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Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study

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Aims The impact of insulin secretagogues (ISs) on long-term major clinical outcomes in type 2 diabetes remains unclear. We examined mortality and cardiovascular risk associated with all available ISs compared with metformin in a nationwide study.

Methods and results All Danish residents >20 years, initiating single-agent ISs or metformin between 1997 and 2006 were followed for up to 9 years (median 3.3 years) by individual-level linkage of nationwide registers. All-cause mortality, cardiovascular mortality, and the composite of myocardial infarction (MI), stroke, and cardiovascular mortality associated with individual ISs were investigated in patients with or without previous MI by multivariable Cox proportional-hazard analyses including propensity analyses. A total of 107 806 subjects were included, of whom 9607 had previous MI. Compared with metformin, glimepiride (hazard ratios and 95% confidence intervals): 1.32 (1.24–1.40), glibenclamide: 1.19 (1.11–1.28), glipizide: 1.27 (1.17–1.38), and tolbutamide: 1.28 (1.17–1.39) were associated with increased all-cause mortality in patients without previous MI. The corresponding results for patients with previous MI were as follows: glimepiride: 1.30 (1.11–1.44), glibenclamide: 1.47 (1.22–1.76), glipizide: 1.53 (1.23–1.89), and tolbutamide: 1.47 (1.17–1.84). Results for gliclazide [1.05 (0.94–1.16) and 0.90 (0.68–1.20)] and repaglinide and [0.97 (0.81–1.15) and 1.29 (0.86–1.94)] were not statistically different from metformin in both patients without and with previous MI, respectively. Results were similar for cardiovascular mortality and for the composite endpoint.

Conclusion Monotherapy with the most used ISs, including glimepiride, glibenclamide, glipizide, and tolbutamide, seems to be associated with increased mortality and cardiovascular risk compared with metformin. Gliclazide and repaglinide appear to be associated with a lower risk than other ISs.

Keywords Diabetes type 2 • Insulin secretagogues • Metformin • Mortality • Cardiovascular disease • Population

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Introduction

Despite the lack of definitive evidence concerning their long-term cardiovascular safety and efficacy, insulin secretagogues (ISs) are widely used in type 2 diabetes. In addition to lifestyle intervention, monotherapy with oral glucose-lowering agents is generally the initial treatment strategy in type 2 diabetes. In the context of the suggested legacy effect of glucose-lowering agents in the 10-year follow-up of the UK Prospective Diabetes Study (UKPDS), the impact of the initial treatment in type 2 diabetes may be crucial in terms of long-term risk.[1] Primarily on the basis of the results of the UKPDS metformin substudy, metformin is the primary drug of choice in type 2 diabetes.[2] Nevertheless, the long-term cardiovascular safety and efficacy of metformin compared with different ISs remains unclear. Despite the extensive use of ISs, few randomized studies have assessed long-term mortality outcomes related to monotherapy with individual ISs.[3,4] In The University Group Diabetes Program (UGDP), tolbutamide was associated with increased total and cardiovascular mortality, causing the premature discontinuation of the tolbutamide arm in the study.[4] On the contrary, the initial UKPDS study found no effect of other older sulphonylureas (SUs), i.e. chlorpropamide and glibenclamide on macrovascular disease complications or mortality .[3] Nevertheless, the results of the UGDP led to a change of product labelling in the USA, including a warning about the potential for increased cardiovascular mortality that persists for all SUs marketed in the USA. Few observational studies focused on long-term mortality associated with subsets of individual ISs, of which none included metformin as a comparator.[5–7] In particular, glibenclamide has been reported to increase overall and cardiovascular mortality when compared with other ISs such as gliclazide and glimepiride,[5,6] whereas glibenclamide was not associated with an increased mortality risk in a recent large observational study when compared with glimepiride.[7] Most studies of individual ISs as monotherapy focused on populations with a broad range of cardiovascular risk profiles only,[4–6] or included patients receiving combination therapy.[6]

To date, there are no reports comparing outcomes between all available ISs and metformin and with the enormous costs of adequately powered large randomized clinical trials, it is unlikely that such trials will ever be conducted. We therefore performed a nationwide study to compare the mortality and cardiovascular risk related to monotherapy with available ISs compared with metformin in patients with high and low cardiovascular risk as defined by previous myocardial infarction (MI).

Methods

Data sources

All residents in Denmark are assigned a unique, permanent civil registration number enabling individual-level cross-linkage of nationwide administrative registries. The Danish Registry of Medicinal Product Statistics (National Prescription Registry) keeps information about all dispensed drug prescriptions from pharmacies since 1995, registered according to the international Anatomical Therapeutic Chemical (ATC) system. All hospitalizations since 1978 are registered in the National Patient Registry[8] At discharge, each hospitalization is registered with one primary diagnosis and, if appropriate, secondary diagnoses according to the International Classification of Diseases (ICD)—the 8th revision (ICD-8) before 1994, and the 10th revision (ICD-10) from 1994 onwards. Information about causes of death is recorded in the National Causes of Death Register.

