metformin from 2000 were selected, providing they received treatment for a minimum of 180 days. The index date was defined as that of the first sulfonylurea 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 a) the end of the recorded data, b) 90 days from regimen change, or c) five years plus 180 days from the index date.

For controls that 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^2 test. Differences in survival in Kaplan–Meier (KM) analysis were compared using the log-rank test.

Candidate covariates for modeling survival comprised age, Charlson comorbidity index, [24] gender, smoking status, prior anti-platelet therapy, prior lipid-lowering therapy, prior anti-hypertensive therapy, index year, and study arm. Glycated hemoglobin (HbA1c), systolic blood pressure, total cholesterol, creatinine, and BMI were not considered because their large proportions of missing data in controls.Prior major adverse cardiac events (MACE) 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 one or two units, depending on whether they did or did not have complications, respectively. Here, group status indicated diabetes status. The Charlson index was modified to subtract one unit from all patients with diabetes so that uncomplicated diabetes contributed nothing to the index, and diabetes with complications contributed one unit. Other comorbidities contributed to the index conventionally.

Continuous variables (age and modified Charlson) were modeled 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 three years.

Modeling 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 nonparametric 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 one represent a decrease in survival time; values greater than one represent prolonged survival.

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

Extensive sub-group 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 one, two, or three 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.[27]

Results

78,241 subjects treated with metformin and 12,222 treated with sulfonylurea 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 sulfonylurea monotherapy

Patients in the sulfonylurea group were older than those treated with metformin (mean age of 67.8 versus 61.2, respectively; $p<0.001$). Patients in the sulfonylurea 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 sulfonylurea group than in the metformin group (2.3 versus 1.9; $p<0.001$). There was also a higher percentage of people who had previously had cancer (14% versus 10%; $p<0.001$) and/or MACE (16% versus 10%; $p<0.001$) in the sulfonylurea group. Conversely, a higher percentage of people in the metformin group had previously been prescribed lipid-lowering therapy (50% versus 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 highest for those treated with metformin (32.4 kg/m^2 versus 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 versus 6; p<0.001). In addition, people in the metformin group were more likely to have had a previous MACE (10% versus 6%; p<0.001) and to have previously received prescriptions for lipid-lowering (50% versus 20%; p<0.001), antihypertensive (66% versus 39%; p<0.001), and/or anti-platelet medications (36% versus 19%; p<0.001) (Figure 1). Non-diabetic controls had less morbidity than cases.

Sulfonylurea monotherapy compared with matched control group

The Charlson index was higher for patients in the sulfonylurea group than for those in the control group (2.3 versus 0.8; p<0.001) as was the number of GP contacts in the year prior to index date (11.7 versus 6.5; p<0.001) (Table 1). In addition, people in the sulfonylurea group were more likely to have had a MACE (16% versus 9%; p<0.001) and to have previously received prescriptions for lipid-lowering (35% versus 17%; p<0.001), antihypertensive (64% versus 45%; p<0.001), and/or anti-platelet therapies (38% versus 25%; p<0.001) (Figure 1). Controls had far less morbidity than cases.

Numbers of deaths and crude event rates

In total there were 7,498 deaths, corresponding to an unadjusted event rate of 18.1 deaths per 1,000 person-years. Unadjusted event rates were highest in the sulfonylurea group and lowest in the metformin group (50.9 vs 14.1 per 1,000 person-years respectively; p<0.001) (Table 2). Similarly, unadjusted event rates were higher in sulfonylurea-treated patients compared with matched controls

(50.9 vs 28.7 per 1,000 person-years, respectively; p<0.001) but surprisingly were lower in those treated with metformin compared with matched controls (14.1 vs 15.2 per 1,000 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. Favoring metformin, these survival curves show that overall there was little discernible difference between metformin cases and non-diabetic controls (p=0.037; Figure 2a). This was not the case in those treated with sulfonylureas vs controls, where those treated with sulfonylureas had markedly reduced survival (p<0.001; Figure 2b). KM curves are also presented for patients aged 71–75 years: the most frequent age group for incident sulfonylurea initiation (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 vs controls (p<0.001) and reduced survival in the sulfonylurea group vs 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 sulfonylurea (Figure 3: final model).

These patterns remained generally consistent across a wide range of clinically relevant sub-groups (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 ≥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 seen with metformin when used in people with a prior history of each prophylactic treatment sub-group.

