Risk of Major Adverse Cardiovascular Events, Severe Hypoglycemia, and All-Cause Mortality for Widely Used Antihyperglycemic Dual and Triple Therapies for Type 2 Diabetes Management: A Cohort Study of All Danish Users

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OBJECTIVE

The vast number of antihyperglycemic medications and growing amount of evidence make clinical decision making difficult. The aim of this study was to investigate the safety of antihyperglycemic dual and triple therapies for type 2 diabetes management with respect to major adverse cardiovascular events, severe hypoglycemia, and all-cause mortality in a real-life clinical setting.

RESEARCH DESIGN AND METHODS

Cox regression models were constructed to analyze 20 years of data from the Danish National Patient Registry with respect to effect of the antihyperglycemic therapies on the three end points.

RESULTS

A total of 66,807 people with type 2 diabetes were treated with metformin (MET) plus a combination of second- and third-line therapies. People on MET plus sulfonylurea (SU) had the highest risk of all end points, except for severe hypoglycemia, for which people on MET plus basal insulin (BASAL) had a higher risk. The lowest risk of major adverse cardiovascular events was seen for people on a regimen including a glucagon-like peptide 1 (GLP-1) receptor agonist. People treated with MET, GLP-1, and BASAL had a lower risk of all three end points than people treated with MET and BASAL, especially for severe hypoglycemia. The lowest risk of all three end points was, in general, seen for people treated with MET, sodium–glucose cotransporter 2 inhibitor, and GLP-1.

CONCLUSIONS

Findings from this study do not support SU as the second-line treatment choice for patients with type 2 diabetes. Moreover, the results indicate that adding a GLP-1 in people treated with MET and BASAL could be considered, especially if those people suffer from severe hypoglycemia.

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Management of type 2 diabetes focuses on prevention or delay of complications without reducing quality of life for the individual. Lifestyle management, education, support, and control of cardiovascular risk factors and blood glucose levels are cornerstone components in this management (1). Comprehensive lifestyle management and metformin (MET) use is the first-line therapy (2), but other additional glucose-lowering medications often become necessary, and the vast number of medications available combined with the growing evidence regarding efficacy and safety make decision making difficult. A position statement by the American Diabetes Association and the European Association for the Study of Diabetes was published in 2012, 2015, and 2018 (2) with the aim of providing a summary of this evidence for practitioners in the U.S. and Europe. Identification of evidence was carried out via a systematic search for randomized clinical trials (RCTs), systematic reviews, and meta-analyses. Many RCTs have been conducted, and in recent years they have included large cardiovascular outcomes trials (CVOTs) with durations of 2–5 years. For example, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (n = 9,340) demonstrated a hazard ratio (HR) for major adverse cardiovascular events (MACE) of 0.87 (95% CI 0.78–0.97) for liraglutide compared with placebo (3). The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (n = 7,020) demonstrated an HR for MACE of 0.86 (95% CI 0.74–0.99) for empagliflozin compared with placebo (4). Also, on the end point of severe hypoglycemia, evidence from RCTs exists (3–6). All of these trials provide strong evidence of the use of a single compound but not the use of drugs from a specific class. Furthermore, the exclusion criteria typically limit real-world generalizability. For example, the EMPA-REG OUTCOME trial included 15 exclusion criteria (7), and some of them might not be assessed as contraindications for prescription of empagliflozin by the patient's general practitioner. Finally, dual therapy with MET plus the trial drug is typically under investigation, but triple therapy is also prevalent, and the safety consequences of drug–drug interactions in RCTs are difficult to investigate, because the CVOTs are very expensive. Observational studies have the potential to provide an insight into the real-world evidence of the safety of different drug classes in dual and triple therapies.

The aim of this study was to investigate the safety of widely used antihyperglycemic dual and triple therapies for type 2 diabetes management with respect to MACE, severe hypoglycemia, and all-cause mortality in all Danish users in a real-life clinical setting.