Study population

The study population comprised all individuals aged 20 years and above who initiated single-agent treatment with an IS or metformin between 1997 and 2006.

Glucose-lowering therapy

Claimed prescriptions of monotherapy with glimepiride, gliclazide, glibenclamide, glipizide, tolbutamide, repaglinide, or metformin were registered within consecutive 3-month intervals. If no prescriptions were registered for a particular interval, we estimated the available medication from that available in up to three previous 3-month periods to take account of potential stockpiling of pills. Patients receiving insulin monotherapy ($n = 8783$) and combination therapy ($n = 3434$) only were excluded.

Prior myocardial infarction

Prior MI was identified as a hospitalization with MI as the primary or secondary diagnosis (ICD-10 codes I21–I22 and ICD-8 code 410) up to 19 years before the study inclusion.

Co-morbidity

Co-morbidity was assessed by registration of hospital admissions 1 year before the inclusion date. Diagnoses listed in *Table 1* and the Charlson co-morbidity index, based on ICD-10 codes, were used.[9]

Concomitant medical treatment (Anatomical Therapeutic Chemical)

Medical treatment with aspirin (ATC code: MB01AC06), statins (C10AA), beta-blockers (C07), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (RASi) (C09), nitrates (C01D), calcium channel blockers (C08), and other antihypertensive drugs (C02) drugs were registered as prescription claims up to 6 months before the inclusion date and during follow-up.

Outcome measures

Outcome measures were: all-cause mortality, cardiovascular death (I00–I99), and the composite of MI (I21–I22), stroke (I61–I64), or cardiovascular death.

Statistical analysis

Time-dependent, multivariable Cox proportional-hazard regression models were constructed for the full population of patients receiving monotherapy with ISs or metformin to estimate differences among risk groups with patient age as the underlying time variable. All Cox models were censored for deaths from causes unrelated to the endpoint of interest. Due to the time-dependent analysis, patients were not considered at risk in a given treatment group before initiating the treatment and they left the treatment group if the treatment was modified or terminated. With this approach, any patient could belong to any treatment group but only during exposure to treatment. All models were adjusted for age, sex, calendar year of initiation of glucose-lowering pharmacotherapy, gross income, co-morbidity, and time-dependent adjustment for cardiovascular medical treatment during follow-up.

In addition, matched samples of the individual ISs and metformin were constructed based on the propensity to receive metformin, quantified by