With regard to decreased survival in subjects with diabetes treated with sulfonylurea compared with metformin, those initiated at a younger age were at a particularly increased relative risk (≤53 years: STR=0.34; 95% CI 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 three years' continuous exposure to concomitant cardioprotective prophylaxis had no notable impact on relative STRs for metformin and sulfonylureas (Figure 3: model variants 1–3).

Discussion

We have shown that in a contemporary UK population, use of metformin for 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 sulfonylurea monotherapy was associated with increased mortality.

There remains considerable conjecture about the relative merits of metformin versus sulfonylureas.[4] Reported differences in safety generally favour metformin. If one accepts that there exists a difference in outcome between these two glucose-lowering medications favouring metformin, it has not yet been established whether this is due to the beneficial impact of metformin or a detrimental impact of sulfonylureas. 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 sulfonylureas had consistently reduced survival versus non-diabetic controls. There also remained a difference in outcome between those taking metformin and sulfonylurea, 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.[7,12,28] Importantly, these data not only demonstrate once again a better outcome with metformin relatively to sulfonylurea but 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 UKPDS, where obese patients receiving metformin had lower incidence of diabetes-related endpoints, including all-cause mortality when compared with intensive treatment with sulfonylureas or insulin.[29] A relative benefit of metformin has also been reported in various observational studies.[30,31,32,33,34,35,36,37] Mixed results were observed, however, in meta-analyses with metformin versus comparators or placebo. A significant cardiovascular benefit was observed in trials comparing metformin versus placebo/no therapy (odds ratio 0.79; p=0.031) but not in active-comparator trials (odds ratio 1.03; p=0.89).[38] Meta-analysis of currently available RCT data does not support the hypothesis that metformin lowers cancer risk by one-third. Eligible trials also showed no significant effect of metformin on all-cause mortality. However, limitations include heterogeneity, absent cancer data from two trials, and short follow-up, especially for mortality.[39] This included increased risk of cancer in both observational studies[40,41,42] and meta-analyses.[43,44]

Study limitations

Our study included a large number of patients 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.[45]

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 to the understandably high percentage of missing data in controls. This may impact on the comparison between metformin monotherapy and sulfonylurea 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 sulfonylureas 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.[46] Therefore, it is likely 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 likely to be receiving exercise and lifestyle interventions and close monitoring and control of blood pressure and cholesterol levels. Hypertension and hypercholesterolemia 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 whilst on this specific regimen. We remain unsure about how relative survival changes relative to those

without diabetes once glucose-lowering treatment is intensified, although metformin plus sulfonylurea combination therapy remains concerning[7,28]. Here, this was not the case for people treated with sulfonylurea monotherapy, where 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

Author contributions

Professor Currie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Currie, Bannister, Holden.

Acquisition of data: Currie, Jenkins-Jones.

Analysis and interpretation of data: Currie, Bannister, Holden, Morgan, Halcox, Schernthaner.

Drafting of the manuscript: Currie, Bannister, Holden.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Bannister, Holden.

Obtained funding: Currie.

Administrative, technical, and material support: Jenkins-Jones.

Study supervision: Currie.

Conflict of interest disclosures

C.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.