RESEARCH DESIGN AND METHODS

Study Design

To investigate the aim, time-to-event analyses were applied on a registry cohort consisting of all Danish adults with diabetes. MACE, severe hypoglycemia, and death are relatively rare events, and registry data as compared with data from RCTs are thus particularly useful to address the aim of this study, as several years of follow-up on different treatments are available. Furthermore, time-to-event analyses are unique because the outcome is not only about whether the event occurred or not, but also when it occurred after treatment initiation. Data were extracted from the Danish National Patient Registry, the Danish Central Person Registry, the Danish Register of Causes of Death, and the National Pharmacological Database based on the ICD-10 system and the Anatomical Therapeutical Chemical (ATC) classification system. Diagnosis of diabetes was based on the date of dispense of the first glucose-lowering treatment (ATC: A10A and A10B). By merging these medication data with sex and birthday from the Danish Central Person Registry, all Danish patients diagnosed with type 2 diabetes, including patients from the primary care sector, could be obtained. For each person, the last treatment regimen including MET (ATC: A10BA01) and one or two of the following medication classes were then identified: dipeptidyl peptidase 4 inhibitors (DPP-4i) (ATC: A10BH), sulfonylureas (SUs) (ATC: A10BB), sodium–glucose cotransporter 2 inhibitor (SGLT2i) (ATC: A10BK), glucagon-like peptide 1 receptor agonist (GLP-1-RA) (ATC: A10BJ), basal insulin (BASAL) (ATC: A10AC and A10AE), and pioglitazone (ATC: A10BG03). The products were identified for each year, and if the year only contained the products of interest mentioned, the year was assessed as valid. Periods with prescriptions of any other products, such as bolus or mix insulin, were excluded. The regimen should have been prescribed at least twice, and the first date of product prescription for the regimen defined treatment start date. Treatment end date was set to 31 December of the last valid year because no other products were prescribed that year, and it is assumed that the patient adhered to treatment throughout the year. The eight most widely used regimens in Denmark were selected for investigation. Less used regimens were excluded due to the resultant low number of MACE, severe hypoglycemia, and deaths leading to statistically insignificant results. Furthermore, selection of the eight most widely used regimens was considered as an objective method to exclude regimens that are either not popular or had not become popular yet, instead of a subjective selection of regimens of interest.

End Points

The end points in this study were MACE, severe hypoglycemia, and all-cause mortality. The classic three-point MACE used in this study is a composite end point of nonfatal acute myocardial infarctions, nonfatal ischemic strokes, and cardiovascular deaths. Nonfatal acute myocardial infarctions (ICD-10: DI21) and nonfatal ischemic strokes (ICD-10: DI61) were found in the Danish National Patient Registry. Cardiovascular deaths (ICD-10: DI00–DI99) were found in the Danish Register of Causes of Death. Severe hypoglycemic episodes (ICD-10: DE159–DE162) were found in the Danish National Patient Registry. Only hypoglycemic episodes specified as the primary cause of admission were selected. Therefore, a hypoglycemic episode was in this study defined as an event leading to hospitalization, for which the primary cause for hospitalization was hypoglycemia. All-cause mortality was defined as all-cause deaths found in the Danish Register of Causes of Death.

Sources of Data

The Danish National Patient Registry was established in 1977 and initially covered information on inpatients in somatic wards (8). It has been expanded and now includes information on all patients in Danish hospitals (8). The validity of registrations is high, especially for components of MACE (9–12). Moreover, the validity of hypoglycemia as primary

Table 1—List of dual and triple antihyperglycemic therapies under investigation in this study