Table 1 Baseline characteristics

	Metformin	Glimepiride	Gliclazide	Glibenclamide	Glipizide	Tolbutamide	Repaglinide	*P*-value
No previous myocardial infarction ($n = 98\,199$)								
Frequency (%)[a]	43 340 (54.3)	36 313 (37.0)	5926 (6.0)	12 495 (12.7)	6965 (7.1)	5335 (5.4)	2513 (2.6)	<0.001
1997–99 ($n = 30\,764$)[b]	4561 (14.8)	8310 (27.0)	1568 (5.1)	7796 (25.3)	4128 (13.7)	3257 (10.6)	747 (2.4)	<0.001
2000–02 ($n = 36\,512$)[b]	13 624 (37.3)	13 748 (37.7)	1912 (5.2)	3014 (8.2)	1594 (4.3)	1302 (3.6)	1233 (3.4)	<0.001
2003–05 ($n = 46\,153$)[b]	25 155 (50.1)	14 255 (30.9)	2446 (5.3)	1685 (3.7)	1243 (2.6)	776 (1.7)	533 (1.2)	<0.001
Age (years)[c]	52.5 ± 14.0	60.9 ± 13.3	60.0 ± 13.2	63.2 ± 13.7	63.0 ± 13.5	64.4 ± 13.5	57.9 ± 12.6	<0.001
Men, frequency (%)	22 067 (50.9)	20 071 (55.3)	3345 (56.5)	6798 (54.4)	3771 (54.1)	2872 (53.8)	1407 (56.0)	<0.001
Person (years)	75 957	75 742	11 730	29 038	16 130	12 337	4925	<0.001
Treatment duration (years)[c]	1.76 ± 1.58	2.11 ± 1.75	2.10 ± 1.75	2.35 ± 2.08	2.35 ± 2.08	2.36 ± 2.13	1.97 ± 1.76	<0.001
Co-morbidity[d]								
Congestive heart failure	478 (1.1)	894 (2.5)	96 (1.6)	299 (2.4)	168 (2.4)	140 (2.6)	18 (0.7)	<0.001
Cardiac dysrhythmia	715 (1.6)	1176 (3.2)	125 (2.1)	379 (3.0)	226 (3.2)	152 (2.8)	38 (1.5)	<0.001
Peripheral vascular disease	128 (0.3)	228 (0.6)	31 (0.5)	87 (0.7)	63 (0.9)	47 (0.9)	14 (0.6)	<0.001
Cerebrovascular disease	692 (1.6)	1013 (2.8)	81 (1.4)	348 (2.9)	197 (2.8)	177 (3.3)	30 (1.2)	<0.001
Chronic pulmonary disease	659 (1.5)	959 (2.6)	92 (1.6)	304 (2.4)	197 (2.8)	141 (2.6)	29 (1.2)	<0.001
Peptic ulcer disease	161 (0.3)	291 (0.8)	31 (0.5)	93 (0.7)	81 (1.1)	57 (1.1)	14 (0.6)	<0.001
No previous myocardial infarction								
Liver disease	114 (0.3)	229 (0.6)	27 (0.5)	66 (0.5)	45 (0.6)	59 (1.1)	7 (0.3)	<0.001
Chronic renal failure	22 (0.1)	80 (0.2)	3 (0.1)	25 (0.2)	20 (0.3)	13 (0.2)	3 (0.1)	<0.001
Acute renal failure	24 (0.1)	62 (0.2)	8 (0.1)	15 (0.1)	12 (0.2)	10 (0.2)	2 (0.1)	<0.001
Shock	84 (0.2)	175 (0.5)	14 (0.2)	39 (0.3)	25 (0.4)	21 (0.4)	3 (0.1)	<0.001
Malignancy	432 (1.0)	907 (2.5)	112 (1.9)	315 (2.5)	170 (2.4)	136 (2.5)	46 (1.8)	<0.001
Charlson index	0.06 ± 0.3	0.14 ± 0.5	0.09 ± 0.4	0.13 ± 0.5	0.14 ± 0.5	0.14 ± 0.5	0.08 ± 0.4	<0.001
Concomitant cardiovascular medication, frequency (%)[d]								
Aspirin	12 122 (28.0)	11 321 (31.2)	1770 (29.9)	3210 (25.7)	1827 (26.2)	1403 (26.3)	665 (26.5)	<0.001
Statins	11 296 (26.1)	8348 (23.0)	1280 (21.6)	1735 (13.9)	1145 (16.4)	743 (14.0)	617 (24.6)	<0.001
RASi	21 943 (50.6)	17 346 (47.8)	2754 (46.5)	4743 (54.0)	2767 (39.7)	1885 (35.3)	1113 (44.3)	<0.001
Beta-blockers	12 090 (27.9)	10 692 (29.4)	1713 (28.9)	3007 (24.1)	1729 (24.8)	1192 (22.3)	623 (24.8)	<0.001
Nitrates	4491 (10.4)	5372 (14.8)	800 (13.5)	2469 (19.8)	1043 (15.0)	721 (13.5)	290 (11.4)	<0.001
Calcium blockers	11 849 (27.3)	10 666 (29.4)	1714 (28.9)	3213 (25.7)	1903 (29.3)	1432 (26.8)	672 (26.7)	<0.001
Other antihypertensives	1699 (3.9)	1460 (4.0)	289 (4.9)	362 (2.9)	218 (3.1)	165 (3.1)	97 (3.9)	<0.001