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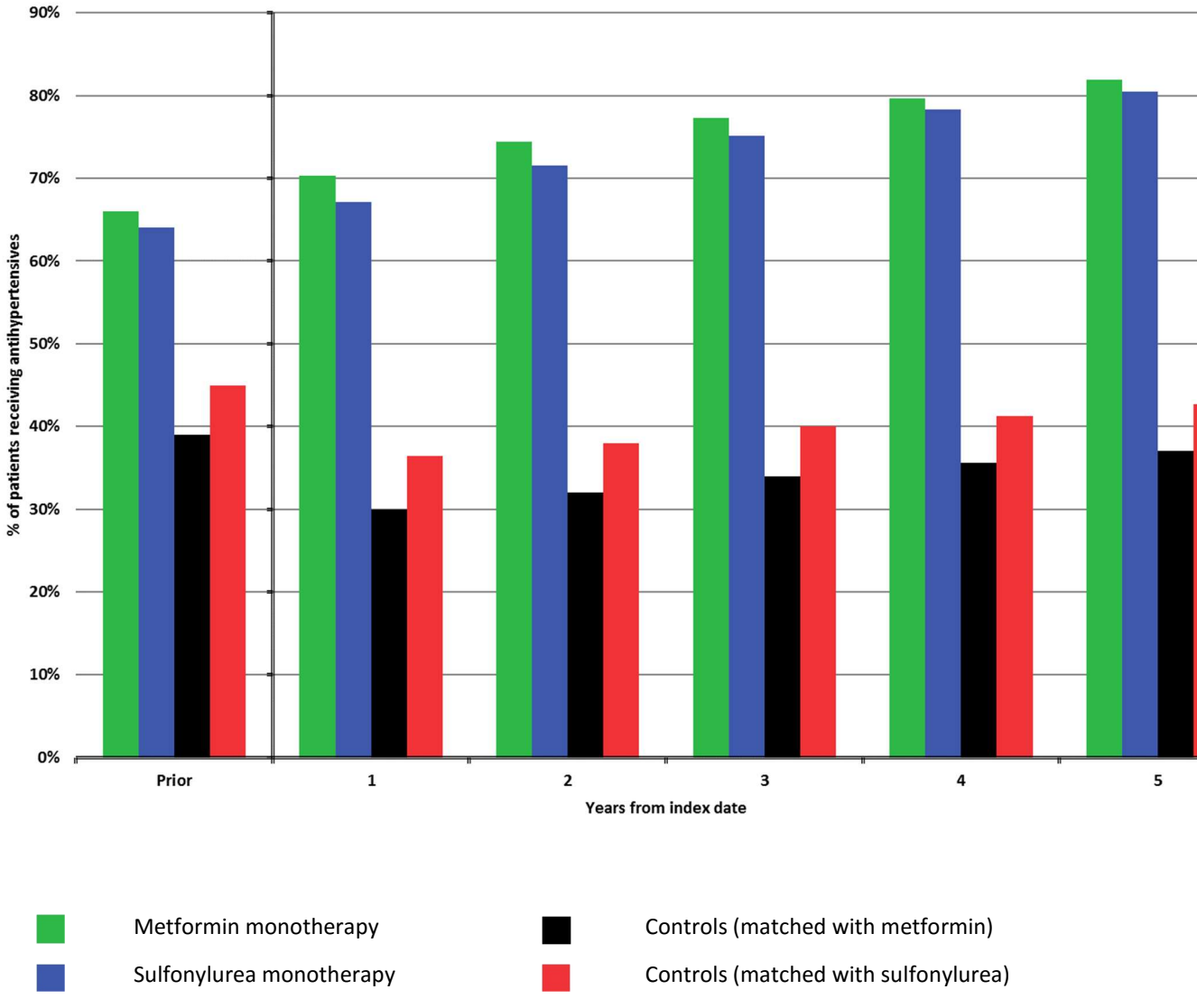
Role of the sponsors

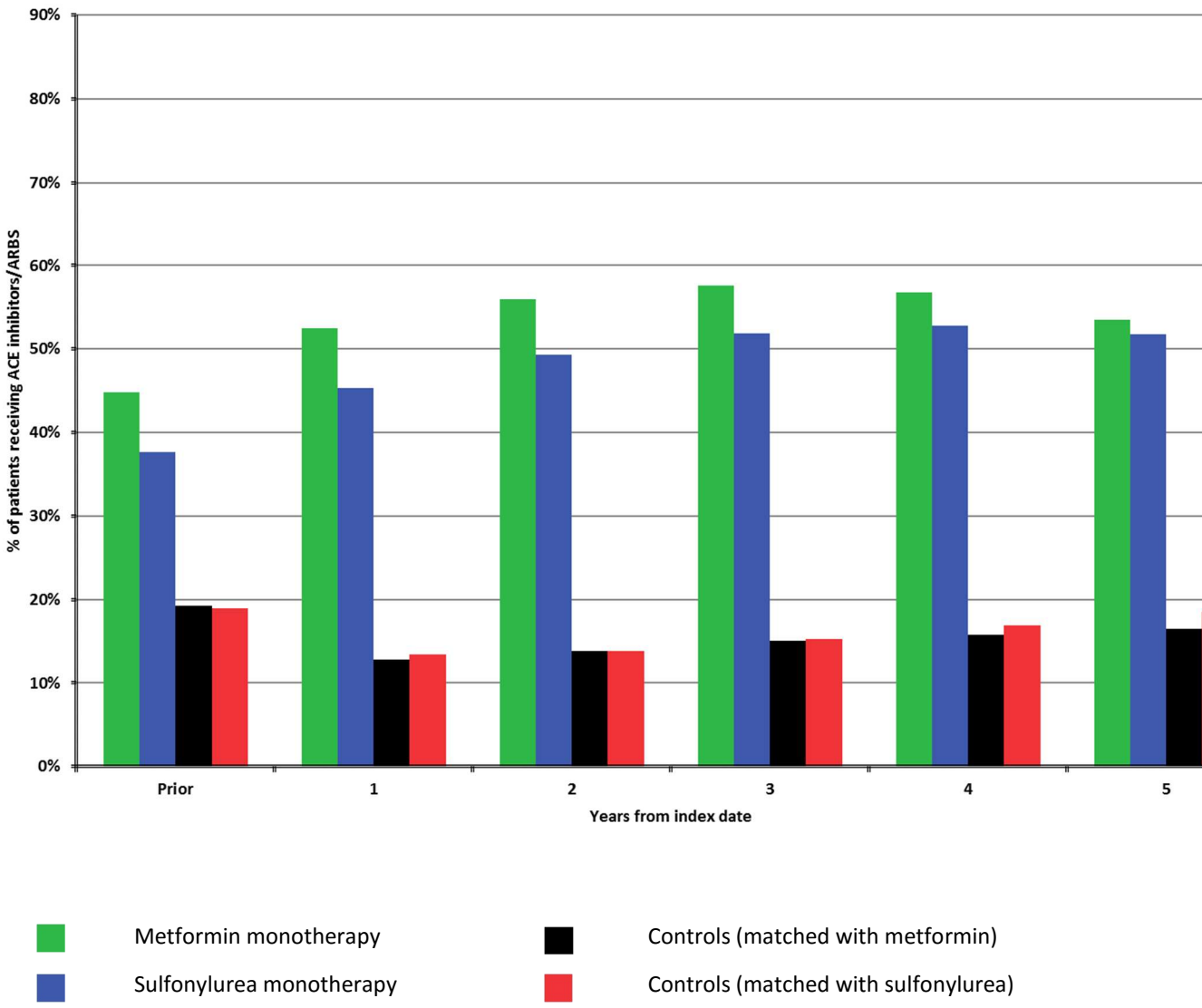
This article has been reviewed by AstraZeneca/Bristol-Myers Squibb for scientific content. The funding agencies had no other role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to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