Therapy	Abbreviation	Number of users of regimen	Compound	Percentage of users of compound[a]
Dual therapy				
MET + DPP-4i	MET + DPP-4	9,703	MET	100.0
			Sitagliptin	67.7
			Vildagliptin	14.2
			Saxagliptin	6.2
			Alogliptin	1.7
			Linagliptin	10.2
MET + sulfonylurea	MET + SU	24,983	MET	100.0
			Glibenclamide	16.5
			Tolbutamide	4.0
			Glipizide	10.3
			Gliclazide	10.3
			Glimepiride	59.0
MET + SGLT2i	MET + SGLT2	3,405	MET	100.0
			Dapagliflozin	49.7
			Canagliflozin	3.4
			Empagliflozin	46.9
MET + GLP-1-RA	MET + GLP-1	6,515	MET	100.0
			Exenatide	2.2
			Liraglutide	96.2
			Lixisenatide	0.1
			Dulaglutide	1.5
MET + basal insulin	MET + BASAL	12,906	MET	100.0
			Insulin (human)	53.2
			Insulin glargine	26.0
			Insulin detemir	17.0
			Insulin degludec	3.8
Triple therapy				
MET + DPP-4i + SU	MET + DPP-4 + SU	2,551	MET	100.0
			Sitagliptin	73.5
			Vildagliptin	11.0
			Saxagliptin	7.0
			Alogliptin	1.5
			Linagliptin	7.0
			Glibenclamide	4.4
			Tolbutamide	0.2
			Glipizide	3.2
			Gliclazide	14.4
			Glimepiride	77.8
MET + SGLT2i + GLP-1-RA	MET + SGLT2 + GLP-1	1,823	MET	100.0
			Dapagliflozin	54.5
			Canagliflozin	2.8
			Empagliflozin	42.6
			Exenatide	2.2
			Liraglutide	92.9
			Lixisenatide	0.4
			Dulaglutide	4.6
MET + GLP-1-RA + basal insulin	MET + GLP-1 + BASAL	4,921	MET	100.0
			Exenatide	1.5
			Liraglutide	96.3
			Lixisenatide	0.5
			Dulaglutide	1.6
			Insulin (human)	25.7
			Insulin glargine	43.9
			Insulin detemir	20.7
			Insulin degludec	9.7

The percentage of users of each compound within each drug class and treatment regimen is presented in the last column. [a]Within each drug class of each treatment regimen.

Table 2—Characteristics at baseline for people included in this study

	MET + DPP-4	MET + SU	MET + SGLT2	MET + GLP-1	MET + BASAL	MET + DPP-4 + SU	MET + SGLT2 + GLP-1	MET + GLP-1 + BASAL
Number of people	9,703	24,983	3,405	6,515	12,906	2,551	1,823	4,921
Age (years), mean (SD)	66 (12)	67 (12)	59 (12)	58 (12)	65 (12)	67 (11)	57 (11)	61 (10)
Sex (%)								
Female	40.3	41.5	36.2	47.1	39.5	38.1	35.2	40.8
Male	59.7	58.5	63.8	52.9	60.5	61.9	64.8	59.2
Diabetes duration (years), mean (SD)	7 (6)	5 (5)	6 (5)	7 (5)	9 (6)	10 (6)	9 (5)	11 (6)
Start of treatment (year), median (IQR)	2016 (2014–2017)	2008 (2002–2013)	2017 (2016–2017)	2015 (2013–2017)	2014 (2010–2016)	2015 (2012–2017)	2017 (2016–2017)	2016 (2013–2017)
Patient-years of exposure	18,993	69,404	3,310	16,688	33,176	5,742	2,859	12,057
MACE during follow-up,[a] *n* (R)[b]	412 (2.2)	3,902 (5.6)	37 (1.1)	169 (1.0)	1,082 (3.3)	164 (2.9)	23 (0.8)	161 (1.3)
Severe hypoglycemia during follow-up,[a] *n* (R)[b]	7 (0.0)	866 (1.2)	1 (0.0)	8 (0.0)	374 (1.1)	39 (0.7)	0 (0.0)	35 (0.3)
Died during follow-up, *n* (R)[b]	1,234 (6.5)	13,915 (20.0)	43 (1.3)	373 (2.2)	3,442 (10.4)	468 (8.2)	19 (0.7)	281 (2.3)
Highest completed education (%)								
High school graduate or lower	50.3	65.0	45.1	43.4	57.4	56.9	42.5	47.5
Above high school graduate	48.6	33.7	54.3	56.0	41.5	42.0	57.0	51.9
Income (%)								
Low	50.5	72.5	37.1	40.3	61.0	57.7	30.4	44.0
Normal	33.0	18.8	43.4	41.2	26.9	28.9	46.5	38.0
High	16.0	8.0	18.8	18.3	11.5	12.9	22.9	17.8
Charlson comorbidity index, mean (SD)	1.4 (1.9)	1.1 (1.7)	1.0 (1.5)	1.1 (1.6)	1.9 (2.1)	1.4 (1.8)	1.2 (1.5)	1.7 (1.8)
History of alcohol abuse (%)	6.2	4.8	6.1	6.0	8.1	5.1	4.0	5.5
History of nonfatal MACE (%)	8.7	7.1	8.3	6.9	10.0	8.8	7.4	8.5
History of severe hypoglycemia (%)	1.7	1.2	0.6	1.0	3.1	1.3	0.9	2.0
History of CKD (%)	2.6	0.9	0.6	0.9	1.9	1.8	1.0	1.7
Use of antidepressants (%)	10.4	7.8	11.2	11.9	12.9	10.2	11.4	13.5
Use of opioids (%)	58.0	41.2	57.0	59.8	58.5	54.0	58.4	62.9
Use of anxiolytics (%)	29.4	26.2	26.3	29.6	30.7	28.4	25.7	28.9
Use of antihypertensives (%)	4.5	3.9	3.9	4.4	5.4	5.2	4.1	6.5
Use of antithrombotics (%)	55.8	48.6	44.2	49.8	61.2	58.6	50.9	62.8
Use of statins (%)	81.1	47.4	78.9	80.8	76.8	84.7	88.2	91.8