Previous myocardial infarction ($n = 9607$)								
Frequency (%)[a]	2906 (30.2)	3894 (43.3)	517 (6.9)	1168 (12.2)	660 (7.3)	501 (5.6)	186 (2.1)	<0.001
1997–99 ($n = 2614$)[b]	279 (10.7)	754 (28.8)	133 (5.1)	691 (26.4)	376 (14.4)	306 (11.7)	50 (1.9)	<0.001
2000–02 ($n = 3221$)[b]	921 (28.6)	1448 (45.0)	163 (5.1)	303 (9.4)	162 (5.0)	121 (3.8)	95 (2.9)	<0.001
2003–05 ($n = 4041$)[b]	1706 (42.2)	1692 (41.9)	221 (5.5)	174 (4.3)	122 (3.0)	74 (1.8)	41 (1.0)	<0.001
Age (years)[c]	65.8 ± 10.7	70.9 ± 11.0	70.5 ± 10.9	70.9 ± 11.0	70.5 ± 10.4	71.2 ± 114	68.2 ± 10.3	<0.001
Men, frequency (%)	2125 (73.1)	2738 (70.3)	358 (69.3)	817 (70.0)	460 (69.7)	325 (64.9)	131 (70.4)	<0.001
Person (years)	5189	8261	1080	2917	1523	1150	1412	<0.001
Treatment duration (years)[c]	1.67 ± 1.48	1.98 ± 1.60	1.96 ± 1.78	2.28 ± 1.96	2.19 ± 1.90	2.12 ± 1.98	2.04 ± 1.76	<0.001
Co-morbidity, frequency (%)[d]								
Congestive heart failure	141 (4.9)	430 (11.0)	44 (8.5)	139 (11.9)	67 (10.2)	66 (13.2)	15 (8.1)	<0.001
Cardiac dysrhythmia	138 (4.8)	340 (8.7)	27 (5.2)	101 (7.4)	50 (7.6)	44 (8.9)	13 (7.0)	<0.001
Peripheral vascular disease	21 (0.7)	63 (1.6)	6 (1.2)	24 (1.7)	12 (1.8)	12 (2.4)	0	<0.001
Cerebrovascular disease	69 (2.4)	170 (4.4)	17 (3.2)	42 (3.6)	28 (4.2)	24 (4.8)	6 (3.2)	<0.001
Chronic pulmonary disease	93 (3.2)	209 (5.4)	27 (5.2)	67 (5.7)	34 (5.2)	29 (5.8)	7 (3.8)	<0.001
Peptic ulcer disease	24 (0.8)	48 (1.2)	7 (1.4)	25 (2.1)	8 (1.2)	13 (2.6)	1 (0.5)	<0.001
Liver disease	4 (0.1)	8 (0.2)	0	6 (0.5)	4 (0.6)	0	1 (0.5)	<0.001
Previous myocardial infarction								
Chronic renal failure	3 (0.1)	33 (0.9)	0	13 (1.1)	5 (0.7)	5 (1.0)	1 (0.5)	<0.001
Acute renal failure	5 (0.2)	20 (0.5)	2 (0.4)	3 (0.3)	2 (0.3)	4 (0.8)	1 (0.5)	<0.001
Shock	7 (0.2)	34 (0.9)	2 (0.4)	5 (0.4)	4 (0.6)	6 (1.2)	1 (0.5)	<0.001
Malignancy	29 (1.0)	73 (1.9)	6 (1.2)	28 (2.4)	12 (1.8)	16 (3.2)	3 (1.6)	<0.001
Charlson index	0.23 ± 0.6	0.40 ± 0.8	0.28 ± 0.6	0.41 ± 0.7	0.35 ± 0.7	0.42 ± 0.8	0.28 ± 0.6	<0.001
Concomitant cardiovascular medication, frequency (%)								
Aspirin	2120 (73.0)	2682 (68.9)	353 (68.3)	699 (59.9)	413 (62.6)	290 (57.9)	131 (70.4)	<0.001
Statins	1909 (65.7)	2054 (52.8)	279 (54.0)	457 (39.1)	256 (38.8)	188 (37.5)	105 (56.5)	<0.001
RASi	2085 (71.8)	2699 (69.3)	342 (66.2)	673 (57.6)	408 (61.8)	281 (56.1)	121 (65.1)	<0.001
Beta-blockers	2171 (74.7)	2826 (72.6)	362 (70.0)	713 (61.0)	416 (63.0)	278 (55.5)	123 (66.1)	<0.001
Nitrates	1850 (63.7)	2615 (67.2)	357 (69.1)	754 (64.6)	408 (61.8)	326 (65.1)	125 (67.2)	<0.001
Calcium blockers	1545 (53.2)	2095 (53.8)	286 (55.3)	570 (48.8)	313 (47.4)	255 (50.9)	115(61.8)	<0.001
Other antihypertensives	138 (4.9)	176 (4.5)	23 (4.5)	49 (4.2)	27 (4.1)	15 (3.0)	11 (5.9)	<0.001

[a]Percentages of the total population.
[b]Percentages of all patients in the respective time period.
[c]Mean ± standard deviation.
[d]Percentages of all patients in the respective treatment group.

logistic regression using the greedy match algorithm conditional on baseline variables [gmatch macro for SAS, © Mayo Clinic College of Medicine http://ndc.mayo.edu/mayo/research/biostat/upload/gmatch.sas (access ed 15 October 2009]. C-statistics ranged from 0.71 to 0.87 indicating good discriminative power.

Cumulative mortality was estimated by adjusted Kaplan–Meyer plots for the first (baseline) monotherapy treatment only. For all analyses, a two-sided *P*-value of <0.05 was considered significant.

All statistical calculations were performed using the SAS statistical software package version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

On 1 January 1997, there were 4 107 126 inhabitants in Denmark aged >20 years without previous use of glucose-lowering medications; of these 107 806(2.6%) initiated monotherapy with ISs or metformin [9607 (8.9%) with previous MI] and were included. During the observation period, most patients (77%) received only one IS or metformin as monotherapy. In 22 and 23% of patients without and with previous MI, respectively, the treatment regimen changed during follow-up.

Baseline characteristics are summarized in *Table 1* and in Supplementary material online, *Table S1* for propensity analyses. Since patients were able to shift to monotherapy during follow-up, the sum of individuals in the different monotherapy groups adds up to more than the total study population. A total of 75 354 patients without previous MI and 6448 with previous MI entered the propensity analysis (Supplementary material online, *Table S1*). Event rates are accessible in Supplementary material online, *Table S2*. A total of 76 473 (70.9%) patients received ISs, with glimepiride [$n=$ 40 207(52.6%)] being the most used agent (*Table 1*). On average, lower age and co-morbidities were found in patients treated with metformin and repaglinide, while those treated with gliclazide had lower co-morbidity. Owing to interactions with previous MI ($P<$ 0.01), results were presented for patients with and without previous MI separately. Since interactions between individual ISs varied across different endpoints and risk groups, subgrouping of ISs was not feasible.