Figure 1 | Use of cardiovascular prophylactic medications during the study follow-up

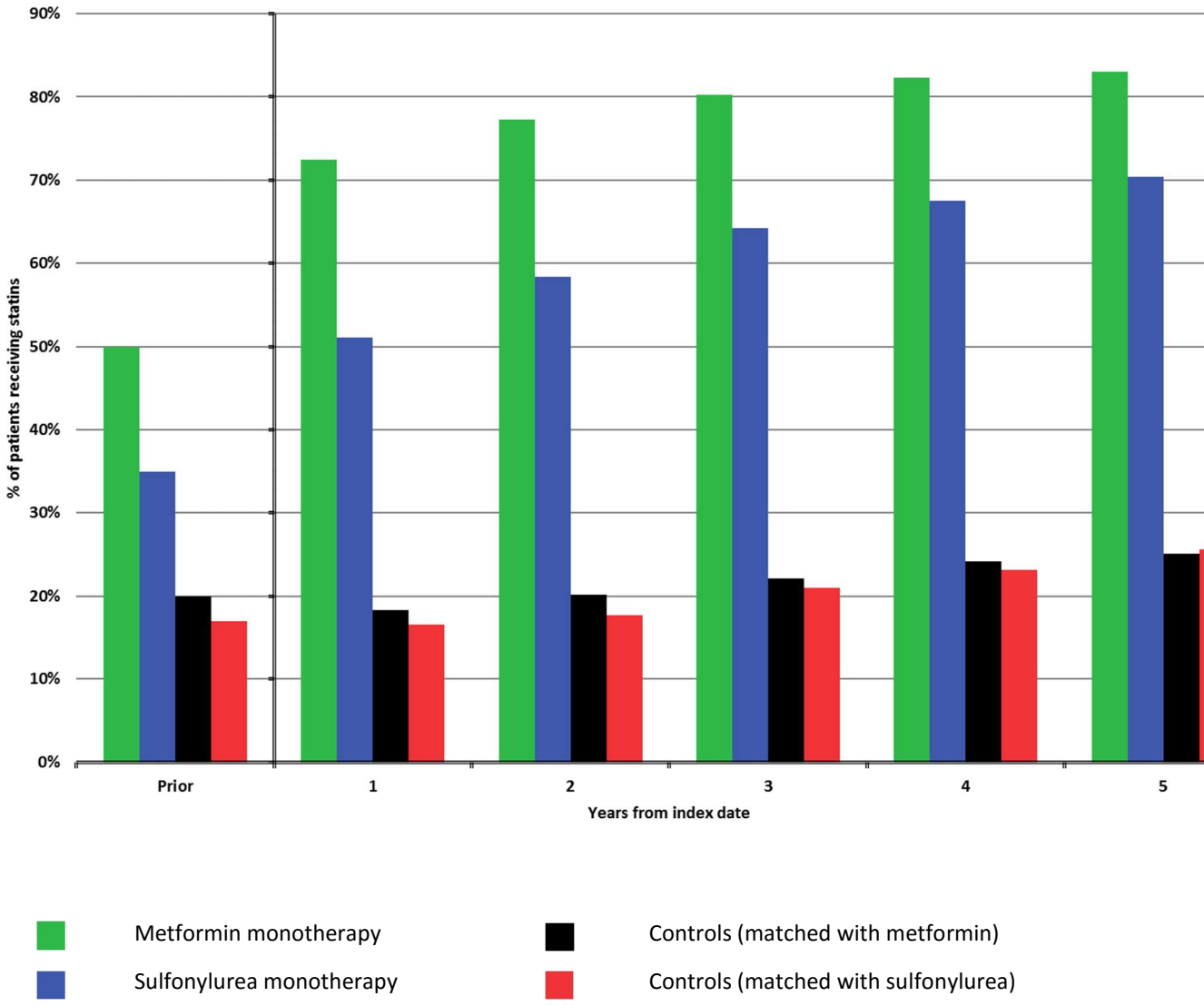
