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Effectiveness and safety of metformin and other glucose-lowering treatments in 51 675 patients with type 2 diabetes: A cohort study from the Swedish National Diabetes Register (NDR)

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Abstract

Objective: To evaluate the risks of cardiovascular disease (CVD), lactic acidosis, serious infections and mortality in a large sample of pharmacologically treated patients with type 2 diabetes in clinical practice, with particular emphasis on metformin.

Design: Population-based retrospective cohort study.

Setting: Hospital outpatient clinics and primary care in Sweden between July 2004 and December 2010.

Participants: 51675 men and women with type 2 diabetes, registered in the Swedish National Diabetes Register (NDR), and on continuous glucose-lowering treatment.

Main outcome measures: Risks of CVD, acidosis/serious infection and all-cause mortality, associated with each treatment regimens, were analysed in all patients and in subgroups with different estimated glomerular filtration rate (eGFR) intervals. Covariance adjustment and propensity scores were used to adjust for baseline covariates.

Results: Insulin in monotherapy showed an increased risk of fatal/non-fatal CVD and all-cause mortality compared to metformin in monotherapy, hazard ratio (HR) 1.18 (95 % confidence interval: 1.07 to 1.29) and 1.34 (1.19 to 1.50), respectively. Metformin showed a reduced risk of any acidosis/serious infection, HR 0.85 (0.74 to 0.97), and all-cause mortality, 0.87 (0.77 to 0.99) in patients with eGFR 45-60 mL/min/1.73 m^2, and was not associated with increased risk of all-cause mortality, acidosis/serious infection or CVD in patients with renal impairment.

Conclusions: Metformin-based therapies were associated with reduced risks of severe endpoints, also after different adjustments for patient characteristics. Results were consistent in patients with renal impairment, and no increased risk of acidosis/serious infection was seen. In clinical practice, the benefits of metformin use clearly outbalance the risk of severe side effects.

Article summary

Article focus

To evaluate the risks of cardiovascular disease (CVD), acidosis/serious infection and mortality associated with metformin and other glucose-lowering treatments, in a cohort of 51 675 type 2 diabetes patients, and in subgroups with different degrees of renal impairment.

Key messages

Metformin was associated with reduced risk of CVD, acidosis/serious infection and all-cause mortality compared to insulin, and a reduced risk of all-cause mortality compared to other oral hypoglycemic agents.

The effects were consistent in patients with renal impairment (eGFR 45-60 mL/min/1.73 m^2), and there were no increased risk of acidosis/serious infection even in patients with low renal function.

Strengths and limitations of this study

A large cohort with comprehensive data on patient characteristics was studied.

A composite endpoint including diagnosis of acidosis, shock, acute renal failure and serious infections was used to evaluate the occurrence of lactic acidosis.

Introduction

Type 2 diabetes mellitus (DM2) is a common disease, which causes major morbidity and mortality due to micro- and macrovascular complications (1). A range of glucose lowering agents with different properties aims at preventing these complications. The UK Prospective Diabetes Study (UKPDS) demonstrated a reduction in cardiovascular disease (CVD) and all-cause mortality in the subgroup of obese DM2 patients treated with metformin compared to sulfonylureas, insulin or diet alone (2, 3). Further beneficial effects with metformin have also been recognized (4, 5). On account of this, international treatment guidelines recommend metformin as first line pharmacological treatment in DM2 patients (6-9).

Metformin have been considered causing increased risk of lactic acidosis. Consequently, metformin treatment have been contraindicated in patients at risk of developing lactic acidosis, e.g. patients with cardiovascular and renal disease (10). Given the high prevalence of micro- and macrovascular disease in the DM2 population (11), a relatively large proportion was comprehended by the contraindications. However, several studies have suggested this concern to be exaggerated (12-14).

In the light of these findings, most guidelines have become less strict towards metformin treatment in these patients (6, 8). However, there is still a great need for clinical and epidemiological studies investigating the overall effects of metformin in patients considered vulnerable to such treatment. Therefore, the aim of this survey was to investigate benefits and risks associated with different glucose-lowering medications, in a cohort of 51 675 DM2 patients in clinical practice, and in subgroups of patients with different degrees of renal impairment.

Material and Methods

In this population-based, longitudinal study information was linked from four national registers in Sweden; the national diabetes register (NDR), the prescribed drug register (15), the patient register, and the cause of death register (16, 17). NDR is based and administered in Göteborg, Sweden. Since the establishment in 1996, NDR has been working with systematic quality improvement, research and development in the field of Diabetes Mellitus.

In 2009, NDR covered 262 333 patients with type 1 diabetes mellitus (DM1) and DM2 (18-21). Physicians and nurses in hospital outpatient clinics and primary health care clinics report to the NDR at least annually, via the Internet or via direct transfer of data from medical records databases. All included patients have agreed to be registered before inclusion.

Study population

This study, approved by the central ethical review board at the University of Gothenburg, comprises 51 675 DM2 patients. All DM2 patients aged ≥40 to <85 years, and registered in the NDR between July 1, 2004 and December 31, 2007 were eligible for inclusion in the study (Appendix Figure 1). DM2 was defined as treatment with diet only, or oral hypoglycemic agents (OHA) only, or onset age of diabetes ≥40 years and treatment with insulin only or combined with OHA. Patients had to be registered in the NDR one year prior to and one year following their first prescription of glucose-lowering treatment. In order to achieve adequate length of the follow up period, they had to be initiated on glucose-lowering treatment before 2007 to be included.

Baseline occurred twelve months after the first prescription of glucose-lowering medication. Only patients who had filled at least three prescriptions or 18 fills of multi-dose dispensed drugs during this twelve months period were included in the study. Patients who had collected both ordinary prescriptions and multi-dose dispensed drugs were excluded. Thus, twelve months of continuous glucose-lowering medication at baseline was ensured. The patients were classified according to glucose-lowering treatment, and clinical characteristics were analysed at baseline. Patients missing values for baseline characteristics were excluded from the analysis. Other OHA consisted of patients treated with all OHAs other than metformin. The vast majority of this group, however, was treated with sulphonylureas (SU).

Baseline

Variables assessed at baseline are presented in Table 1. History of congestive heart failure (CHF), and CVD were defined as at least one event of CHF or CVD respectively, anytime between the year of 1987 and the start of the study. History of serious infections was defined as at least one severe infection within six months prior to baseline, and the variable

previous hospitalization as hospitalization for at least three consecutive days within six months prior to baseline.

The patients were screened using local methods, but guidelines were available to ensure the use of similar methodology in all centres. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A smoker was a patient smoking one or more cigarettes per day, or a pipe daily, or who had stopped smoking within the past three months. Cumulative microalbuminuria was defined as urine albumin excretion >20 μ g/min in two out of three consecutive tests. Laboratory analyses, including total cholesterol (TC) and HDL-Cholesterol (HDL-C) were carried out at local laboratories. HbA1c analyses are quality assured in Sweden by regular calibration with Mono-S, a HPLC method. HbA1c values were converted to the National Glycohemoglobin Standardization Program (NGSP) standard levels (22). Non-HDL-cholesterol (non-HDL-C) was calculated by subtracting HDL-C from TC. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) equation (23).

Follow up

All patients were followed from baseline until the occurrence of an endpoint event, or otherwise, until censor date of December 31, 2010. Patients who experienced an endpoint event between first prescription and baseline were excluded from the analysis of that specific endpoint. Patients changing treatment during the study were not censored, and endpoint events were attributed the on-going treatment at the time of the event. Mean follow up was 3.9 years. The five endpoints analysed were fatal/non-fatal CVD, fatal CVD, acidosis/serious infection, fatal acidosis/serious infection and all-cause mortality. CVD was defined as diagnosis of myocardial infarction, angina pectoris, intracerebral haemorrhage, cerebral infarction, unspecified stroke, peripheral vascular disease (PVD), or intervention with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), whichever occurred first. Acidosis/serious infection was defined as diagnosis of acidosis, serious infection, shock, or acute renal failure, which were regarded as signs of lactic acidosis. Serious infections requiring hospitalization for anti-infectious treatment as well as acidosis, shock, and acute renal failure requiring treatment in hospital, usually intensive care thus, registered in the inpatient register, were included in the composite endpoint. The

international classifications of diseases-10 codes for all endpoints are given in Appendix Materials. Fatality was defined as an event followed by death in the subsequent 28 days.

Statistical Methods

Baseline characteristics were compared, unadjusted, using ANOVA and logistic regression (Table 1). Propensity scores were estimated using boosted CART (24), since logistic regression did not achieve good balance. Baseline characteristics were then compared using logistic regression or OLS regression, adjusted for octiles of the propensity score (Appendix Table 1). Unadjusted survival of the endpoints by treatment groups in all patients was estimated with the Kaplan-Meier estimator (Figure 1).

Cox regression models were used to estimate hazard ratios (HR) for all endpoints in groups of patients with different glucose-lowering treatments, and metformin only as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides (Table 3). HR were also estimated in patients with insulin only or other OHA only compared to metformin only, adjusted by stratification for octiles of propensity scores as described above (Table 5). HR were estimated in subgroups with different eGFR intervals (Table 6), for metformin, insulin or other OHA, with any other glucose-lowering treatment as reference. Adjustment was made for same covariates as in Table 3.

Functional form of continuous covariates were checked using a Kolmogorov-type supremum test (25) and in some models it was found suitable to add a quadratic term for age or diabetes duration. The proportional hazards (PH) assumption was checked by including the interaction between covariates and log of follow up time. Violations of the PH assumption were handled by stratifying on the violating covariate, or by modelling the effect as time dependent (26). Additional checks of the form of the time dependence were made using plots of scaled Schoenfeld residuals (27).

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA), except Kaplan-Meier curves produced in SPSS version 18 (SPSS Inc., Chicago, USA), and

propensity scores estimated using the package TWANG in R (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was considered statistically significant.

Role of the funding source

The Region Västra Götaland and the Swedish Association of Local Authorities and Regions fund the NDR. This study was also supported by an unrestricted research grant from BMS, France. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Patients

Table 1 gives the distribution between treatments and clinical characteristics at baseline, unadjusted. The total population presented a mean (±SD) age of 65.3±9.8 years with mean diabetes duration of 9.4±8.0 years, and a mean HbA1c of 7.3±3.3 %. The proportion of females were 41.9 % and 14.0 % of the population were smokers. Mean BMI was 29.5±5.1 kg/m^2, mean systolic blood pressure 140 mmHg, mean Non-HDL 3.5 mmol/L, and mean eGFR 78.1±21.9 mL/min/1.73 m^2. 21.4 % had history of CVD, 5.9 % history of CHF, and 2.9 % history of serious infections. There were statistically significant differences between the groups in all variables. Patients on insulin-based treatments presented longer diabetes duration, higher mean HbA1c, more often microalbuminuria and history of CVD, CHF and serious infections than the population in general.

Patients treated with metformin generally presented high eGFR and BMI. Patients on metformin in monotherapy were the youngest participants, with the shortest diabetes duration, and had a low mean HbA1c. They also relatively seldom had history of CVD, CHF or serious infections. Patients treated with other OHA in monotherapy presented the highest mean age, the lowest mean HbA1c and the lowest mean BMI. After adjustment with propensity score, all differences in baseline characteristics except for history of CHF, and BMI were erased (Appendix Table 1). CHF and BMI were further adjusted for with stratification and as a covariate, respectively.

Table 2 gives time of exposure to the glucose-lowering agents and proportions of patients changing treatment, in each group. The proportions changing treatment ranged between 56.5 % and 93.9 %. Comparison of baseline characteristics in patients who changed treatment and patients who did not change treatment, showed significant differences, with e.g. more frequent history of CVD, CHF and serious infections in patients who did not change treatment, ($P<0.05$).

Outcomes

Figure 1 shows unadjusted time to an event of all-cause mortality, any CVD, and any acidosis/serious infection in each treatment group. The steepest decreases of curves were seen with insulin only and insulin in combination with other OHA. Table 3 gives HR with 95 % confidence intervals (CI) for all endpoints, adjusted for covariates as given in the Table. All treatments were associated with significantly increased risks of all-cause mortality and any CVD compared to metformin only, with HR ranging from 1.47 (95 % CI: 1.35 to 1.61) to 1.15 (1.05 to 1.27) for all-cause mortality and from 1.40 (1.24 to 1.58) to 1.11 (1.03 to 1.20) for any CVD. Insulin only and other OHA only also showed a significantly increased risk of fatal CVD. All treatments except metformin in combination with other OHA were associated with a significantly increased risk of any acidosis/serious infection, and insulin only or in combination with metformin showed an increased risk of fatal acidosis/serious infection. Relatively few fatal events occurred during follow-up (Table 4), contributing to the wider confidence intervals for these risk estimates.