All-cause death

Multivariable and propensity-matched analyses revealed a consistent increase in all-cause deaths associated with glimepiride, glibenclamide, glipizide, and tolbutamide compared with metformin in patients with and without previous MI (*Figures 1* and *2*, *Tables 2* and *3*, and Supplementary material online, *Table S2*). Results for

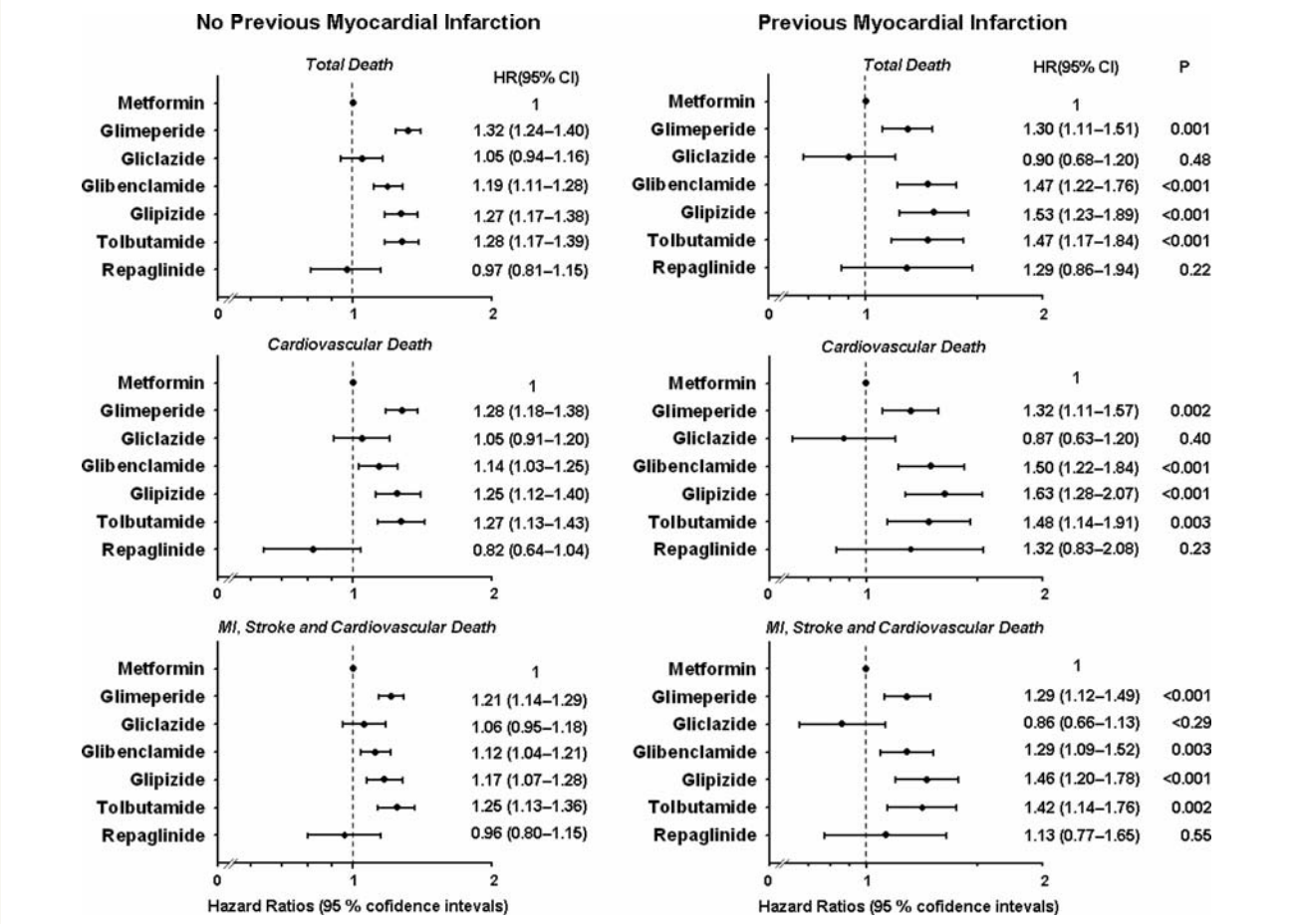

Figure 1 Hazard ratios (95% CI) for different endpoints in relation to monotherapies with different glucose-lowering agents according to previous myocardial infarction.