a) Antihypertensives



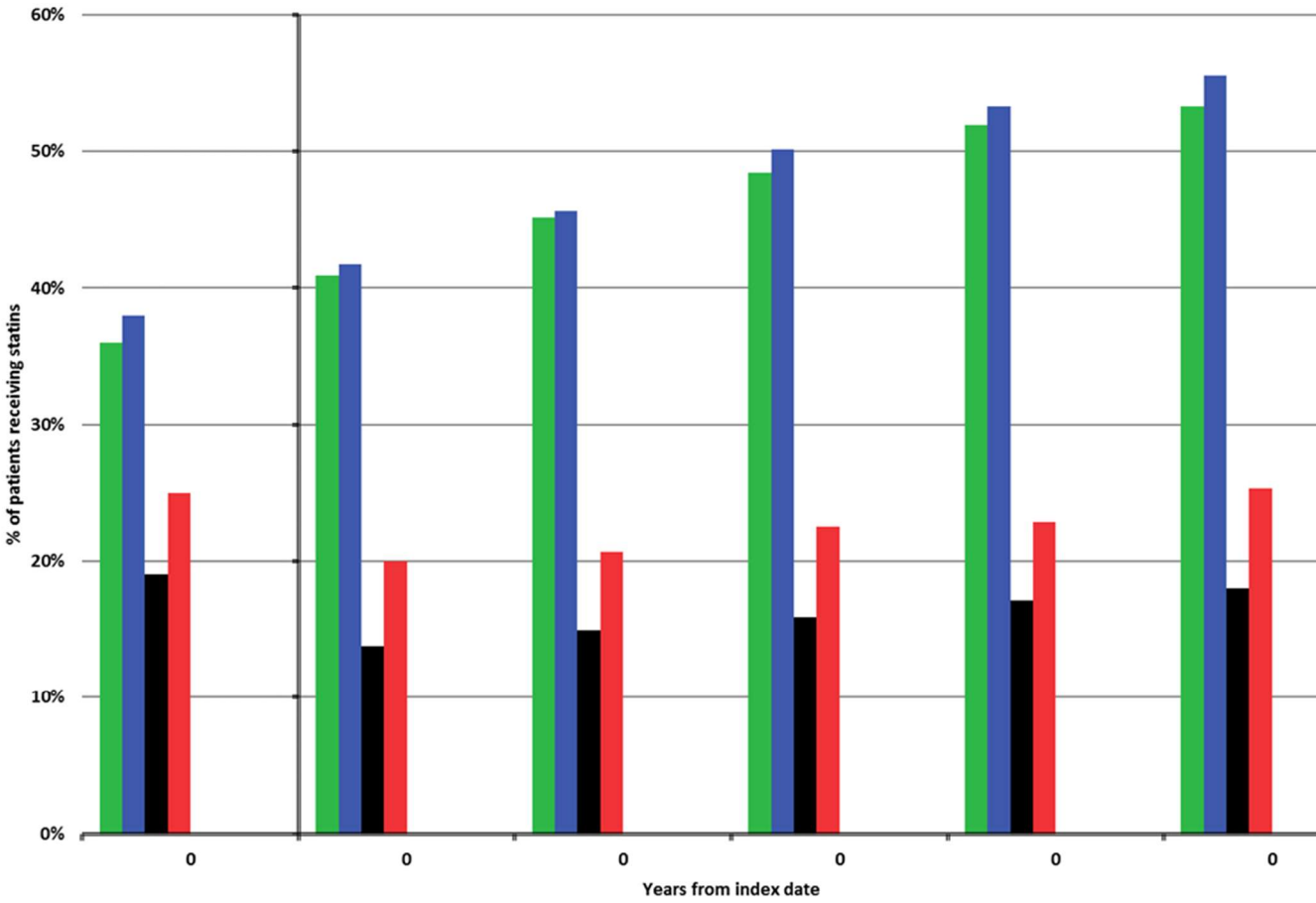
b) ACE inhibitors/Angiotensin II antagonists