[a]Only first event per person contributed. [b]R is rate (number of events per 100 patient-years of exposure).

cause for admission is deemed high. The Danish Register of Causes of Death contains information about all deaths since 1875 and is managed by the National Board of Health (13). The National Pharmacological Database is a nationwide register of medication sold after 1996 (14).

Statistical Analysis

Descriptive statistics are presented with mean and SD, median and interquartile range (IQR), or percentage of people. Unadjusted time to MACE, severe hypoglycemia, and death is illustrated with Kaplan-Meier curves. Cox proportional hazards models were applied to estimate unadjusted and adjusted effects of the therapies on the three end points. The unadjusted estimates are presented in a table, and the adjusted estimates are presented in a forest plot. Included people were considered censored at the first date of emigration, death, end of treatment, 5 years after start of treatment, or end of follow-up (31 December 2017). The cutoff at 5 years was chosen because data on SGLT2i have existed for ∼5 years with the European Medicines Agency's approval of dapagliflozin in 2012 (15). Start date of antihyperglycemic treatment defined baseline. To avoid immortal time bias, adjustment was only carried out from information prior to baseline. The Cox models were adjusted for age, sex, diabetes duration, history of chronic kidney disease (CKD) (ICD-10: DN18), history of nonfatal MACE (i.e., any MACE prior to baseline excluding cardiovascular deaths), treatment start date, highest completed education, and income. Age and diabetes duration were calculated as the number of years from date of birth and date of diagnosis, respectively, to baseline. Highest completed education was stratified in a high school graduate (or less) or above high school graduate. Yearly gross income per person was stratified in low (<200,000 Danish krone [DKK] or ∼30,000 U.S. dollars [USD]), normal (200,000–500,000 DKK or ∼30,000–75,000 USD), or high (>500,000 DKK or ∼75,000 USD). The model of MACE was further adjusted for Charlson comorbidity index (16), use of antihypertensive agents (ATC: C02), use of antithrombotic agents (ATC: B01), and use of statins (ATC: C10AA) prior to baseline. The model of severe hypoglycemia was further adjusted for history of severe hypoglycemia. The model of all-cause mortality was further adjusted for Charlson comorbidity index, history of alcohol abuse (ICD-10: DF10 and DZ721), use of antidepressants (ATC: N06AA), use of opioids (ATC: N02A), use of anxiolytics (ATC: N05B), use of antihypertensive