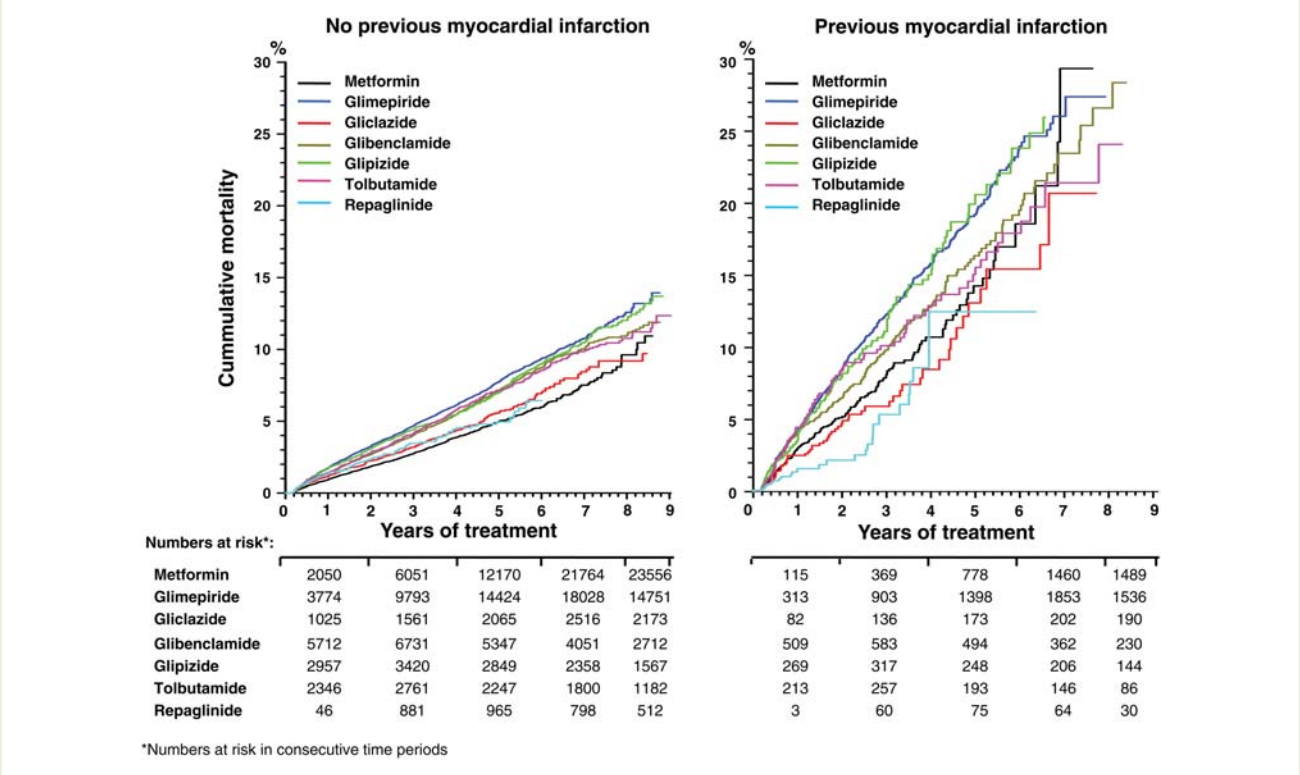

Figure 2 Multivariable adjusted Kaplan–Meier plots demonstrating the cumulative mortality for the first glucose-lowering treatment course only according to previous myocardial infarction.

gliclazide and repaglinide were not statistically different from metformin. Gliclazide was associated with a significantly lower risk than other SUs ($P < 0.001$ for all comparisons), whereas the risk with this agent was not statistically different from that of repaglinide ($P = 0.4–0.5$) in patients with and without previous MI, respectively.

Cardiovascular death

Similar results to those observed for all-cause death were obtained for cardiovascular death in all analyses (*Figures 1* and *2*, *Tables 2 and 3*, and Supplementary material online, *Table S2* and *Figures 1* and *2*).

Myocardial infarction, stroke, or cardiovascular death

Results for the combined endpoint were similar to those for cardiovascular death in most analyses (*Figures 1* and *2*, *Tables 2 and 3*, and Supplementary material online, *Table S2*). In the propensity analyses of patients without previous MI, gliclazide showed a small, but significant increase in risk for the combined endpoint compared with metformin monotherapy (*Table 3*).

Additional analyses

Similar results as those presented were obtained in sub-studies of patients who did not change therapy during follow-up, in studies of the initial (baseline) monotherapy treatment course alone, and in studies where monotherapy was ensured for at least 3 months prior to an event.

Discussion

This nationwide study showed that compared with metformin, increased mortality and cardiovascular risk was associated with most first- and second-generation SUs (glimepiride, glibenclamide, glipizide, and tolbutamide). This study is the first, to our knowledge, to analyse major cardiovascular endpoints with all currently approved ISs monotherapies in a nationwide setting.