Table 5 gives HR with 95 % CI for all endpoints with insulin only or other OHA only compared to metformin only, adjusted for propensity score. Insulin was associated with significantly increased risks of any CVD, HR 1.18 (1.07 to 1.29), all-cause mortality, HR 1.34 (1.19 to 1.50), and also acidosis/serious infection and fatal acidosis/serious infection, HR 1.28 (1.14 to 1.43) and 1.45 (1.07 to 1.97). When comparing other OHA only to metformin only, a borderline significantly increased risk was seen for all-cause mortality, HR 1.13 (1.01 to 1.27).

Table 6 gives HR with 95 % CI for any CVD, any acidosis/serious infection and all-cause mortality, in subgroups of patients with different eGFR intervals, adjusted for covariates as given in the Table. Treatments with metformin, insulin, or other OHA in any combination

were compared to any other treatment. Metformin-based treatments were associated with reduced risks of any acidosis/serious infection HR 0.85 (0.74 to 0.97) and all-cause mortality HR 0.87 (0.77 to 0.99) in the subgroup of patients with eGFR 45-60 mL/min/1.73 m^2. Similar results were seen in the subgroup with eGFR >60 mL/min/1.73 m^2, HR 0.91 (0.84 to 0.98) for any acidosis/serious infection and 0.87 (0.81 to 0.94) for all-cause mortality. Both insulin and other OHA were associated with increased risk of all-cause mortality in patients with eGFR >60 mL/min/1.73 m^2. Insulin was also associated with increased risk of any acidosis/serious infection in patients with eGFR 30-45, or >60 mL/min/1.73 m^2, and increased risk of any CVD in patients with eGFR 30-45, 45-60, or >60 mL/min/1.73 m^2.

Discussion

This population-based observational study demonstrates pronounced beneficial effects of metformin in clinical practice. As expected, there were significant differences in clinical characteristics between the groups. These differences, however, disappeared after adjustment with propensity scores. Still, metformin in monotherapy showed a significantly reduced risk of any CVD, all-cause mortality, any acidosis/serious infection and fatal acidosis/serious infection compared to insulin in monotherapy. A borderline significant risk reduction of all-cause mortality was also shown compared to other OHA in monotherapy.

The increased risk associated with insulin treatment could be due to these patients presenting a more severe disease. However, an increased risk caused by insulin *per se* cannot be ruled out. Others have reported similar effects associated with insulin treatment (28-33), but the literature is not consistent in this matter (34-36). Results from a large clinical trial investigating the effects of insulin treatment on CVD (37) are expected to be presented in the near future, and will hopefully bring clarity in this matter.

The beneficial effects of metformin, shown in this survey, are consistent with previous findings. The UKPDS demonstrated a reduction in all-cause mortality in the sub-group of obese DM2 patients treated with metformin compared to diet, insulin or SU (2). The sustainability of the effect was confirmed in a ten-year post-interventional follow-up (3). Another clinical trial indicated reduced risk of macrovascular events in insulin treated DM2

patients when adding metformin compared to placebo (5).

Subgroup analyses with patients presenting different degrees of renal impairment were conducted, and did not show any increased risk of CVD, acidosis/serious infection or all-cause mortality associated with metformin-based treatments in patients with eGFR 30-45, 45-60, or >60 mL/min/1.73 m^2. Rather, metformin-based treatments were associated with reduced risks of all cause mortality and acidosis/serious infection in patients with eGFR 45-60 or >60 mL/min/1.73 m^2. The prevalence of renal impairment differed between the groups, with patients presenting an eGFR <45 mL/min/1.73 m^2 being rare in metformin-based treatments. However, the prevalence of eGFR 45-60 mL/min/1.73 m^2 ranged between 10.7 % and 14.4 % in these patients (Table 1), and did not differ much from other patients. Consequently, the subgroup with eGFR 45-60 mL/min/1.73 m^2 was based on a surprisingly large material, while the subgroup with eGFR 30-45 mL/min/1.73 m^2 constituted relatively few patients.

A recently published observational study (14) examined the effects of metformin in patients with advanced cardiovascular disease, thus considered vulnerable to metformin. The results indicated significantly reduced risk of all cause mortality in patients treated with metformin compared to other glucose-lowering treatments. Results were consistent in a subgroup of patients with renal impairment (eGFR 30-60 mL/min/1.73 m^2). The survey, however, only analysed all-cause mortality, and could therefore not detect potential cases of lactic acidosis. Furthermore, glucose-lowering treatments were only specified as metformin use or not, and no adjustments for crucial covariates such as HbA1c or diabetes duration were made. Several studies have failed to demonstrate increased incidence rate of lactic acidosis in DM2 patients treated with metformin. Thus, DM2 with its comorbidities or any glucose lowering treatment rather than metformin use *per se* have been suggested to be risk factors for lactic acidosis (12).

The large population, 51 675 DM2 patients, and comprehensive adjustments for covariates are apparent strengths of the present survey. Data are collected from the NDR database with a currently estimated coverage of more than 90 % of all patients in hospital outpatient clinics and almost 80 % of all patients in primary care in Sweden, suggesting it to be highly

representative of clinical practice. Risk calculations were made, adjusted for covariates with propensity scores and in Cox regression models. The propensity score achieved perfectly well balanced groups regarding baseline characteristics indicating the robustness of this statistical analysis. The Cox regression models enabled more comprehensive comparisons between several glucose-lowering regimens. We also presented exposure time for the different glucose-lowering treatments, but unfortunately there was no useful information about doses.

Despite comprehensive adjustments, covariates of possible importance could have been missed. Thus, the presence of allocation bias may not be fully avoided. Furthermore, patients who changed glucose-lowering treatment during the study were not censored. It could be that patients with advancing disease more frequently changed to a specific glucose-lowering medication, diluting the results observed. Comparison of baseline characteristics indicated higher proportions of history of CVD, CHF and serious infections in patients changing treatment. This could have affected the results, even though the proportions of patients changing treatment were high in all groups. Very few events of diagnosed lactic acidosis occurred during the follow-up, and thus analyses with lactic acidosis as an endpoint would not provide desirable strength. Therefor, a composite endpoint (acidosis/serious infections) including diagnosis of acidosis (n=167), shock (n=17), acute renal failure (n=914) and serious infections (n=4782), was used. This complicates the evaluation of lactic acidosis *per se*, although this diagnosis in practice only occurs in combination with severe infections or CVD. Furthermore, lactic acidosis reported with use of biguanides mostly involve phenformine, which was withdrawn from the market, as lactic acidosis was 20 times more frequent than with metformin (38). The patient group treated with other OHA, were mainly treated with SU and to a very limited degree with glitazones, acarbose or DPP-4 inhibitors during the study period. Investigation of the individual effectiveness of these agents would however be of interest in the future.

In conclusion, this nation-wide observational study of 51 675 DM2 patients supports the previously observed effectiveness of metformin. Metformin was associated with reduced risk of all-cause mortality compared to both insulin and other OHA, and for several additional endpoints compared to insulin. The results were consistent in a subgroup of

patients with renal impairment, and no increased risk of acidosis/serious infection was seen. Together with previous findings, this constitutes evident support to the less strict approach to metformin treatment in patients with renal impairment, advocated in most guidelines. Thus, considerably more DM2 patients may be considered for treatment with metformin.

Data sharing

No additional data available.

Author contributions

NE, LS, BZ, JC, AMS, JMJ, KEO, SG and BE contributed to the conception and design. LS, JC and AMS contributed to the acquisition of data and performed the calculations. LS, NE, JC, BZ, SG, AMS and BE contributed to the analysis and interpretation of data. NE and BE contributed to drafting the article. NE, BE, BZ, JZ, AMS, LS, KEO, SG and JMJ contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

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Conflict of interest

BE has served as a lecturer for all pharmacological companies manufacturing glucose lowering agents and participated in advisory boards for Eli Lilly Sweden AB and Eli Lilly & Co, Sanofi-aventis, Sweden, Boehringer Ingelheim AB, Sweden, and MSD, Sweden.

Disclaimer

Björn Zethelius (BZ) is employed by the Medical Products Agency (MPA), Uppsala Sweden. BZ has not received any financial support or other benefits from BMS France or any commercial sponsor. Results and views of the present study represent the authors and not necessarily any official views of the MPA where BZ is employed.

Figure legends

Table 1: Baseline characteristics in all 51,675 type 2 diabetes patients and in groups based on glucose-lowering treatments. Means ± one standard deviation (SD) and frequencies (%) are given. There were statistically significant differences ($p < 0.001$) in all variables between the groups.

Table 2: Time of exposure (months) to specific glucose-lowering agents, and proportions changing treatment (%) in each group.

Table 3: Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with metformin only as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Table 4: Numbers and frequencies (%) of endpoint events in each treatment group.

Table 5: Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with insulin only and patients with metformin only as reference, or in patients with other OHA only and patients with metformin only as reference. Each comparison was adjusted by stratification with octiles of propensity scores.

Table 6: Adjusted hazard ratios (HR) with 95% confidence intervals for any CVD, any acidosis/serious infection, and all-cause mortality in subgroups of patients with different eGFR intervals. HR associated with the examined agent in any combination is given with any other glucose-lowering treatment as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Figure 1: Time (months) to event of all-cause mortality (a), any CVD (b), and any acidosis/serious infection (c) in each treatment group, unadjusted.

Appendix Table 1: Baseline characteristics in groups of patients treated with metformin only, insulin only, or other OHA only, applied in Cox regression analyses presented in Table 5. Means ± standard deviation (SD) and proportions (%) of clinical variables at baseline. P values are given for comparison between metformin only and insulin only, and between metformin only and other OHA only, unadjusted and after adjustment by stratification for octiles of propensity scores applied for each comparison.

Appendix Figure 1: Enrollment of patients.

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Table 1. Baseline characteristics in all 51,675 type 2 diabetes patients and in groups based on glucose-lowering treatments.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin + insulin + other OHA	Total
N	14 697 (28 %)	8 807 (17 %)	7 109 (14 %)	12 291 (24 %)	5 171 (10%)	1 365 (2.6 %)	2 235 (4.3 %)	51 675 (100 %)
Age (Years)	63.8 (9.7)	65.4 (9.7)	64.6 (8.8)	65.2 (10.5)	69.7 (9.5)	69.6 (9.1)	64.7 (8.5)	65.3 (9.8)
HbA1c (%)	6.9 (3.1)	7.3 (3.2)	7.7 (3.4)	7.6 (3.4)	6.9 (3.0)	7.7 (3.3)	7.9 (3.4)	7.3 (3.3)
< 6.9	8131 (55.3%)	3296 (37.4%)	1710 (24.1%)	3433 (27.9%)	2898 (56.0%)	326 (23.9%)	361 (16.2%)	20155 (39.0%)
6.9 - 8.8	6037 (41.1%)	4982 (56.6%)	4240 (59.6%)	7045 (57.3%)	2139 (41.4%)	845 (61.9%)	1478 (66.1%)	26766 (51.8%)
> 8.8	529 (3.6%)	529 (6.0%)	1159 (16.3%)	1813 (14.8%)	134 (2.6%)	194 (14.2%)	396 (17.7%)	4754 (9.2%)
Systolic blood pressure (mmHg)	139.4 (16.6)	141.2 (16.9)	140.8 (16.8)	138.9 (18.0)	141.4 (17.5)	141.9 (18.2)	141.9 (16.4)	140.1 (17.2)
Diabetes duration (Years)	4.6 (4.3)	8.9 (5.9)	11.6 (7.0)	14.3 (10.4)	7.5 (6.2)	11.6 (6.8)	12.0 (6.2)	9.4 (8.0)
eGFR (mL/min/1.73 m^2)	82.0 (20.2)	80.4 (21.1)	79.2 (21.5)	73.6 (23.8)	73.8 (21.1)	68.9 (22.4)	79.5 (21.2)	78.1 (21.9)
<45	231 (1.6%)	222 (2.5%)	238 (3.3%)	1370 (11.1%)	404 (7.8%)	214 (15.7%)	63 (2.8%)	2742 (5.3%)
45-60	1572 (10.7%)	1167 (13.3%)	1024 (14.4%)	1955 (15.9%)	888 (17.2%)	255 (18.7%)	316 (14.1%)	7177 (13.9%)
>60	12894 (87.7%)	7418 (84.2%)	5847 (82.2%)	8966 (72.9%)	3879 (75.0%)	896 (65.6%)	1856 (83.0%)	41756 (80.8%)
BMI (Kg/m^2)	30.7 (4.9)	29.9 (4.9)	31.6 (5.0)	27.4 (4.8)	27.2 (4.5)	28.3 (4.9)	31.1 (5.1)	29.5 (5.1)
Non-HDL-C (mmol/L)	3.64 (1.00)	3.53 (0.98)	3.39 (0.97)	3.35 (0.98)	3.60 (0.99)	3.52 (1.04)	3.39 (0.94)	3.50 (0.99)
Microalbuminuria	21.0%	25.9%	33.8%	30.8%	24.2%	34.4%	34.5%	27.2%
Previous hospitalisation	11.5%	11.6%	18.1%	23.1%	15.5%	22.9%	15.2%	16.1%
Female sex	44.7%	40.0%	43.5%	40.2%	39.2%	39.8%	41.4%	41.9%
History of CVD	15.9%	17.6%	25.9%	26.4%	21.4%	30.2%	24.6%	21.4%
History of CHF	3.5%	3.9%	7.3%	8.9%	6.4%	10.1%	5.5%	5.9%
History of serious infections	1.8%	1.6%	2.9%	4.9%	2.8%	5.2%	2.7%	2.9%
Cardiac glycosides	2.6%	2.7%	4.1%	3.0%	4.3%	6.2%	4.3%	3.3%
Organic nitrates	6.3%	7.4%	9.7%	8.5%	8.8%	13.0%	10.1%	8.1%
ASA	45.4%	48.8%	57.3%	45.7%	45.9%	55.4%	58.6%	48.6%
Lipid modifying agents	49.9%	54.0%	61.7%	44.8%	44.1%	51.7%	63.6%	51.1%
Antihypertensive agents	71.8%	74.0%	81.9%	66.2%	71.3%	79.5%	83.0%	72.9%
Multi-dose dispensation	1.4%	1.6%	2.7%	3.0%	1.5%	3.7%	2.6%	2.1%
Smoker	14.8%	14.0%	12.8%	14.9%	12.3%	12.2%	13.6%	14.0%

Means ± one standard deviation (SD) and frequencies (%) are given. There were statistically significant differences ($p < 0.001$) in all variables between the groups.