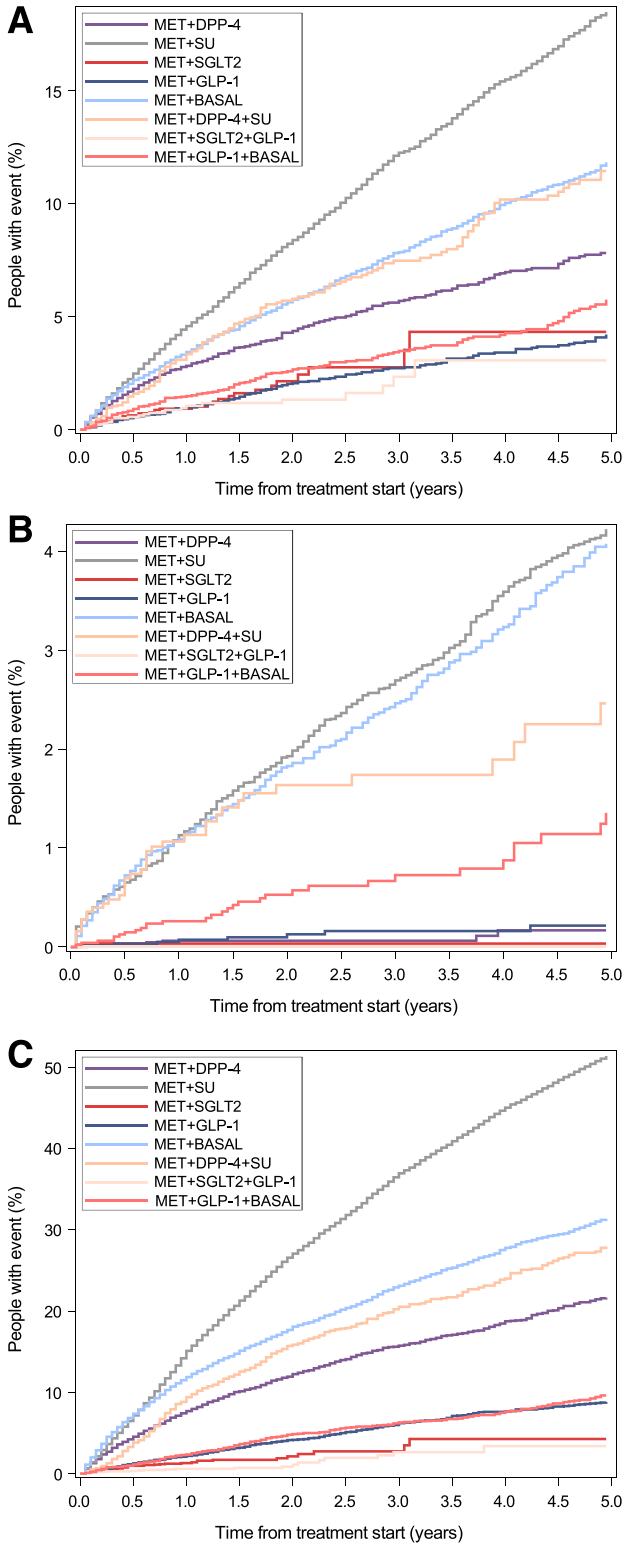

Figure 1—Time to event in a 5-year follow-up after initiation of antihyperglycemic dual and triple type 2 diabetes therapies. *A* is time to MACE, *B* is time to severe hypoglycemia, and *C* is time to death.

agents (ATC: C02), use of antithrombotic agents (ATC: B01), and use of statins (ATC: C10AA) prior to baseline. Comorbidities related to MACE were excluded from the index, and the comorbidities searched for prior to baseline and associated scores were as follows: cardiac insufficiency (1, ICD-10: DI50, DI110, DI130, and DI132), cardiovascular disease (1, ICD-10: DI70, DI71, DI72, DI73, DI74, and DI77), cerebrovascular disease (1, ICD-10: DI60, DI61–DI69, DG45, and DG46), dementia (1, ICD-10: DF00–DF03, DF051, and DG30), chronic pulmonary disease (1, ICD-10: DJ40–DJ47, DJ60–DJ67, DJ684, DJ701, DJ703, DJ841, DJ920, DJ961, DJ982, and DJ983), connective tissue disease (1, ICD-10: DM05, DM06, DM08, DM09, DM30, DM31, DM32, DM33, DM34, DM35, DM36, and DD86), peptic ulcer (1, ICD-10: DK221 and DK25–DK28), mild liver disease (1, ICD-10: DB18, DK700–DK703, DK709, DK71, DK73, DK74, and DK760), hemiplegia (1, ICD-10: DG81 and DG82), nephrological disease (2, ICD-10: DI12, DI13, DN00–DN05, DN07, DN11, DN14, DN17, DN19, and DQ61), late-diabetic complications (2, ICD-10: DE102–DE108 and DE112–DE118), solid cancers (2, ICD-10: DC00–DC75), leukemia (2, ICD-10: DC91–DC95), lymphoma (2, ICD-10: DC81–DC85, DC88, DC90, and DC96), moderate to severe liver disease (3, ICD-10: DB150, DB160, DB162, DB190, DK704, DK72, DK766, and DI85), metastatic cancer (6, ICD-10: DC76–DC80), and AIDS (6, ICD-10: DB21–DB24). Finally, a subgroup analysis of time to MACE in which patients were stratified in risk of cardiovascular disease defined as history of nonfatal MACE or not was conducted. The models were adjusted for age, sex, diabetes duration, education, income, Charlson comorbidity index, history of CKD, use of antihypertensive agents, use of antithrombotic agents, use of statins, and date of treatment initiation.