In accordance with the UGDP,[4] we demonstrated an increased risk with tolbutamide in patients with and without previous MI. Other retrospective cohort studies supported our results by indicating increased total[5,6] and cardiovascular mortality[5] associated with glibenclamide compared with glimepiride,[5] and gliclazide.[5,6] In contrast, no differences in all-cause mortality were observed for glibenclamide, glipizide, and glimepiride in a recent large observational study, although a non-significant trend towards increased mortality was found for glibenclamide and glipizide compared with glimepiride in patients with documented coronary artery disease (CAD).[7] Supporting our results was the demonstration of a dose-dependent increase in all-cause mortality with first-generation SUs and glibenclamide in contrast to metformin.[10] Furthermore, in the DIGAMI study, diabetes patients with acute MI were allocated to glucose-insulin infusion followed by

Table 2 Frequencies of events

	Events no (%)		
	All-cause death	Cardiovascular death	MI, stroke, or cardiovascular death
No previous myocardial infarction			
Metformin	1548 (3.6)	827 (1.9)	1646 (3.8)
Glimepiride	4081 (11.2)	2251 (6.2)	3517 (9.7)
Gliclazide	442 (7.5)	256 (4.3)	440 (7.4)
Glibenclamide	1546 (12.4)	876 (7.0)	1376 (11.0)
Glipizide	947 (13.6)	559 (8.0)	820 (11.8)
Tolbutamide	794 (14.8)	457 (8.6)	687 (12.8)
Repaglinide	147 (5.9)	69 (2.8)	138 (5.5)
Total	9505 (9.7)	5295 (5.4)	8624 (8.8)
Previous myocardial infarction			
Metformin	213 (7.3)	169 (5.8)	245 (8.4)
Glimepiride	737 (18.9)	591 (15.2)	751 (19.3)
Gliclazide	63 (12.2)	48 (9.3)	63 (12.2)
Glibenclamide	265 (22.2)	207 (17.7)	267 (22.9)
Glipizide	141 (21.4)	115 (17.4)	154 (23.3)
Tolbutamide	120 (24.0)	94 (18.8)	114 (22.8)
Repaglinide	26 (14.0)	21 (11.3)	28 (15.1)
Total	1565 (16.3)	1245 (13.0)	1622 (16.9)

subcutaneous insulin treatment or conventional therapy for 12 months.[11] Interestingly, a more favourable effect was evident in patients with an MI and not previously treated with insulin, who by virtue of study assignment to insulin treatment theoretically avoided any possible toxicity of SUs.[11] Conversely, the UKPDS,[3] and A Diabetes Outcome Progression Trial (ADOPT),[12] did not find glibenclamide to be associated with increased risk, although neither of these studies was designed or powered for cardiovascular events. The UKPDS is the only randomized trial focusing on patients at low risk,[3] and mortality studies with individual ISs in patients at increased cardiovascular risk are sparce.[4,7,13] In a recent Danish regional registry study of MI patients, however, glibenclamide, glipizide, and tolbutamide were associated with increased mortality within 1 year, whereas glimepiride and gliclazide showed lower risk.[13]

SUs and, in particular, glibenclamide have been linked to interference with the protective effect of ischaemic pre-conditioning of the heart, by binding to cardiac sulphonylurea 2A receptors.[14] Indeed, in patients with established ischaemic heart disease, glibenclamide but not glimepiride and gliclazide may diminish myocardial pre-conditioning.[15,16] Our findings of increased risk with most ISs, including glimepiride, may therefore suggest the contribution of mechanisms other than interference with ischaemic pre-conditioning. A protective effect of metformin and possibly of gliclazide and repaglinide (rather than a detrimental effect of other ISs) could be hypothesized, but the precise relationships and mechanisms underlying these effects await further studies. Since the UKPDS in 1998, evidence has definitely evolved

Table 3 Propensity analyses demonstrating hazard ratios (95% confidence intervals) for different endpoints in relation to monotherapies with different glucose-lowering agents according to previous myocardial infraction