c) Statins


90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% of patients receiving statins
Prior
1
2
3
4
5
Years from index date
Metformin monotherapy
Sulfonylurea monotherapy
Controls (matched with metformin)
Controls (matched with sulfonylurea)

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 yea

Figure 2 | Kaplan-Meier curves comparing a) metformin monotherapy with their matched control group without diabetes, b) sulfonylurea monotherapy with their matched control group without diabetes, and c) patients aged 71 to 75 years at baseline for all four cohorts (reported because it is the most frequent five-year interval in subjects exposed to sulfonylurea monotherapy)

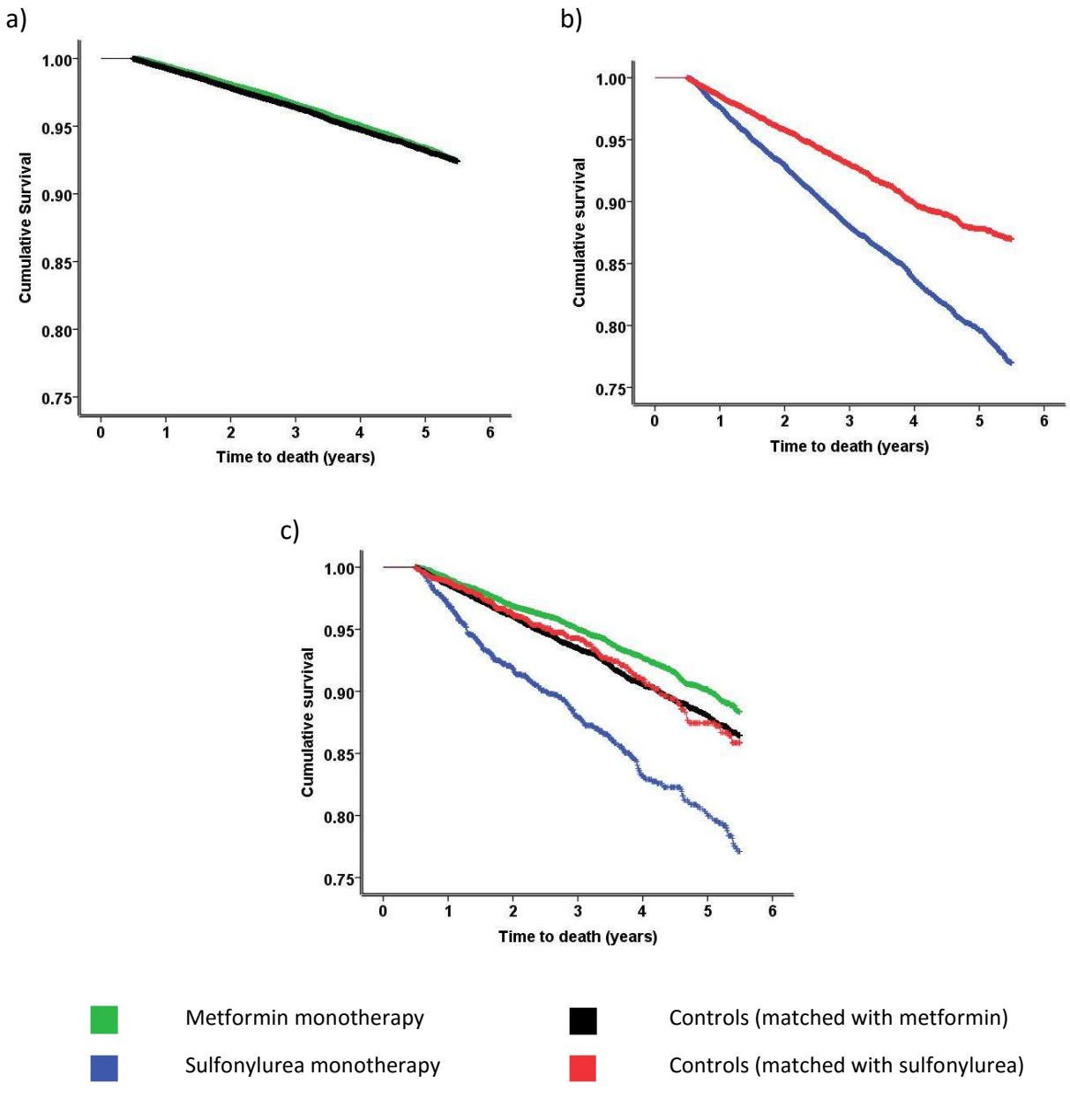
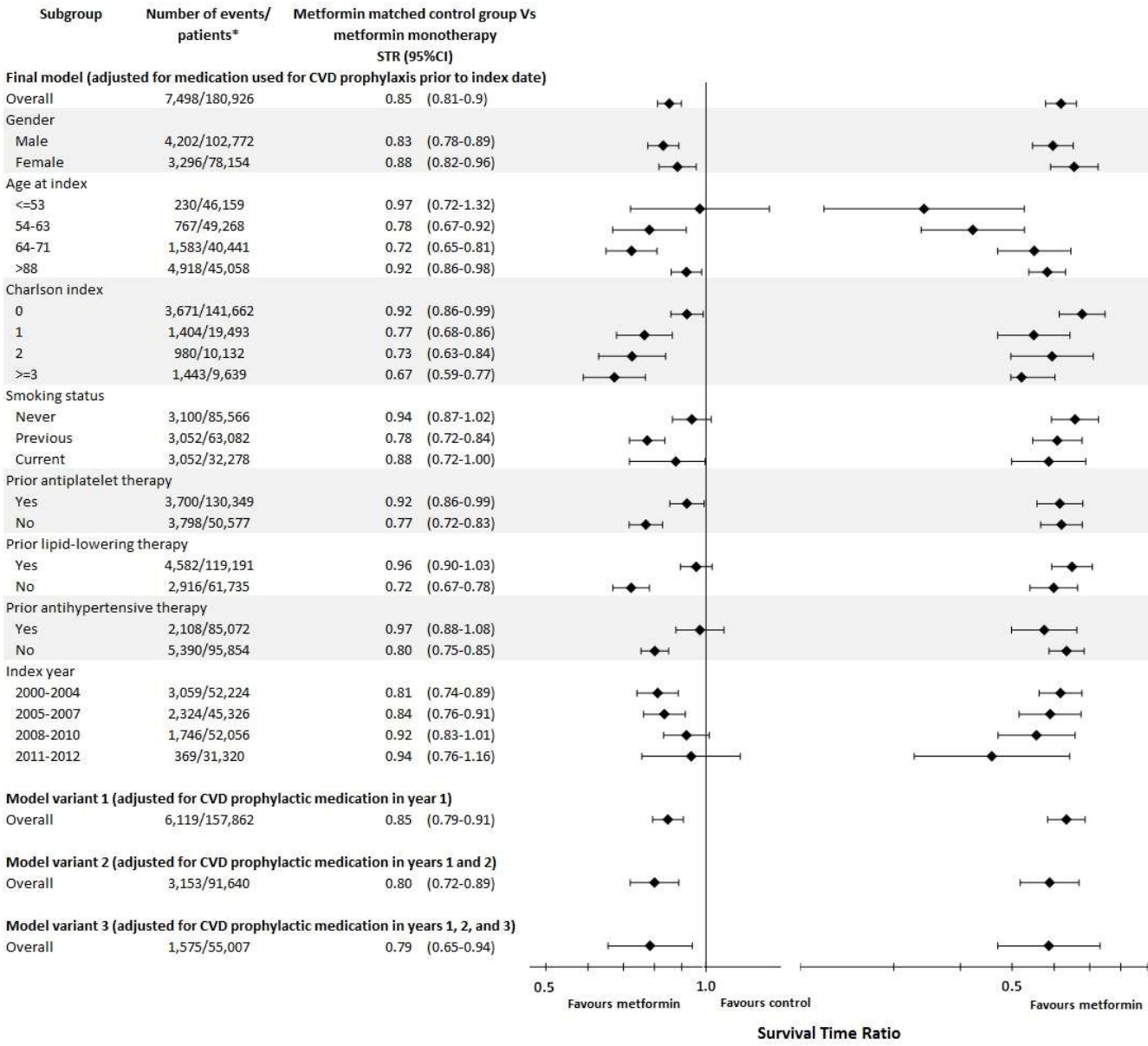