Data and Resource Availability

Data are available through Danmarks Statistik (https://www.dst.dk), and all authorized research organizations can apply for access. Access for international researchers can only be gained if they are affiliated with a Danish research organization.

RESULTS

The number of users of A10B medication and/or BASAL was 463,037, with 63% on monotherapy. The dual and triple therapies are presented in Table 1. As can be observed, no regimen including pioglitazone was found among the eight most widely used regimens in Denmark. The abbreviations presented in the table will be used throughout the rest of the article. Table 2 shows the characteristics of the people included in the study. Unknown cases for income and highest completed education were present but constituted ~1% and are thus not included in the table. However, they were present in the statistical models. For each regimen, the median (and IQR) start year is presented to indicate the distribution of users. For example, 25% of patients on MET + SU initiated treatment between 2013 and 2017 (75% quartile is 2013). In Fig. 1, Kaplan-Meier curves for the five dual and three triple therapies are shown, and Table 3 shows unadjusted estimated effects of the therapies with the most frequently used regimen of MET + SU as reference. The adjusted estimates are illustrated in the forest plot of Fig. 2 with MET + SU as reference. It can be noticed that risk of MACE, severe hypoglycemia, and all-cause mortality is reduced for all regimens compared with MET + SU, except for MET + BASAL, in which the risk of severe hypoglycemia is increased. People treated with MET + SGLT2, MET + GLP-1, or the combination MET + SGLT2 + GLP-1 have a lower risk of MACE compared with MET + SU, MET + BASAL, and MET + DPP-4, and the risk reduction is slightly larger for MET + GLP-1 (HR 0.51 [95% CI 0.43–0.60]) than MET + SGLT2 (HR 0.67 [95% CI 0.48–0.94]). People treated with MET + GLP-1 + BASAL have a lower risk of MACE (HR 0.55 [95% CI 0.46–0.66]) than people treated with MET + BASAL (HR 0.82 [95% CI 0.75–0.89]). Treatment with MET + DPP-4, MET + SGLT2, or MET + GLP-1 results in a decreased risk of severe hypoglycemia. The risk of severe hypoglycemia for MET + BASAL is high and even higher than MET + SU but not statistically significant (HR 1.09 [95% CI 0.93–1.29]), but a treatment with MET + GLP-1 + BASAL results in a reduced risk of severe hypoglycemia (HR 0.47 [95% CI 0.32–0.69]) compared with MET + SU. No severe hypoglycemic

Table 3—Unadjusted HRs for antihyperglycemic dual and triple type 2 diabetes therapies from the Cox proportional hazards models are shown together with 95% CIs and *P* values

Models	HR (95% CI)	*P*
Time to MACE		
MET + DPP-4	0.47 (0.42–0.52)*	<0.0001
MET + SU	1	—
MET + SGLT2	0.23 (0.17–0.32)*	<0.0001
MET + GLP-1	0.21 (0.18–0.25)*	<0.0001
MET + BASAL	0.64 (0.60–0.69)*	<0.0001
MET + DPP-4 + SU	0.62 (0.53–0.73)*	<0.0001
MET + SGLT2 + GLP-1	0.17 (0.12–0.26)*	<0.0001
MET + GLP-1 + BASAL	0.29 (0.24–0.34)*	<0.0001
Time to severe hypoglycemia		
MET + DPP-4	0.04 (0.02–0.08)*	<0.0001
MET + SU	1	—
MET + SGLT2	0.03 (0.00–0.19)*	0.0003
MET + GLP-1	0.05 (0.03–0.10)*	<0.0001
MET + BASAL	0.95 (0.83–1.09)*	0.4640
MET + DPP-4 + SU	0.70 (0.50–0.97)*	0.0318
MET + SGLT2 + GLP-1	0.00-Inf [a]	0.9027
MET + GLP-1 + BASAL	0.27 (0.19–0.39)*	<0.0001
Time to death		
MET + DPP-4	0.39 (0.36–0.41)*	<0.0001
MET + SU	1	—
MET + SGLT2	0.08 (0.06–0.10)*	<0.0001
MET + GLP-1	0.13 (0.12–0.15)*	<0.0001
MET + BASAL	0.58 (0.55–0.60)*	<0.0001
MET + DPP-4 + SU	0.49 (0.44–0.54)*	<0.0001
MET + SGLT2 + GLP-1	0.04 (0.03–0.06)*	<0.0001
MET + GLP-1 + BASAL	0.14 (0.13–0.16)*	<0.0001

Reference therapy is MET + SU. [a]No events during follow-up. *Statistically significant result ($P < 0.05$).