Table 2: Time of exposure (months) to specific glucose-lowering agents, and proportions changing treatment (%) in each group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin + insulin + other OHA
Mean Exposure time to metformin	49,4	51,0	46,3				48,9
Mean Exposure time to insulin			51,8	55,3		54,1	53,4
Mean Exposure time to Other Oral		49,1			45,3	39,5	48,3
Change treatment (%)	80.8 %	80.5 %	81.8 %	91.3 %	88.4 %	56.5 %	93.9 %

Table 3. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with metformin only as reference

	Metformin only	Insulin only	Other OHA only	Insulin + other OHA	Metformin + other OHA	Metformin + insulin	Metformin + Insulin + other OHA
Any CVD	Reference	1.28 (1.19-1.37)***	1.13 (1.04-1.23)**	1.40 (1.24-1.58)***	1.11 (1.03-1.20)**	1.28 (1.19-1.38)***	1.33 (1.19-1.49)***
Fatal CVD	Reference	1.41 (1.18-1.68)***	1.30 (1.08-1.56)**	1.17 (0.91-1.51)	*	*	1.21 (0.92-1.58)
Acidosis/serious infection	Reference	1,37 (1,26-1,50)***	1,16 (1,04-1,28)**	1,31 (1,13-1,51)***	1,04 (0,95-1,14)	1,20 (1,09-1,32)***	1,15 (1.00-1,32)*
Fatal acidosis/serious infection	Reference	1,63 (1,29-2,07)***	1,28 (0,98-1,67)	1,32 (0,91-1,89)	0,94 (0,72-1,23)	1,41 (1,08-1,83)*	1,12 (0,73-1,67)
All-cause mortality	Reference	1.47 (1.35-1.61)***	1.30 (1.18-1.44)***	1.30 (1.12-1.50)***	1.15 (1.05-1.27)**	1.25 (1.13-1.38)***	1.31 (1.14-1.52)***

* P<0.05
** P<0.01
*** P<0.001

*Non-proportional hazards, group excluded from analysis.

Table 4: Numbers and frequencies (%) of endpoint events in each treatment group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin+ insulin + other OHA
Any CVD	1734 (3.3%)	1287 (4%)	1338 (5.4%)	2389 (5.9%)	929 (5.2%)	334 (7.8%)	415 (5.4%)
Fatal CVD	264 (0.5%)	230 (0.6%)	276 (1%)	681 (1.4%)	237 (1.2%)	94 (1.8%)	74 (0.8%)
Acidosis/serious infection	1154 (2.1%)	843 (2.5%)	899 (3.4%)	1867 (4.3%)	623 (3.3%)	235 (5%)	259 (3.1%)
Fatal acidosis/serious infection	127 (0.2%)	95 (0.3%)	124 (0.4%)	325 (0.7%)	109 (0.5%)	41 (0.8%)	29 (0.3%)
All-cause mortality	971 (1.7%)	834 (2.4%)	818 (2.9%)	2002 (4.2%)	745 (3.7%)	258 (4.9%)	250 (2.8%)

Table 5. Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with insulin only and patients with metformin only as reference, or in patients with other OHA only and patients with metformin only as reference

	Events/Patients N/N	Events/Patients N/N	Hazard ratio (95% CI)	P-value
	Insulin only	**Metformin only**	**Insulin Vs metformin**	
Fatal/nonfatal CVD	2389 / 11427	1734 / 14317	1.18 (1.07-1.29)	<0.001
Fatal CVD	681 / 12285	264 / 14696	1.12 (0.91-1.40)	0.29
All-cause mortality	2002 / 12291	971 / 14697	1.34 (1.19-1.50)	<0.001
Acidosis/serious infection	1867 / 11860	1154 / 14517	1.28 (1.14-1.43)	<0.001
Fatal acidosis/serious infection	325 / 12284	127 / 14697	1.45 (1.07-1.97)	0.019
	Other OHA	**Metformin only**	**Other OHA Vs metformin**	
Fatal/nonfatal CVD	929 / 4964	1734 / 14317	1.02 (0.93-1.12)	0.71
Fatal CVD	237 / 5171	264 / 14696	1.03 (0.84-1.26)	0.80
All-cause mortality	745 / 5171	971 / 14697	1.13 (1.01-1.27)	0.032
Acidosis/serious infection	623 / 5062	1154 / 14517	1.05 (0.94-1.18)	0.41
Fatal acidosis/serious infection	109 / 5171	127 / 14697	1.13 (0.83-1.53)	0.44

Each comparison was adjusted by stratification with octiles of propensity scores.

Table 6. Adjusted hazard ratios (HR) with 95% confidence intervals for any CVD, any acidosis/serious infection, and all-cause mortality in subgroups of patients with different eGFR intervals. HR associated with the examined agent in any combination is given with any other glucose-lowering treatment as reference.

	30 <= eGFR < 45			45 <= eGFR < 60			eGFR >= 60			All patients	
	N (% of total)	Events (% of total)	HR (95 % CI)	N (% of total)	Events (% of total)	HR (95 % CI)	N (% of total)	Events (% of total)	HR (95 % CI)	N	Events
Any CVD											
Metformin	670 (35.4%)	210 (30.7%)	1.00 (0.83-1.19)	3839 (57.7%)	849 (51.2%)	0.94 (0.84-1.05)	27083 (67.3%)	3698 (63.4%)	0.98 (0.92-1.05)	31628	4774
Insulin	1180 (62.3%)	474 (69.2%)	1.30 (1.02-1.64)*	3201 (48.1%)	930 (56.1%)	1.24 (1.09-1.42)**	16718 (41.5%)	2853 (48.9%)	1.19 (1.11-1.27)***	21503	4476
Other OHA	702 (37.1%)	241 (35.2%)	1.03 (0.85-1.26)	2450 (36.8%)	608 (36.7%)	1.05 (0.93-1.18)	13552 (33.7%)	2065 (35.4%)	1.03 (0.97-1.09)	16817	2965
Total in group	1894	685		6655	1657		40239	5829			
Any acidosis/serious infection											
Metformin	1352 (66.1%)	361 (71.6%)	0.98 (0.79-1.21)	4000 (57.5%)	557 (49.4%)	0.85 (0.74-0.97)*	27618 (67.3%)	2444 (60.6%)	0.91 (0.84-0.98)*	32345	3155
Insulin	1302 (63.7%)	366 (72.6%)	1.34 (1.02-1.76)*	3406 (48.9%)	652 (57.9%)	1.07 (0.91-1.26	17152 (41.8%)	2057 (51%)	1.22 (1.12-1.32)***	22310	3260
Other OHA	738 (36.1%)	166 (32.9%)	*	2555 (36.7%)	379 (33.6%)	0.87 (0.75-1.00)	13852 (33.7%)	1375 (34.1%)	1.02 (0.95-1.09)	17265	1960
Total in group	2044	504		6960	1127		41048	4034			
All-cause mortality											
Metformin	715 (33.3%)	179 (27%)	1.02 (0.84-1.24)	4079 (56.8%)	558 (46.5%)	0.87 (0.77-0.99)*	28015 (67.1%)	2120 (56.9%)	0.87 (0.81-0.94)***	32848	2873
Insulin	1386 (64.6%)	468 (70.5%)	1.16 (0.91-1.47)	3550 (49.5%)	701 (58.4%)	1.12 (0.95-1.31)	17565 (42.1%)	1921 (51.5%)	1.29 (1.19-1.41)***	23000	3328
Other OHA	766 (35.7%)	222 (33.4%)	0.97 (0.79-1.19)	2626 (36.6%)	429 (35.7%)	0.97 (0.84-1.11)	14049 (33.6%)	1375 (36.9%)	1.10 (1.02-1.19)*	17578	2087
Total in group	2146	664		7177	1201		41756	3729			

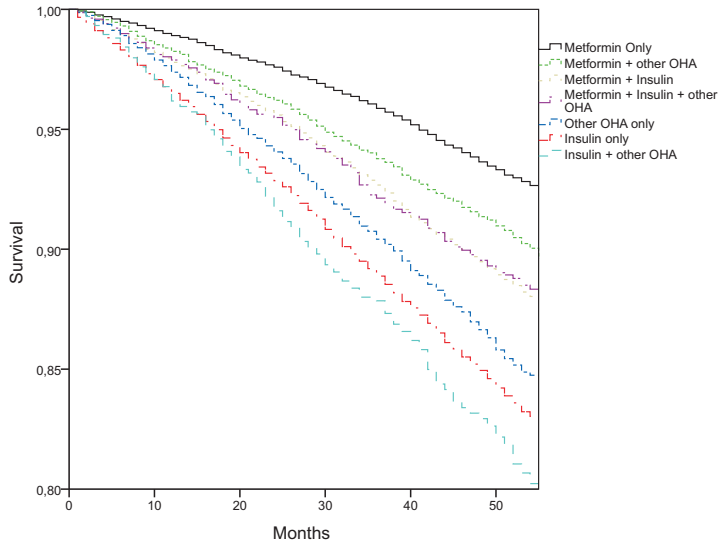
* P<0.05
** P<0.01
*** P<0.001

* Non-proportional hazards, group excluded from analysis.