	All-cause death		Cardiovascular death		MI, stroke, or cardiovascular death	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
No previous myocardial infarction						
Metformin[a]	1		1		1	
Glimepiride ($n = 22\,340$)	1.27 (1.18–1.36)	<0.001	1.26 (1.14–1.39)	0.001	1.29 (1.20–1.39)	<0.001
Gliclazide ($n = 4739$)	1.05 (0.91–1.21)	0.50	1.15 (0.95–1.39)	0.15	1.18 (1.02–1.36)	0.03
Glibenclamide ($n = 7412$)	1.13 (1.02–1.25)	0.03	1.13 (0.98–1.31)	0.10	1.16 (1.04–1.29)	0.009
Glipizide ($n = 4981$)	1.16 (1.03–1.30)	0.02	1.24 (1.06–1.46)	0.009	1.24 (1.09–1.40)	0.001
Tolbutamide ($n = 3879$)	1.12 (0.99–1.26)	0.08	1.16 (0.98–1.36)	0.02	1.17 (1.03–1.33)	<0.001
Repaglinide ($n = 1931$)	1.00 (0.78–1.29)	0.98	1.03 (0.37–2.83)	0.96	0.87 (0.49–1.54)	0.87
Previous myocardial infarction						
Metformin[a]	1		1		1	
Glimepiride ($n = 1952$)	1.30 (1.08–1.57)	0.007	1.29 (1.04–1.60)	0.02	1.22 (1.30–1.46)	0.03
Gliclazide ($n = 447$)	0.85 (0.61–1.17)	0.32	0.75 (0.52–1.08)	0.87	0.71 (0.52–1.99)	0.04
Glibenclamide ($n = 594$)	1.34 (1.03–1.75)	0.031	1.40 (1.04–1.88)	0.03	1.10 (0.85–1.41)	0.50
Glipizide ($n = 515$)	1.58 (1.19–2.09)	0.002	1.53 (1.06–2.21)	0.02	1.54 (1.12–2.10)	0.008
Tolbutamide ($n = 329$)	1.46 (1.06–2.01)	0.02	1.85 (1.67–2.92)	0.009	1.44 (1.01–2.05)	0.04
Repaglinide ($n = 163$)	1.15 (0.68–1.98)	0.91	1.10 (0.61–2.00)	0.75	1.10 (0.67–1.82)	0.69

[a]Patients in each group of ISs were matched on an equal number of patents receiving metformin.

indicating a safer cardiovascular profile for metformin than for other oral glucose-lowering agents.[17] Moreover, there have been surprisingly few reports on lactate acidosis, the potentially most severe complication with metformin.[18] Accordingly, in 2007, the US product label was modified to remove the heart failure contraindication.

Recent studies have reported reduced cardiac ventricular mass,[19] and reduced cardiovascular and cancer mortality in patients with type 2 diabetes treated with gliclazide when compared with glibenclamide.[6] Repaglinide predominantly targets the post-prandial blood glucose rise, which is thought to be associated with increased cardiovascular risk.[20] Furthermore, less progression of the carotid intima-media thickness was reported in patients receiving repaglinide compared with glimepiride.[21] Overall, our study adds to these smaller studies by demonstrating that treatment with gliclazide and repaglinide may be associated with improved cardiovascular outcomes. Due to lower numbers of these ISs, however, we cannot exclude that the lack of statistical significance for gliclazide and repaglinide could be due to lack of study power. Interestingly, in the Action in Diabetes and Vascular Disease (ADVANCE) study all patients were assigned to gliclazide in the intensive treatment arm,[22] which could explain the lower cardiovascular risk in these patients as opposed to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, where other glucose-lowering agents were predominantly used.[23]

The present study has several strengths. Owing to the nationwide setting, we avoided selection bias related to sex, age, income, willingness to participate, participation in the labour market, and links to physicians or health insurance plans. The confirmation of our results in sensitivity analyses of patients not switching therapy and analysis with inclusion of the first single-agent treatment course only ruled out the possible confounding effect of other previous treatment regimens. The diagnosis of MI and stroke in the National Patient Registry has proved to be valid with a positive predictive value of 93% for MI[24] and 74–97% for stroke.[25] The National Prescription Register is linked to the partial reimbursement policy for drug expenses by the national health security systems, and has been shown to be accurate.[26]

Some limitations should be acknowledged. The effect of unmeasured confounders cannot be discounted. Well-known risk factors such as lipid disorders, hypertension, body mass index, smoking, physical activity, dietary factors, and blood glucose regulation were not accessible, although this limitation was addressed by using time-dependent adjustments for concomitant cardiovascular medications, as proxies for other risk factors. There remains a theoretical possibility of metformin use in patients without overt diabetes such as in high-risk patients to prevent diabetes or in those with polycystic ovarian syndrome (PCO). However, it seems unlikely that the more beneficial mortality outcome data for metformin may be due to metformin treatment in such patients. Finally, we did in fact not find any registered metformin use in patients diagnosed with PCO. A similar duration of diabetes was ascertained by inclusion of patients initiating glucose-lowering medications during follow-up only. Confounding by indication is an important bias to be acknowledged in observational studies such as ours e.g. patients with renal failure and heart failure were likely to preferentially receive an IS rather than metformin. Furthermore, co-morbidities were in general lower in patients treated with metformin, gliclazide, and repaglinide, i.e. leaving room for confounding by indication. By performing propensity analyses on matched populations with balanced covariates, however, we believe that this potential bias was reasonably dealt with (see Supplementary material online, *Table S1*).

In conclusion, we demonstrated increased mortality and cardiovascular risk associated with the most used ISs in patients at relatively low and high cardiovascular risk, when compared with metformin; the risk associated with gliclazide and repaglinide was not statistically significantly different from metformin. The notion that individual ISs can exhibit clinically important differences in their safety profile warrants further studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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