Figure 3 | Forest plot showing adjusted survival time ratios (STR), overall and for relevant diabetes-related subgrou
with metformin monotherapy versus non-diabetic controls (left-hand pane) and metformin monotherapy versus su



Notes:

Final model 1: Covariates were age, modified Charlson index, gender, smoking status, prior anti-platelet the
lowering therapy (yes/no), prior anti-hypertensive 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 w
received antihypertensive, lipid-lowering, or antiplatelet therapy in the first year of study, year of study ind
Patients censored within the first year were excluded.

Model variant 2: Covariates were age, modified Charlson index, gender, smoking status, a score based on w
received antihypertensive, lipid-lowering or antiplatelet therapy in the first two years of study, year of stud
arm. Patients were excluded if they were censored within the first two years and had received a different co
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 w
received antihypertensive, lipid-lowering or antiplatelet therapy in the first three years of study, year of stu
arm. Patients were excluded if they were censored within the first three years and had received a different
antihypertensive, antiplatelet, and lipid-lowering therapy in those years.

*The total number of patients in the complete model including patients in the control group matched with s
presented in this figure).

Table 1 | Baseline characteristics

Parameter	Metformin		Sulfonylurea		Control (matched with metformin)	
Number of people, n (%)	78,241	(43)	12,222	(7)	78,241	(43)
Age at index, mean (SD)	61.2	(12.7)	67.8	(12.8)	61.2	(12.7)
Males, n (%)	44,286	(57)	7,100	(58)	44,286	(57)
Smoking status						
Non-smoker, n(%)	36,781	(47)	6,002	(49)	36,781	(47)
Ex- smoker, n(%)	27,662	(35)	3,879	(32)	27,662	(35)
Current smoker, n(%)	13,798	(18)	2,341	(19)	13,798	(18)
HbA1c, mean (SD), %	8.6	(1.8)	9.2	(2.1)		
Systolic BP, mean (SD), mmHg	138.5	(16.8)	139.7	(19.5)	136.2	(16.6)
Total cholesterol, mean (SD), µmol/l	5.0	(1.2)	5.1	(1.3)	5.1	(1.1)
Serum creatinine, mean (SD), µmol/l	84.2	(18.9)	97.9	(33.8)	89.1	(25.8)
BMI, mean (SD), kgm2	32.4	(5.9)	27.1	(4.9)	27.4	(5.0)
Charlson index*, mean (SD)	1.9	(1.3)	2.3	(1.7)	0.7	(1.2)
GP contacts in the year prior, mean (SD)	11.3	(9.9)	11.7	(10.6)	6.0	(7.8)
Prior cancer, n (%)	7,553	(10)	1,698	(14)	7,550	(10)
Prior MACE, n (%)	8,162	(10)	1,995	(16)	5,058	(6)
Prior lipid-lowering therapy, n (%)	39,407	(50)	4,303	(35)	15,913	(20)
Prior antihypertensive therapy, n (%)	52,016	(66)	7,779	(64)	30,585	(39)
Prior antiplatelet therapy, n (%)	28,285	(36)	4,656	(38)	14,619	(19)

* Unmodified Charlson comorbidity index

Table 2 | Crude event rate per 1,000 person-years for all-cause mortality for patients with type 2 diabe
sulfonylurea monotherapy, metformin monotherapy, or their respective matched, non-diabe

	Parameter	Metformin	Sulfonylurea	Controls (matched with metform
Overall	Number of deaths	2,663	1,418	2,669
	Follow-up period (years)*	184,708	27,879	175,614
	Crude event rate	14.4	50.9	15.2
Age <60 years	Number of deaths	249	75	223
	Follow-up period (years)*	74,986	6,236	72,560
	Crude event rate	3.3	12.0	3.1
Age 60–70 years	Number of deaths	654	235	713
	Follow-up period (years)*	62,034	8,252	59,365
	Crude event rate	10.5	28.5	12.0
Age >70 years	Number of deaths	1,760	1,108	1,733
	Follow-up period (years)*	47,689	13,391	43,689
	Crude event rate	36.9	82.7	39.7

*Excluding the first 180 days following the index date

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