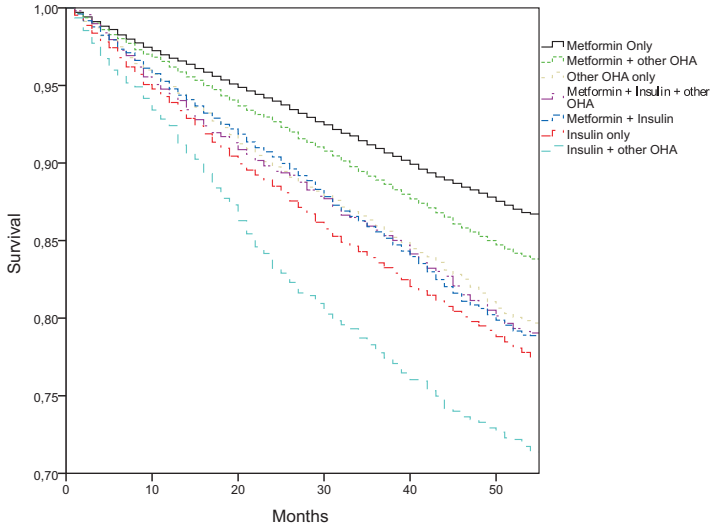
Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Figure 1. Time (months) to event of all-cause mortality (a), any CVD (b), and any infection/acidosis (c) in each treatment group, unadjusted

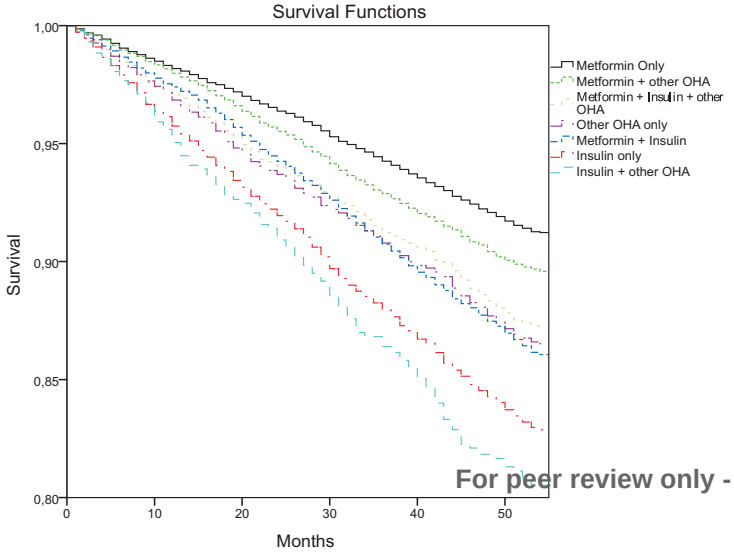
a. All-cause mortality



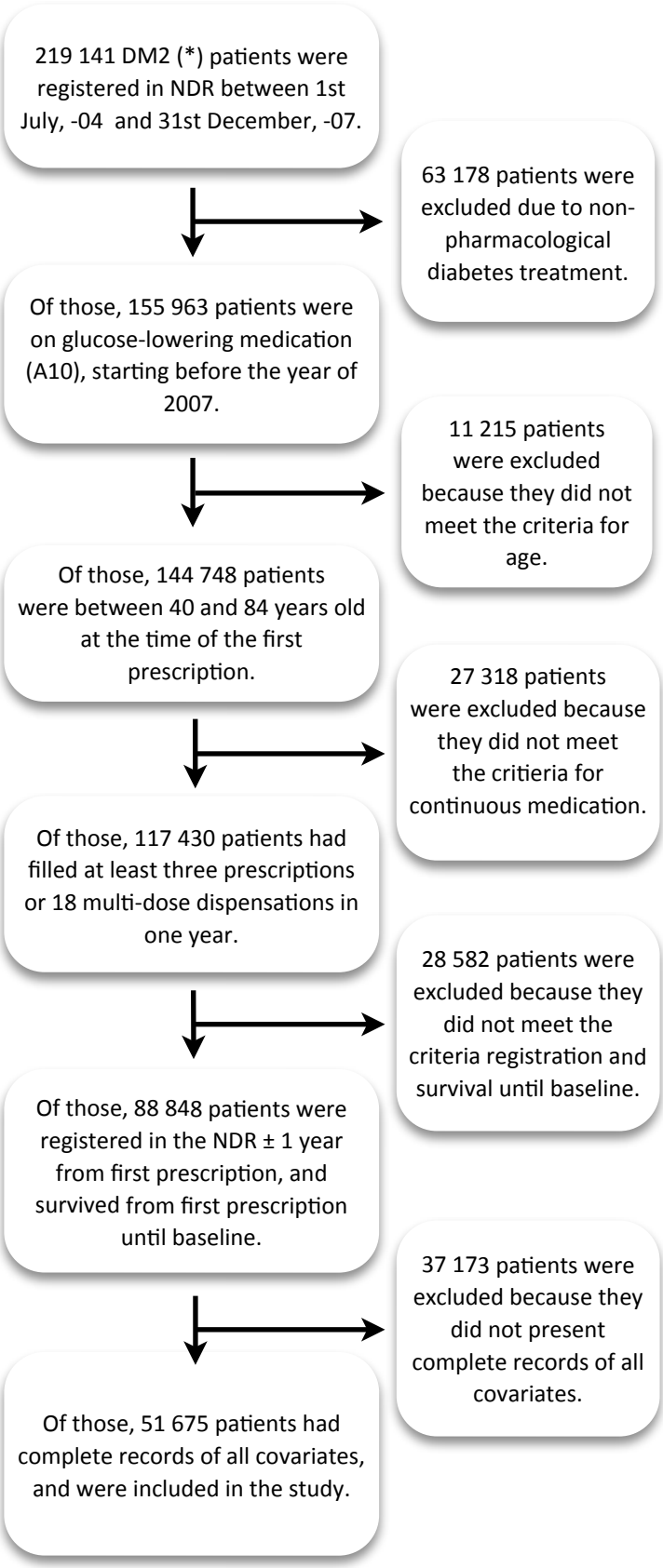
b. Any CVD



c. Any acidosis/infection



Appendix Figure 1. Enrollment of patients



* DM2 is Type 2 Diabetes Mellitus

Appendix Table 1. Baseline characteristics in groups of patients treated with metformin only, insulin only, or other OHA only, applied in Cox regression analyses presented in Table 5.

	Metformin Only	Insulin only	Other OHA only	P metformin only/ insulin only Unadjusted	P metformin only/ insulin only Adjusted for PS	P metformin only/ other OHA only Unadjusted	P metformin only/ other OHA only Adjusted for PS
N	14697	12291	5171				
Age (Years)	63.8 (9.7)	65.2 (10.5)	69.7 (9.5)	<0.001	0.49	<0.001	0.126
HbA1c (%)	51.9 (10.4)	60.0 (13.6)	51.4 (9.5)	<0.001	0.46	0.002	0.24
Systolic blood pressure (mmHg)	139.4 (16.6)	138.9 (18.0)	141.4 (17.5)	0.018	0.96	<0.001	0.164
Diabetes duration (Years)	4.6 (4.3)	14.3 (10.4)	7.5 (6.2)	<0.001	0.78	<0.001	0.37
eGFR (mL/min/1.73 m^2)	82.0 (20.2)	73.6 (23.8)	73.8 (21.1)	<0.001	0.94	<0.001	0.177
BMI (Kg/m^2)	30.7 (4.9)	27.4 (4.8)	27.2 (4.5)	<0.001	0.53	<0.001	0.008
Non-HDL-C (mmol/L)	3.64 (1.00)	3.35 (0.98)	3.60 (0.99)	<0.001	0.78	0.008	0.62
Microalbuminuria	21.0%	30.8%	24.2%	<0.001	0.46	<0.001	0.50
Previous hospitalisation	11.5%	23.1%	15.5%	<0.001	0.57	<0.001	0.73
Female sex	44.7%	40.2%	39.2%	<0.001	0.73	<0.001	0.59
History of CVD	15.9%	26.4%	21.4%	<0.001	0.97	<0.001	0.111
History of CHF	3.5%	8.9%	6.4%	<0.001	0.022	<0.001	0.74
History of serious infections	1.8%	4.9%	2.8%	<0.001	0.96	<0.001	0.72
Cardiac glycosides	2.6%	3.0%	4.3%	0.064	0.96	<0.001	0.196
Organic nitrates	6.3%	8.5%	8.8%	<0.001	0.61	<0.001	0.45
ASA	45.4%	45.7%	45.9%	0.56	0.58	0.52	0.65
Lipid modifying agents	49.9%	44.8%	44.1%	<0.001	0.88	<0.001	0.94
Antihypertensive agents	71.8%	66.2%	71.3%	<0.001	0.38	0.58	0.81
Multi-dose dispensation	1.4%	3.0%	1.5%	<0.001	0.97	0.54	0.97
Smoker	14.8%	14.9%	12.3%	0.77	0.104	<0.001	0.28

Means ± standard deviation (SD) and proportions (%) of clinical variables at baseline. P values are given for comparison between metformin only and insulin only, and between metformin only and other OHA only, unadjusted and after adjustment by stratification for octiles of propensity scores applied for each comparison.

Definitions of the endpoints (Appendix Text)

Cardiovascular disease (CVD)

CVD was defined as diagnosis of myocardial infarction (ICD-10 code I21), angina pectoris (ICD-10 code I20.0), intracerebral haemorrhage, cerebral infarction, unspecified stroke (ICD-10 codes I61, I63, I64 and I679), peripheral vascular disease (PVD, ICD-10 codes E105, E115, E145, I702, I731, I739 and I792), or intervention with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), whichever occurred first.

Acidosis/serious infection

Acidosis/infection was defined as diagnosis of acidosis or chock (ICD-10 codes E10.1, E10.1A, E10.1D, E10.1X, E11.1, E11.1A, E11.1D, E11.1X, E13.1, E14.1, E87.2, R57.1, R57.2, R57.8 or R57.9, or diagnosis of serious infection (ICD-10 codes A00-A09, A15-A19, A32.7, A39-A41, A42.7, A48, B37.7, I00-I02, I33, I38, I39, J13-J18, J85, J86, K25, K61, K80.0, K80.3, K80.4, K81, K83.0, K85, K86, M00, M46.2, M72.6, M86.0, M86.1, M86.8 or M86.9 or acute renal failure (ICD-10 codes N10.9 or N17.

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Effectiveness and safety of metformin ~~and other glucose-lowering treatments~~ in 51 675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish National Diabetes Register ~~(NDR)~~

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Abstract

Objective: To evaluate the ~~risks of cardiovascular disease (CVD), lactic acidosis, serious infections and mortality~~ effectiveness and safety of metformin use in clinical practice in a large sample of pharmacologically treated patients with type 2 diabetes ~~in clinical practice, with particular emphasis on metformin~~ and different levels of renal function.

Design: Observational study between July 2004 and December 2010, mean follow-up 3.9 years.

Setting: Hospital outpatient clinics and primary care in Sweden.

Participants: 51675 men and women with type 2 diabetes, registered in the Swedish National Diabetes Register, and on continuous glucose-lowering treatment with oral hypoglycemic agents (OHA) or insulin.

Main outcome measures: Risks of cardiovascular disease (CVD), all-cause mortality, acidosis/serious infection, associated with each treatment regimens, were analysed in all patients and in subgroups with different estimated glomerular filtration rate (eGFR) intervals. Covariance adjustment and propensity scores were used to adjust for several baseline risk factors and characteristics at Cox regression.

Results: ~~Insulin in monotherapy showed an increased risk of fatal/non-fatal CVD and all-cause mortality compared to metformin in monotherapy, hazard ratio (HR) 1.18 (95 % confidence interval: 1.07 to 1.29) and 1.34 (1.19 to 1.50), respectively. Metformin showed a reduced risk of any acidosis/serious infection, HR 0.85 (0.74 to 0.97), and all-cause mortality, 0.87 (0.77 to 0.99) in patients with eGFR 45-60 mL/min/1.73 m^2, and was not associated with increased risk of all-cause mortality, acidosis/serious infection or CVD in patients with renal impairment.~~

Compared to metformin in monotherapy, hazard ratios (HR) for fatal/nonfatal CVD and all-cause mortality with all other OHAs combined (approximately 80% sulphonylureas) in monotherapy were 1.02 (95 % confidence interval 0.93-1.12) and 1.13 (1.01-1.27), while 1.18 (1.07-1.29) and 1.34 (1.19-1.50) with insulin in monotherapy, adjusting using propensity scores.

Metformin, compared to any other treatment, showed reduced risks of acidosis/serious infection, adjusted HR 0.85 (0.74-0.97), and all-cause mortality, HR 0.87 (0.77-0.99), in patients with eGFR 45-60 mL/min/1.73 m^2, and no increased risks of all-cause mortality,

acidosis/serious infection or CVD were found in patients with eGFR 30-45 mL/min/1.73 m^2.

Conclusions: Metformin~~-based therapies were associated with reduced risks of severe endpoints, also after different adjustments for patient characteristics. Results were consistent in patients with renal impairment, and no increased risk of acidosis/serious infection was seen.~~ showed lower risk than insulin for CVD and all-cause mortality, and slightly lower risk for all-cause mortality compared to other OHA, in these 51675 patients followed for 4 years. Patients with renal impairment showed no increased risk of CVD, all-cause mortality or acidosis/serious infection. In clinical practice, the benefits of metformin use clearly outbalance the risk of severe side effects.

Introduction

Type 2 diabetes mellitus (DM2) is a common disease, which causes major morbidity and mortality due to micro- and macrovascular complications (1). A range of glucose-lowering agents with different properties aims at preventing these complications. The UK Prospective Diabetes Study (UKPDS) demonstrated a reduced risk of all-cause mortality in the subgroup of obese DM2 patients treated with metformin compared to sulfonylureas, insulin or diet alone (2, 3). Further beneficial effects with metformin have been recognized (4, 5). Thus, international treatment guidelines recommend metformin as first line pharmacological treatment in DM2 patients primarily based on the results from the UKPDS sub-study including 342 patients on metformin (6-9).

Metformin have been considered causing increased risk of lactic acidosis. Consequently, metformin treatment have been contraindicated in patients at risk of developing lactic acidosis, e.g. patients with cardiovascular and renal disease (10). Given the high prevalence of micro- and macrovascular disease in the DM2 population (11), a relatively large proportion was comprehended by the contraindications. However, several studies have suggested this concern to be exaggerated (12-14).

In the light of these findings, most guidelines have become less strict towards metformin treatment in these patients (6, 8). However, there is still a great need for clinical and epidemiological studies investigating the overall effects of metformin in patients considered vulnerable to such treatment. Therefore, the aim of this survey was to investigate benefits and risks associated with different glucose-lowering medications, in a cohort of 51 675 DM2 patients in clinical practice, and in subgroups of patients with different degrees of renal impairment.

Material and Methods

In this population-based, longitudinal study information was linked from four national registers in Sweden; the national diabetes register (NDR), the prescribed drug register (15), the patient register, and the cause of death register (16, 17). NDR is based and administered in Göteborg, Sweden. Since the establishment in 1996, NDR has been working with

systematic quality improvement, research and development in the field of Diabetes Mellitus. In 2009, NDR covered 262 333 patients with type 1 diabetes mellitus (DM1) and DM2 (18-21). Physicians and nurses in hospital outpatient clinics and primary health care clinics report to the NDR at least annually, via the Internet or via direct transfer of data from medical records databases. All included patients have agreed to be registered before inclusion.

Study population

This study, approved by the central ethical review board at the University of Gothenburg, comprises 51 675 DM2 patients. All pharmacologically treated DM2 patients aged ≥40 to <85 years, and registered in the NDR between July 1, 2004 and December 31, 2007 were eligible for inclusion in the study (Appendix Figure 1). DM2 was defined as treatment with diet only, or oral hypoglycemic agents (OHA) only, or onset age of diabetes ≥40 years and treatment with insulin only or combined with OHA. Patients had to be registered in the NDR one year prior to and one year following their first prescription of glucose-lowering treatment. In order to achieve adequate length of the follow up period, they had to be initiated on glucose-lowering treatment before 2007 to be included.

~~Baseline occurred twelve months after the first prescription of glucose-lowering medication.~~ In each patient, baseline was defined as occurring after 12 months of continuous use of the prescribed glucose-lowering medication. Only patients who had filled at least three prescriptions or 18 fills of multi-dose dispensed drugs during this twelve months period were included in the study. Patients who had collected both ordinary prescriptions and multi-dose dispensed drugs were excluded. Thus, twelve months of continuous glucose-lowering medication at baseline was ensured. The patients were classified according to glucose-lowering treatment, and clinical characteristics were analysed at baseline. All patients with data available for the analysed variables were included. Other OHA consisted of patients treated with all OHAs other than metformin. The majority of this group (approximately 80%) was treated with sulphonylureas (SU).

Baseline

Variables assessed at baseline are presented in Table 1. History of congestive heart failure (CHF), and CVD were defined as at least one event of CHF or CVD respectively, anytime

between the year of 1987 and the start of the study. History of serious infections was defined as at least one severe infection within six months prior to baseline, and the variable previous hospitalization as hospitalization for at least three consecutive days within six months prior to baseline.

The patients were screened using methods applied at each local centre, but guidelines were available to ensure the use of similar methodology at all centres. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A smoker was a patient smoking one or more cigarettes per day, or a pipe daily, or who had stopped smoking within the past three months. Cumulative microalbuminuria was defined as urine albumin excretion >20 μ g/min in two out of three consecutive tests. Laboratory analyses, including total cholesterol (TC) and HDL-Cholesterol (HDL-C) were carried out at local laboratories. HbA1c analyses are quality assured in Sweden by regular calibration with Mono-S, a HPLC method. HbA1c values were converted to the National Glycohemoglobin Standardization Program (NGSP) standard levels (22). Non-HDL-cholesterol (non-HDL-C) was calculated by subtracting HDL-C from TC. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) equation (23).

Follow up

All patients were followed from baseline until the occurrence of an endpoint event, or otherwise, until censor date of December 31, 2010. Patients who experienced an endpoint event between first prescription and baseline were excluded from the analysis of that specific endpoint. Patients changing treatment during the study were not censored, and endpoint events were attributed the initial treatment. Mean follow up was 3.9 years. The five endpoints analysed were any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection and all-cause mortality. CVD was defined as diagnosis of myocardial infarction, angina pectoris, intracerebral haemorrhage, cerebral infarction, unspecified stroke, peripheral vascular disease (PVD), or intervention with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), whichever occurred first. Acidosis/serious infection was defined as diagnosis of acidosis, serious infection, shock, or acute renal failure, which are frequently associated with lactic acidosis. Serious infections requiring hospitalization for anti-infectious treatment as well as acidosis, shock, and acute

renal failure requiring treatment in hospital, usually intensive care thus, registered in the inpatient register, were included in the composite endpoint. The international classifications of diseases-10 codes for all endpoints are given in Appendix Materials. Fatality was defined as an event followed by death in the subsequent 28 days.

Statistical Methods

Baseline characteristics were compared, unadjusted, using ANOVA and logistic regression (Table 1). Propensity scores were estimated using boosted CART (24), since logistic regression did not achieve good balance. Baseline characteristics were then compared using logistic regression or OLS regression, adjusted for octiles of the propensity score (Appendix Table 1). Unadjusted survival of the endpoints by treatment groups in all patients was estimated with the Kaplan-Meier estimator (Figure 1).

Cox regression models were used to estimate hazard ratios (HR) for all endpoints in groups of patients with different glucose-lowering treatments, and metformin only as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides (Table 2). HR were also estimated in patients with insulin only or other OHA only compared to metformin only, adjusted by stratification for octiles of propensity scores as described above (Table 3). HR were estimated in subgroups with different eGFR intervals (Table 4), for metformin, insulin or other OHA, with any other glucose-lowering treatment as reference. Adjustment was made for same covariates as in Table 2.

Functional form of continuous covariates were checked using a Kolmogorov-type supremum test (25) and in some models it was found suitable to add a quadratic term for age or diabetes duration. The proportional hazards (PH) assumption was checked by including the interaction between covariates and log of follow up time. Violations of the PH assumption were handled by stratifying on the violating covariate, or by modelling the effect as time dependent (26). Additional checks of the form of the time dependence were made using plots of scaled Schoenfeld residuals (27).

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA), except Kaplan-Meier curves produced in SPSS version 18 (SPSS Inc., Chicago, USA), and propensity scores estimated using the package TWANG in R (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was considered statistically significant.

Role of the funding source

The Region Västra Götaland and the Swedish Association of Local Authorities and Regions fund the NDR. LS, AMS, JMJ, and SG were also supported by an unrestricted research grant from BMS, France. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Patients

Table 1 gives the distribution between treatments and clinical characteristics at baseline, unadjusted. The total population presented a mean (±SD) age of 65.3±9.8 years with mean diabetes duration of 9.4±8.0 years, and a mean HbA1c of 7.3±3.3 %. The proportion of females were 41.9 % and 14.0 % of the population were smokers. Mean BMI was 29.5±5.1 kg/m^2, mean systolic blood pressure 140 mmHg, mean Non-HDL 3.5 mmol/L, and mean eGFR 78.1±21.9 mL/min/1.73 m^2. 21.4 % had history of CVD, 5.9 % history of CHF, and 2.9 % history of serious infections. There were statistically significant differences between the groups defined for all variables. Patients on insulin-based treatments presented longer diabetes duration, higher mean HbA1c, more often microalbuminuria and history of CVD, CHF and serious infections than the population in general.

Patients treated with metformin generally presented high eGFR and BMI. Patients on metformin in monotherapy were the youngest participants, with the shortest diabetes duration, and had a low mean HbA1c. They also relatively seldom had history of CVD, CHF or serious infections. Patients treated with other OHA in monotherapy presented the highest mean age, the lowest mean HbA1c and the lowest mean BMI. After adjustment with propensity score, all differences in baseline characteristics except for history of CHF, and BMI were erased (Appendix Table 1). CHF and BMI were further adjusted for with

stratification and as a covariate, respectively. Median daily doses of metformin were approximately 1100 mg in the metformin monotherapy group, 1700 mg in metformin + other OHA, 1700 mg in metformin + insulin and 1900 mg in metformin + insulin + other OHA.

Appendix Table 2 gives time of exposure to the glucose-lowering agents and proportions of patients changing treatment, in each group. The proportions changing treatment ranged between 56.5 % and 93.9 %. Comparison of baseline characteristics in patients who changed treatment and patients who did not change treatment, showed significant differences, with e.g. more frequent history of CVD, CHF and serious infections in patients who did not change treatment, ($P<0.05$).

Outcomes

Figure 1 shows unadjusted time to an event of all-cause mortality, any CVD, and any acidosis/serious infection in each treatment group. The steepest decreases of curves were seen with insulin only and insulin in combination with other OHA. Table 2 gives HR with 95 % confidence intervals (CI) for all endpoints, adjusted for covariates as given in the Table. All treatments were associated with significantly increased risks of all-cause mortality and any CVD compared to metformin only, with HR ranging from 1.47 (95 % CI: 1.35 to 1.61) to 1.15 (1.05 to 1.27) for all-cause mortality and from 1.40 (1.24 to 1.58) to 1.11 (1.03 to 1.20) for any CVD. Insulin only and other OHA only also showed a significantly increased risk of fatal CVD. All treatments except metformin in combination with other OHA were associated with a significantly increased risk of any acidosis/serious infection, and insulin only or in combination with metformin showed an increased risk of fatal acidosis/serious infection. Relatively few fatal events occurred during follow-up (Appendix Table 3), contributing to the wider confidence intervals for these risk estimates. Similar results were seen when using other OHA only as reference group instead of metformin only (Appendix Table 4). This analysis also showed significantly increased risks of all endpoints except fatal CVD associated with insulin only compared to other OHA only. Furthermore, insulin only or in combination with other glucose-lowering agents was constantly associated with increased risk of any CVD compared to other OHA only.

Table 3 gives HR with 95 % CI for all endpoints with insulin only or other OHA only compared to metformin only, adjusted for propensity score. Insulin was associated with significantly increased risks of any CVD, HR 1.18 (1.07 to 1.29), all-cause mortality, HR 1.34 (1.19 to 1.50), and also any acidosis/serious infection and fatal acidosis/serious infection, HR 1.28 (1.14 to 1.43) and 1.45 (1.07 to 1.97). When comparing other OHA only to metformin only, a borderline significantly increased risk was seen for all-cause mortality, HR 1.13 (1.01 to 1.27). The results were identical when analysing SU only instead of other OHA only, and metformin only as reference, with significant HR for all-cause mortality. As shown in Appendix Table 5: HR was 0.99 (0.89-1.09) for any CVD, 1.01 (0.82-1.25) for fatal CVD, 1.15 (1.02-1.30) for all-cause mortality, 1.00 (0.89-1.14) for any acidosis/serious infection, 1.17 (0.85-1.60) for fatal acidosis/serious infection.

As shown in Appendix Table 6, insulin in combination with metformin was associated with a reduced risk for all-cause mortality, HR 0.84 (0.76-0.91) and any acidosis/serious infection, HR 0.86 (0.79-0.94) when compared to insulin only. No reduced risk for CVD was seen. Insulin in combination with other OHA was not associated with reduced risk for any of the endpoints compared to insulin only.

Table 4 gives HR with 95 % CI for any CVD, any acidosis/serious infection and all-cause mortality, in subgroups of patients with different eGFR intervals, adjusted for covariates as given in the Table. Treatments with metformin, insulin, or other OHA in any combination were compared to any other treatment. Metformin-based treatments were associated with reduced risks of any acidosis/serious infection HR 0.85 (0.74 to 0.97) and all-cause mortality HR 0.87 (0.77 to 0.99) in the subgroup of patients with eGFR 45-60 mL/min/1.73 m^2. Similar results were seen in the subgroup with eGFR >60 mL/min/1.73 m^2, HR 0.91 (0.84 to 0.98) for any acidosis/serious infection and 0.87 (0.81 to 0.94) for all-cause mortality. Both insulin and other OHA were associated with increased risk of all-cause mortality in patients with eGFR >60 mL/min/1.73 m^2. Insulin was also associated with increased risk of any acidosis/serious infection in patients with eGFR 30-45, or >60 mL/min/1.73 m^2, and increased risk of any CVD in patients with eGFR 30-45, 45-60, or >60 mL/min/1.73 m^2.

Discussion

This population-based observational study demonstrates beneficial effects of metformin in clinical practice. As expected, there were significant differences in clinical characteristics between the groups. These differences, however, disappeared after adjustment with propensity scores. Still, metformin in monotherapy showed a significantly reduced risk of any CVD, all-cause mortality, any acidosis/serious infection and fatal acidosis/serious infection compared to insulin in monotherapy. A borderline significant risk reduction of all-cause mortality was also shown compared to other OHA in monotherapy. Furthermore, there was no increased risk of severe outcomes in patients with impaired renal function.

~~The increased risk associated with insulin treatment could be due to these patients presenting a more severe disease. However, an increased risk caused by insulin *per se* cannot be ruled out. Others have reported similar effects associated with insulin treatment (28-33), but the literature is not consistent in this matter (34-36). Results from a large clinical trial investigating the effects of insulin treatment on CVD (37) are expected to be presented in the near future, and will hopefully bring clarity in this matter.~~

The beneficial effects of metformin, shown in this survey, are generally consistent with previous findings. The UKPDS demonstrated a reduction in all-cause mortality in the sub-group of obese DM2 patients treated with metformin compared to diet, SU or insulin (2), also confirmed in a 10-year post-interventional follow-up (3). ~~Another clinical trial indicated reduced risk of macrovascular events in insulin treated DM2 patients when adding metformin compared to placebo (4).~~ Furthermore, several recent observational studies have reported reduced risk with metformin compared to all other hypoglycaemic agents for coronary heart disease (CHD) (29, 32), and for total mortality in patients with previous CHD (14), as also seen in this study for total mortality in patients with normal or slightly reduced renal function. In the present study, a reduced risk of total mortality was also found when comparing insulin in combination with metformin to insulin only, although not verifying a finding of reduced risk of macrovascular events in a small clinical trial comparing the addition of metformin to placebo in insulin treated DM2 patients (4).

Interestingly, we found somewhat reduced risk for total mortality, but not for CVD, with

metformin only compared to SU only or other OHA only. These findings were also clearly demonstrated regarding total mortality in two large recent observational studies on DM2 patients from Denmark and Cleveland, US (38, 39). However, the Danish study also found reduced risk for CVD with metformin compared to SU (39), using a propensity score including age, sex, comorbidities, income and cardiac drugs as covariates, and used the score for matching limiting included patients. Possibly our study using propensity score for stratification of all included patients, and also including traditional cardiovascular risk factors as covariates, may better reflect the risk difference between metformin and SU, an important matter for clinical practice with many patients still given SU.

The increased risk for CVD and total mortality with insulin found in the present study could be due to these patients presenting a more severe disease. However, adjustment was made for diabetes duration and HbA1c among other covariates, and an increased risk caused by insulin per se cannot be ruled out, as also has been underlined in other recent observational studies (29-33, 36). Lifestyle measures with weight reduction may be of value for obese patients with insulin included as treatment. The on-going ORIGIN randomised trial comparing insulin glargine with omega-3 fatty acids or placebo for risk of CVD in patients with diabetes at high risk for vascular disease will give further information (37).

Subgroup analyses with patients presenting different degrees of renal impairment were conducted, and did not show any increased risk of CVD, acidosis/serious infection or all-cause mortality associated with metformin-based treatments in patients with eGFR 30-45, 45-60, or >60 mL/min/1.73 m^2. Rather, metformin-based treatments were associated with reduced risks of all-cause mortality and acidosis/serious infection in patients with eGFR 45-60 or >60 mL/min/1.73 m^2. The prevalence of renal impairment differed between the groups, with patients presenting an eGFR <45 mL/min/1.73 m^2 being rare in metformin-based treatments. However, the prevalence of eGFR 45-60 mL/min/1.73 m^2 ranged between 10.7 % and 14.4 % in these patients, and did not differ much from other patients. Consequently, the subgroup with eGFR 45-60 mL/min/1.73 m^2 was based on a surprisingly large material, while the subgroup with eGFR 30-45 mL/min/1.73 m^2 constituted relatively few patients.

A recently published observational study examined the effects of metformin in 19 691 patients with diabetes and advanced cardiovascular disease, thus considered vulnerable to metformin (14). The results indicated significantly reduced risk of all-cause mortality in patients treated with metformin compared to other glucose-lowering treatments. Results were consistent in a subgroup of patients with renal impairment (eGFR 30-60 mL/min/1.73 m^2). The survey, however, only analysed all-cause mortality, and could therefore not detect potential cases of lactic acidosis. Furthermore, the follow up was short (2 years) and did not analyse patients with eGFR 30-45 and 45-60 mL/min/1.73 m^2, separately. Further, glucose-lowering treatments were only specified as metformin use or not, and no adjustments for crucial covariates such as HbA1c or diabetes duration were made. Several studies have failed to demonstrate increased incidence rate of lactic acidosis in DM2 patients treated with metformin. Thus, DM2 with its comorbidities or any glucose-lowering treatment rather than metformin use *per se* have been suggested to be risk factors for lactic acidosis (12).

The large population, 51 675 DM2 patients, and extensive adjustments for many important covariates are apparent strengths of the present survey. Risk calculations were made, adjusted for covariates with propensity scores and in Cox regression models. The propensity score achieved perfectly well balanced groups regarding baseline characteristics indicating the robustness of this statistical analysis. The Cox regression models enabled more comprehensive comparisons between several glucose-lowering regimens. Data are collected from the NDR database with a currently estimated coverage of more than 90 % of all patients in hospital outpatient clinics and almost 80 % of all patients in primary care in Sweden, suggesting it to be highly representative of clinical practice. ~~We also presented exposure time for the different glucose-lowering treatments, but unfortunately there was no useful information about doses.~~ Furthermore, we presented exposure time for the different glucose-lowering treatments and median daily doses of metformin in each treatment group, which showed clinically relevant doses.

Despite extensive adjustments, covariates of possible importance could have been missed. Thus, the presence of allocation bias may not be fully avoided. Furthermore, patients who changed glucose-lowering treatment during the study were not censored. It could be that patients with advancing disease more frequently changed to a specific glucose-lowering

medication, diluting the results observed. Comparison of baseline characteristics indicated higher proportions of history of CVD, CHF and serious infections in patients changing treatment. This could have affected the results, even though the proportions of patients changing treatment were high in all groups. Only eight cases of diagnosed lactic acidosis were reported during the follow-up (4 cases in metformin only, 2 cases in metformin + insulin and 2 cases in insulin only), and thus analyses with lactic acidosis as an endpoint would not provide desirable strength. Therefore, a composite endpoint (acidosis/serious infections), including diagnosis of serious infections (n=4782), acute renal failure (n=914), acidosis (n=167) and shock (n=17), was used. The six most common diagnoses patients were hospitalised for in this composite endpoint were: pneumonia (unspecified), bacterial pneumonia (unspecified), acute renal failure (unspecified), acute tubulo-interstitial nephritis, sepsis (unspecified) and gastroenteritis and colitis of unspecified origin. Altogether this complicates the evaluation of lactic acidosis *per se*, although this diagnosis in practice only occurs in combination with severe infections or CVD. Furthermore, lactic acidosis reported with use of biguanides mostly involve phenformine, which was early withdrawn from the market, as lactic acidosis was 20 times more frequent than with metformin (12). In cases of lactic acidosis, plasma metformin concentration has also not proved to be of any prognostic significance (40). The patient group treated with other OHA, were mainly treated with SU and to a very limited degree with glitazones, acarbose or DPP-4 inhibitors during the study period. Investigation of the individual effectiveness of these agents would however be of interest in the future.

In conclusion, this nation-wide observational study of 51 675 DM2 patients supports the previously observed effectiveness of metformin. Metformin was associated with reduced risk of all-cause mortality compared to both insulin and other OHA, and for several additional endpoints compared to insulin. The results were consistent in a subgroup of patients with renal impairment, and no increased risk of acidosis/serious infection was seen. Together with previous findings, this constitutes evident support to the less strict approach to metformin treatment in patients with renal impairment, advocated in most guidelines. Thus, considerably more DM2 patients may be considered for treatment with metformin.

Data sharing

No additional data available.

Author contributions

NE, LS, BZ, JC, AMS, JMJ, KEO, SG and BE contributed to the conception and design. LS, JC and AMS contributed to the acquisition of data and performed the calculations. LS, NE, JC, BZ, SG, AMS and BE contributed to the analysis and interpretation of data. NE and BE contributed to drafting the article. NE, BE, BZ, JZ, AMS, LS, KEO, SG and JMJ contributed to revising the article critically for important intellectual content and final approval of the version to be submitted.

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Conflict of interest

BE has served as a lecturer for all pharmacological companies manufacturing glucose-lowering agents and participated in advisory boards for Eli Lilly Sweden AB and Eli Lilly & Co, Sanofi-aventis, Sweden, Boehringer Ingelheim AB, Sweden, and MSD, Sweden.

Disclaimer

Björn Zethelius (BZ) is employed by the Medical Products Agency (MPA), Uppsala Sweden. BZ has not received any financial support or other benefits from BMS France or any commercial sponsor. Results and views of the present study represent the authors and not necessarily any official views of the MPA where BZ is employed.

Figure legends

Table 1: Baseline characteristics in all 51,675 type 2 diabetes patients and in groups based on glucose-lowering treatments. Means ± one standard deviation (SD) and frequencies (%) are given. There were statistically significant differences ($p < 0.001$) in all variables between the groups.

~~Table 3~~ Table 2: Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with metformin only as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides.

~~Table 5~~ Table 3: Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with insulin only and patients with metformin only as reference, or in patients with other OHA only and patients with metformin only as reference. Each comparison was adjusted by stratification with octiles of propensity scores.

~~Table 6~~ Table 4: Adjusted hazard ratios (HR) with 95% confidence intervals for any CVD, any acidosis/serious infection, and all-cause mortality in subgroups of patients with different eGFR intervals. HR associated with the examined agent in any combination is given with any other glucose-lowering treatment as reference. Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid-lowering agents and cardiac glycosides.

Figure 1: Time (months) to event of all-cause mortality (a), any CVD (b), and any acidosis/serious infection (c) in each treatment group, unadjusted.

Appendix Table 1: Baseline characteristics in groups of patients treated with metformin only, insulin only, or other OHA only, applied in Cox regression analyses presented in Table 2. Means ± standard deviation (SD) and proportions (%) of clinical variables at baseline. P values are given for comparison between metformin only and insulin only, and between metformin only and other OHA only, unadjusted and after adjustment by stratification for octiles of propensity scores applied for each comparison.

~~Table 2~~ Appendix Table 2: Time of exposure (months) to specific glucose-lowering agents, and proportions changing treatment (%) in each group.

~~Table 4~~ Appendix Table 3: Numbers and frequencies (%) of endpoint events in each treatment group.

Appendix Table 4: Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with other OHA only as reference.

Appendix Table 5: Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with SU only and patients with metformin only as reference.

Appendix Table 6: Appendix Table 6. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) and p-values for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients treated with insulin + other OHA or insulin + metformin, and with insulin only as reference.

Appendix Figure 1: Enrollment of patients.

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Table 1. Baseline characteristics in all 51,675 type 2 diabetes patients and in groups based on glucose-lowering treatments.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin + insulin + other OHA	Total
N	14 697 (28 %)	8 807 (17 %)	7 109 (14 %)	12 291 (24 %)	5 171 (10%)	1 365 (2.6 %)	2 235 (4.3 %)	51 675 (100 %)
Age (Years)	63.8 (9.7)	65.4 (9.7)	64.6 (8.8)	65.2 (10.5)	69.7 (9.5)	69.6 (9.1)	64.7 (8.5)	65.3 (9.8)
HbA1c (%)	6.9 (3.1)	7.3 (3.2)	7.7 (3.4)	7.6 (3.4)	6.9 (3.0)	7.7 (3.3)	7.9 (3.4)	7.3 (3.3)
< 6.9	8131 (55.3%)	3296 (37.4%)	1710 (24.1%)	3433 (27.9%)	2898 (56.0%)	326 (23.9%)	361 (16.2%)	20155 (39.0%)
6.9 - 8.8	6037 (41.1%)	4982 (56.6%)	4240 (59.6%)	7045 (57.3%)	2139 (41.4%)	845 (61.9%)	1478 (66.1%)	26766 (51.8%)
> 8.8	529 (3.6%)	529 (6.0%)	1159 (16.3%)	1813 (14.8%)	134 (2.6%)	194 (14.2%)	396 (17.7%)	4754 (9.2%)
Systolic blood pressure (mmHg)	139.4 (16.6)	141.2 (16.9)	140.8 (16.8)	138.9 (18.0)	141.4 (17.5)	141.9 (18.2)	141.9 (16.4)	140.1 (17.2)
Diabetes duration (Years)	4.6 (4.3)	8.9 (5.9)	11.6 (7.0)	14.3 (10.4)	7.5 (6.2)	11.6 (6.8)	12.0 (6.2)	9.4 (8.0)
eGFR (mL/min/1.73 m^2)	82.0 (20.2)	80.4 (21.1)	79.2 (21.5)	73.6 (23.8)	73.8 (21.1)	68.9 (22.4)	79.5 (21.2)	78.1 (21.9)
<45	231 (1.6%)	222 (2.5%)	238 (3.3%)	1370 (11.1%)	404 (7.8%)	214 (15.7%)	63 (2.8%)	2742 (5.3%)
45-60	1572 (10.7%)	1167 (13.3%)	1024 (14.4%)	1955 (15.9%)	888 (17.2%)	255 (18.7%)	316 (14.1%)	7177 (13.9%)
>60	12894 (87.7%)	7418 (84.2%)	5847 (82.2%)	8966 (72.9%)	3879 (75.0%)	896 (65.6%)	1856 (83.0%)	41756 (80.8%)
BMI (Kg/m^2)	30.7 (4.9)	29.9 (4.9)	31.6 (5.0)	27.4 (4.8)	27.2 (4.5)	28.3 (4.9)	31.1 (5.1)	29.5 (5.1)
Non-HDL-C (mmol/L)	3.64 (1.00)	3.53 (0.98)	3.39 (0.97)	3.35 (0.98)	3.60 (0.99)	3.52 (1.04)	3.39 (0.94)	3.50 (0.99)
Microalbuminuria	21.0%	25.9%	33.8%	30.8%	24.2%	34.4%	34.5%	27.2%
Previous hospitalisation	11.5%	11.6%	18.1%	23.1%	15.5%	22.9%	15.2%	16.1%
Female sex	44.7%	40.0%	43.5%	40.2%	39.2%	39.8%	41.4%	41.9%
History of CVD	15.9%	17.6%	25.9%	26.4%	21.4%	30.2%	24.6%	21.4%
History of CHF	3.5%	3.9%	7.3%	8.9%	6.4%	10.1%	5.5%	5.9%
History of serious infections	1.8%	1.6%	2.9%	4.9%	2.8%	5.2%	2.7%	2.9%
Cardiac glycosides	2.6%	2.7%	4.1%	3.0%	4.3%	6.2%	4.3%	3.3%
Organic nitrates	6.3%	7.4%	9.7%	8.5%	8.8%	13.0%	10.1%	8.1%
ASA	45.4%	48.8%	57.3%	45.7%	45.9%	55.4%	58.6%	48.6%
Lipid modifying agents	49.9%	54.0%	61.7%	44.8%	44.1%	51.7%	63.6%	51.1%
Antihypertensive agents	71.8%	74.0%	81.9%	66.2%	71.3%	79.5%	83.0%	72.9%
Multi-dose dispensation	1.4%	1.6%	2.7%	3.0%	1.5%	3.7%	2.6%	2.1%
Smoker	14.8%	14.0%	12.8%	14.9%	12.3%	12.2%	13.6%	14.0%

Means ± one standard deviation (SD) and frequencies (%) are given. There were statistically significant differences ($p < 0.001$) in all variables between the groups.

Table 2. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with metformin only as reference

	Metformin only	Insulin only	Other OHA only	Insulin + other OHA	Metformin + other OHA	Metformin + insulin	Metformin + Insulin + other OHA
Any CVD	Reference	1.28 (1.19-1.37)***	1.13 (1.04-1.23)**	1.40 (1.24-1.58)***	1.11 (1.03-1.20)**	1.28 (1.19-1.38)***	1.33 (1.19-1.49)***
Fatal CVD	Reference	1.41 (1.18-1.68)***	1.30 (1.08-1.56)**	1.17 (0.91-1.51)	*	*	1.21 (0.92-1.58)
Any acidosis/serious infection	Reference	1,37 (1,26-1,50)***	1,16 (1,04-1,28)**	1,31 (1,13-1,51)***	1,04 (0,95-1,14)	1,20 (1,09-1,32)***	1,15 (1.00-1,32)*
Fatal acidosis/serious infection	Reference	1,63 (1,29-2,07)***	1,28 (0,98-1,67)	1,32 (0,91-1,89)	0,94 (0,72-1,23)	1,41 (1,08-1,83)*	1,12 (0,73-1,67)
All-cause mortality	Reference	1.47 (1.35-1.61)***	1.30 (1.18-1.44)***	1.30 (1.12-1.50)***	1.15 (1.05-1.27)**	1.25 (1.13-1.38)***	1.31 (1.14-1.52)***

* P<0.05
** P<0.01
*** P<0.001

*Non-proportional hazards, group excluded from analysis.

Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Table 3. Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with insulin only and patients with metformin only as reference, or in patients with other OHA only and patients with metformin only as reference

	Events/Patients N/N	Events/Patients N/N	Hazard ratio (95% CI)	P-value
	Insulin only	**Metformin only**	**Insulin only Vs metformin only**	
Any CVD	2389 / 11427	1734 / 14317	1.18 (1.07-1.29)	<0.001
Fatal CVD	681 / 12285	264 / 14696	1.12 (0.91-1.40)	0.29
Any acidosis/serious infection	1867 / 11860	1154 / 14517	1.28 (1.14-1.43)	<0.001
Fatal acidosis/serious infection	325 / 12284	127 / 14697	1.45 (1.07-1.97)	0.019
All-cause mortality	2002 / 12291	971 / 14697	1.34 (1.19-1.50)	<0.001
	Other OHA only	**Metformin only**	**Other OHA only Vs metformin only**	
Any CVD	929 / 4964	1734 / 14317	1.02 (0.93-1.12)	0.71
Fatal CVD	237 / 5171	264 / 14696	1.03 (0.84-1.26)	0.80
Any acidosis/serious infection	623 / 5062	1154 / 14517	1.05 (0.94-1.18)	0.41
Fatal acidosis/serious infection	109 / 5171	127 / 14697	1.13 (0.83-1.53)	0.44
All-cause mortality	745 / 5171	971 / 14697	1.13 (1.01-1.27)	0.032

Each comparison was adjusted by stratification with octiles of propensity scores.

Table 4. Adjusted hazard ratios (HR) with 95% confidence intervals for any CVD, any acidosis/serious infection, and all-cause mortality in subgroups of patients with different eGFR intervals. HR associated with the examined agent in any combination is given with any other glucose-lowering treatment as reference.

	30 <= eGFR < 45			45 <= eGFR < 60			eGFR >= 60			All patients	
	N (% of total)	Events (% of total)	HR (95 % CI)	N (% of total)	Events (% of total)	HR (95 % CI)	N (% of total)	Events (% of total)	HR (95 % CI)	N	Events
Any CVD											
Metformin	670 (35.4%)	210 (30.7%)	1.00 (0.83-1.19)	3839 (57.7%)	849 (51.2%)	0.94 (0.84-1.05)	27083 (67.3%)	3698 (63.4%)	0.98 (0.92-1.05)	31628	4774
Insulin	1180 (62.3%)	474 (69.2%)	1.30 (1.02-1.64)*	3201 (48.1%)	930 (56.1%)	1.24 (1.09-1.42)**	16718 (41.5%)	2853 (48.9%)	1.19 (1.11-1.27)***	21503	4476
Other OHA	702 (37.1%)	241 (35.2%)	1.03 (0.85-1.26)	2450 (36.8%)	608 (36.7%)	1.05 (0.93-1.18)	13552 (33.7%)	2065 (35.4%)	1.03 (0.97-1.09)	16817	2965
Total in group	1894	685		6655	1657		40239	5829			
Any acidosis/serious infection											
Metformin	692 (33.9%)	143 (28.4%)	0.98 (0.79-1.21)	4000 (57.5%)	557 (49.4%)	0.85 (0.74-0.97)*	27618 (67.3%)	2444 (60.6%)	0.91 (0.84-0.98)*	32345	3155
Insulin	1302 (63.7%)	366 (72.6%)	1.34 (1.02-1.76)*	3406 (48.9%)	652 (57.9%)	1.07 (0.91-1.26	17152 (41.8%)	2057 (51%)	1.22 (1.12-1.32)***	22310	3260
Other OHA	738 (36.1%)	166 (32.9%)	*	2555 (36.7%)	379 (33.6%)	0.87 (0.75-1.00)	13852 (33.7%)	1375 (34.1%)	1.02 (0.95-1.09)	17265	1960
Total in group	2044	504		6960	1127		41048	4034			
All-cause mortality											
Metformin	715 (33.3%)	179 (27%)	1.02 (0.84-1.24)	4079 (56.8%)	558 (46.5%)	0.87 (0.77-0.99)*	28015 (67.1%)	2120 (56.9%)	0.87 (0.81-0.94)***	32848	2873
Insulin	1386 (64.6%)	468 (70.5%)	1.16 (0.91-1.47)	3550 (49.5%)	701 (58.4%)	1.12 (0.95-1.31)	17565 (42.1%)	1921 (51.5%)	1.29 (1.19-1.41)***	23000	3328
Other OHA	766 (35.7%)	222 (33.4%)	0.97 (0.79-1.19)	2626 (36.6%)	429 (35.7%)	0.97 (0.84-1.11)	14049 (33.6%)	1375 (36.9%)	1.10 (1.02-1.19)*	17578	2087
Total in group	2146	664		7177	1201		41756	3729			

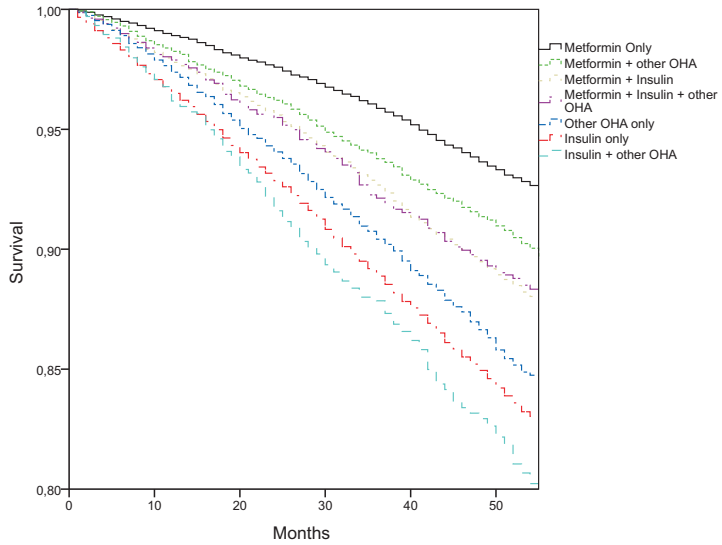
* P<0.05
** P<0.01
*** P<0.001

* Non-proportional hazards, group excluded from analysis.

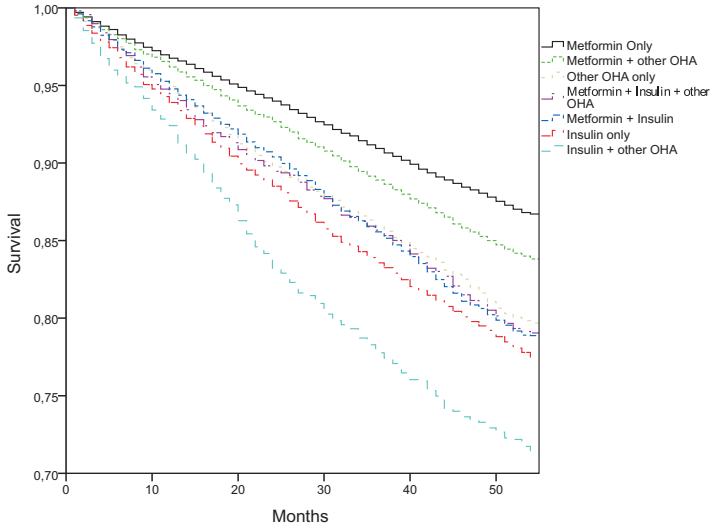
Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Figure 1. Time (months) to event of all-cause mortality (a), any CVD (b), and any infection/acidosis (c) in each treatment group, unadjusted

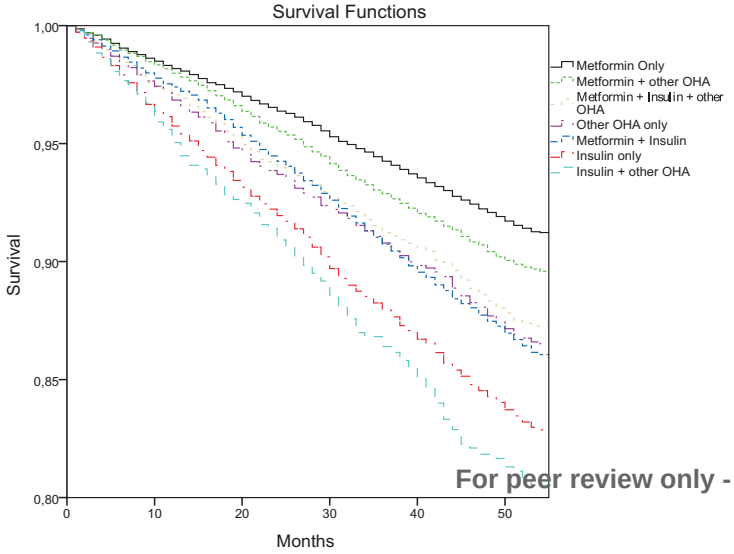
a. All-cause mortality



b. Any CVD



c. Any acidosis/infection



Appendix Table 1. Baseline characteristics in groups of patients treated with metformin only, insulin only, or other OHA only, applied in Cox regression analyses presented in Table 2.

	Metformin Only	Insulin only	Other OHA only	P metformin only/ insulin only Unadjusted	P metformin only/ insulin only Adjusted for PS	P metformin only/ other OHA only Unadjusted	P metformin only/ other OHA only Adjusted for PS
N	14697	12291	5171				
Age (Years)	63.8 (9.7)	65.2 (10.5)	69.7 (9.5)	<0.001	0.49	<0.001	0.126
HbA1c (%)	51.9 (10.4)	60.0 (13.6)	51.4 (9.5)	<0.001	0.46	0.002	0.24
Systolic blood pressure (mmHg)	139.4 (16.6)	138.9 (18.0)	141.4 (17.5)	0.018	0.96	<0.001	0.164
Diabetes duration (Years)	4.6 (4.3)	14.3 (10.4)	7.5 (6.2)	<0.001	0.78	<0.001	0.37
eGFR (mL/min/1.73 m^2)	82.0 (20.2)	73.6 (23.8)	73.8 (21.1)	<0.001	0.94	<0.001	0.177
BMI (Kg/m^2)	30.7 (4.9)	27.4 (4.8)	27.2 (4.5)	<0.001	0.53	<0.001	0.008
Non-HDL-C (mmol/L)	3.64 (1.00)	3.35 (0.98)	3.60 (0.99)	<0.001	0.78	0.008	0.62
Microalbuminuria	21.0%	30.8%	24.2%	<0.001	0.46	<0.001	0.50
Previous hospitalisation	11.5%	23.1%	15.5%	<0.001	0.57	<0.001	0.73
Female sex	44.7%	40.2%	39.2%	<0.001	0.73	<0.001	0.59
History of CVD	15.9%	26.4%	21.4%	<0.001	0.97	<0.001	0.111
History of CHF	3.5%	8.9%	6.4%	<0.001	0.022	<0.001	0.74
History of serious infections	1.8%	4.9%	2.8%	<0.001	0.96	<0.001	0.72
Cardiac glycosides	2.6%	3.0%	4.3%	0.064	0.96	<0.001	0.196
Organic nitrates	6.3%	8.5%	8.8%	<0.001	0.61	<0.001	0.45
ASA	45.4%	45.7%	45.9%	0.56	0.58	0.52	0.65
Lipid modifying agents	49.9%	44.8%	44.1%	<0.001	0.88	<0.001	0.94
Antihypertensive agents	71.8%	66.2%	71.3%	<0.001	0.38	0.58	0.81
Multi-dose dispensation	1.4%	3.0%	1.5%	<0.001	0.97	0.54	0.97
Smoker	14.8%	14.9%	12.3%	0.77	0.104	<0.001	0.28

Means ± standard deviation (SD) and proportions (%) of clinical variables at baseline. P values are given for comparison between metformin only and insulin only, and between metformin only and other OHA only, unadjusted and after adjustment by stratification for octiles of propensity scores applied for each comparison.

Appendix Table 2: Time of exposure (months) to specific glucose-lowering agents, and proportions changing treatment (%) in each group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin + insulin + other OHA
Mean Exposure time to metformin	49,4	51,0	46,3				48,9
Mean Exposure time to insulin			51,8	55,3		54,1	53,4
Mean Exposure time to Other Oral		49,1			45,3	39,5	48,3
Change treatment (%)	80.8 %	80.5 %	81.8 %	91.3 %	88.4 %	56.5 %	93.9 %

Appendix Table 3: Numbers and frequencies (%) of endpoint events in each treatment group.

	Metformin Only	Metformin + other OHA	Metformin + insulin	Insulin only	Other OHA only	Insulin + other OHA	Metformin+ insulin + other OHA
Any CVD	1734 (3.3%)	1287 (4%)	1338 (5.4%)	2389 (5.9%)	929 (5.2%)	334 (7.8%)	415 (5.4%)
Fatal CVD	264 (0.5%)	230 (0.6%)	276 (1%)	681 (1.4%)	237 (1.2%)	94 (1.8%)	74 (0.8%)
Acidosis/serious infection	1154 (2.1%)	843 (2.5%)	899 (3.4%)	1867 (4.3%)	623 (3.3%)	235 (5%)	259 (3.1%)
Fatal acidosis/serious infection	127 (0.2%)	95 (0.3%)	124 (0.4%)	325 (0.7%)	109 (0.5%)	41 (0.8%)	29 (0.3%)
All-cause mortality	971 (1.7%)	834 (2.4%)	818 (2.9%)	2002 (4.2%)	745 (3.7%)	258 (4.9%)	250 (2.8%)

Appendix Table 4. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in all patients, in each treatment group, and with other OHA only as reference

	Other OHA only	Insulin Only	Metformin only	Insulin + other OHA	Metformin + other OHA	Metformin + insulin	Metformin + insulin + other OHA
Any CVD	Reference	1.13 (1.04-1.22)	0.88 (0.81-0.96)	1.24 (1.09-1.41)	0.98 (0.9-1.07)	1.12 (1.03-1.23)	1.17 (1.04-1.32)
Fatal CVD	Reference	1.09 (0.92-1.28)	0.77 (0.64-0.93)	0.91 (0.7-1.16)	*	*	0.93 (0.71-1.22)
Any acidosis/serious infection	Reference	1.19 (1.08-1.31)	0.87 (0.78-0.96)	1.14 (0.97-1.32)	0.9 (0.81-1)	1.04 (0.93-1.16)	1 (0.86-1.16)
Fatal acidosis/serious infection	Reference	1.27 (1.01-1.62)	0.78 (0.6-1.02)	1.03 (0.71-1.48)	0.73 (0.55-0.97)	1.1 (0.83-1.45)	0.88 (0.57-1.32)
All-cause mortality	Reference	1.12 (1.02-1.23)	0.76 (0.69-0.84)	0.99 (0.85-1.14)	0.88 (0.8-0.98)	0.96 (0.86-1.07)	1.01 (0.86-1.17)

*Non-proportional hazards, group excluded from analysis.

Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Appendix Table 5. Adjusted hazard ratios with 95 % confidence intervals for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients with SU only and patients with metformin only as reference

	SU only	**Metformin Only**	**SU only Vs Metformin only**	
	Events/Patients N/N	Events/Patients N/N	Hazard ratio (95% CI)	P-value
Any CVD	788 / 4084	1734 / 14317	0.99 (0.89-1.09)	0.82
Fatal CVD	210 / 4272	264 / 14696	1.01 (0.82-1.25)	0.91
Any acidosis/serious infection	506 / 4178	1154 / 14517	1.0 (0.89-1.14)	0.96
Fatal acidosis/serious infection	94 / 4272	127 / 14697	1.17 (0.85-1.60)	0.34
All-cause mortality	664 / 4272	971 / 14697	1.15 (1.02-1.30)	0.019

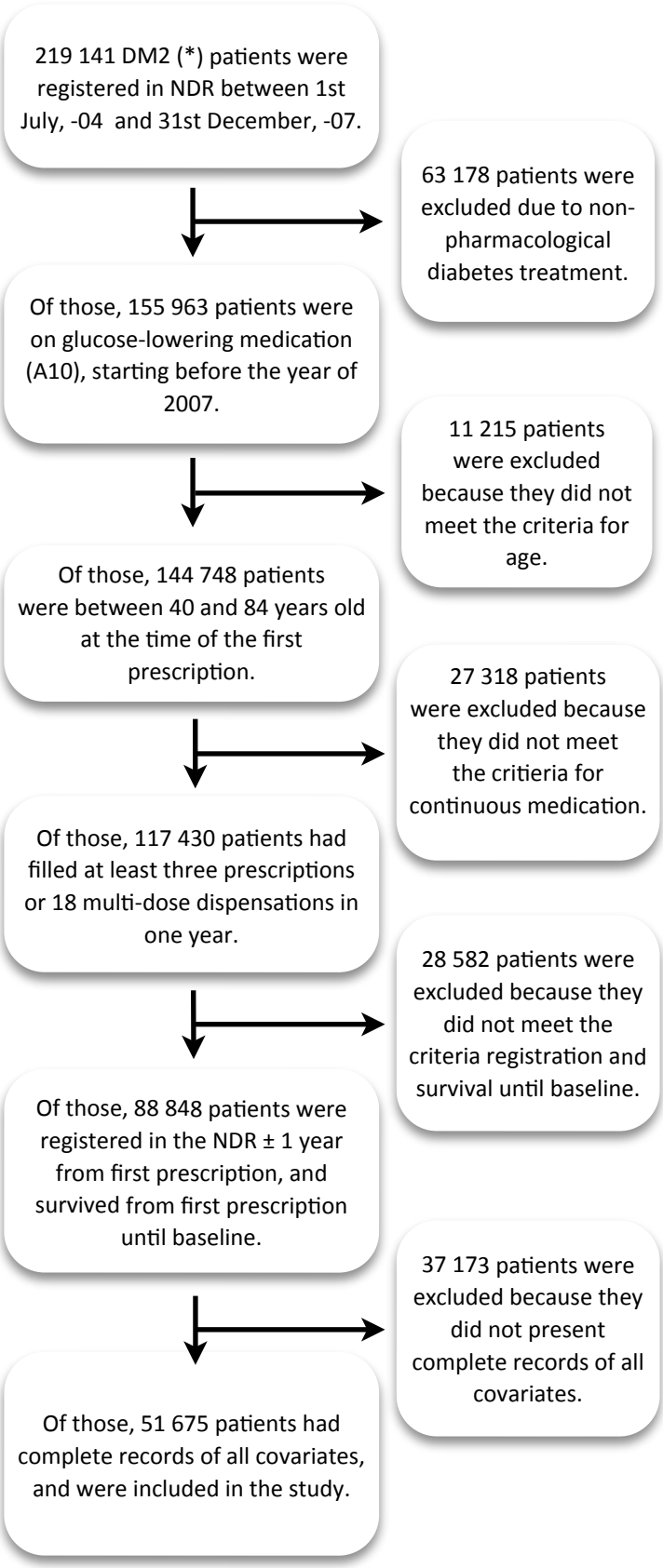
Adjusted by stratification with octiles of propensity scores.

Appendix Table 6. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) and p-values for any CVD, fatal CVD, any acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality in patients treated with insulin + other OHA or insulin + metformin, and with insulin only as reference

	Insulin only	Insulin + other OHA		Insulin + metformin	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Any CVD	Reference	1.10 (0.98-1.23)	0.1154	0.96 (0.89-1.03)	0.2823
Fatal CVD	Reference	0.84 (0.67-1.05)	0.1334	0.90 (0.77-1.05)	0.1687
Any acidosis/serious infection	Reference	0.96 (0.84-1.1)	0.5976	0.86 (0.79-0.94)	0.0007
Fatal acidosis/serious infection	Reference	0.82 (0.58-1.13)	0.2413	0.85 (0.68-1.06)	0.1532
All-cause mortality	Reference	0.89 (0.78-1.01)	0.0766	0.84 (0.76-0.91)	<.0001

Adjustments were made for age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multi-dose dispensation, previous hospitalization, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents and cardiac glycosides.

Appendix Figure 1. Enrollment of patients



* DM2 is Type 2 Diabetes Mellitus

Definitions of the endpoints (Appendix Text)

Cardiovascular disease (CVD)

CVD was defined as diagnosis of myocardial infarction (ICD-10 code I21), angina pectoris (ICD-10 code I20.0), intracerebral haemorrhage, cerebral infarction, unspecified stroke (ICD-10 codes I61, I63, I64 and I679), peripheral vascular disease (PVD, ICD-10 codes E105, E115, E145, I702, I731, I739 and I792), or intervention with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), whichever occurred first.

Acidosis/serious infection

Acidosis/infection was defined as diagnosis of acidosis or chock (ICD-10 codes E10.1, E10.1A, E10.1D, E10.1X, E11.1, E11.1A, E11.1D, E11.1X, E13.1, E14.1, E87.2, R57.1, R57.2, R57.8 or R57.9, or diagnosis of serious infection (ICD-10 codes A00-A09, A15-A19, A32.7, A39-A41, A42.7, A48, B37.7, I00-I02, I33, I38, I39, J13-J18, J85, J86, K25, K61, K80.0, K80.3, K80.4, K81, K83.0, K85, K86, M00, M46.2, M72.6, M86.0, M86.1, M86.8 or M86.9 or acute renal failure (ICD-10 codes N10.9 or N17.