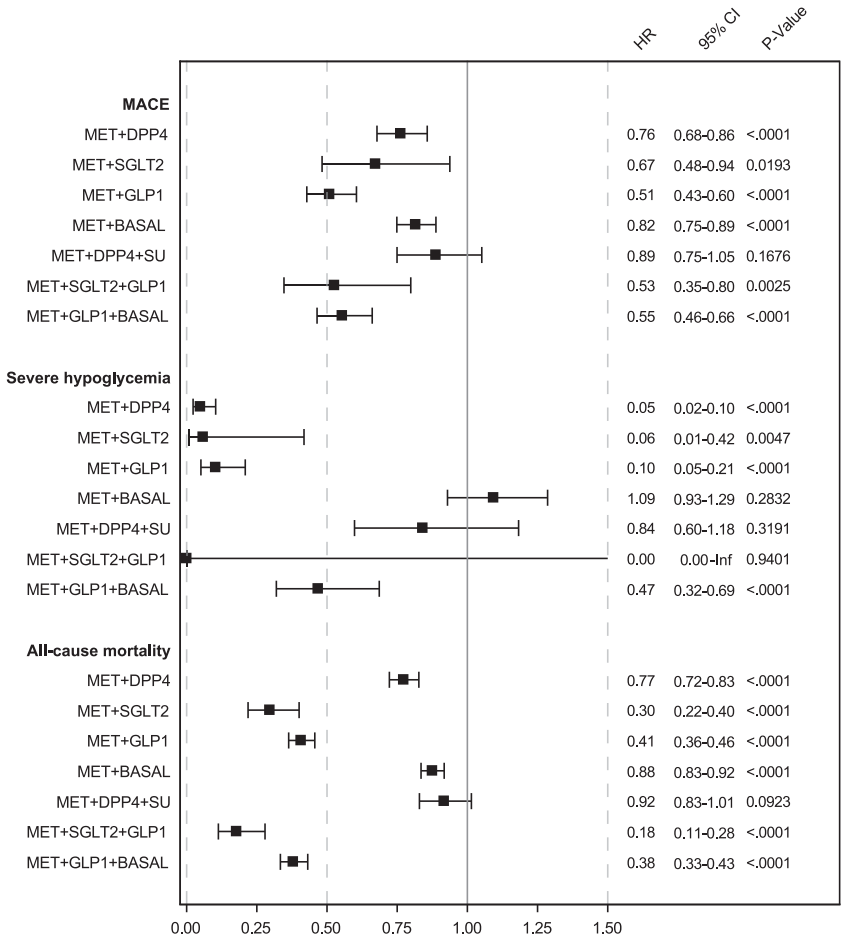

Figure 2—Forest plot showing adjusted HRs for antihyperglycemic dual and triple type 2 diabetes therapies from the Cox proportional hazards models together with 95% CIs and *P* values. Reference therapy is MET + SU. Model for MACE was adjusted for age, sex, diabetes duration, education, income, Charlson comorbidity index, history of nonfatal MACE, history of CKD, use of antihypertensive agents, use of antithrombotic agents, use of statins, and date of treatment initiation. Model for severe hypoglycemia was adjusted for age, sex, diabetes duration, education, income, history of severe hypoglycemia, history of nonfatal MACE, history of CKD, and date of treatment initiation. Model for all-cause mortality was adjusted for age, sex, diabetes duration, education, income, Charlson comorbidity index, history of alcohol abuse, history of nonfatal MACE, history of CKD, use of antidepressants, use of opioids, use of anxiolytics, use of antihypertensive agents, use of antithrombotic agents, use of statins, and date of treatment initiation. For MET + SGLT2 + GLP-1, no severe hypoglycemic events occurred for any patients during follow-up.

episodes occurred during follow-up for patients on MET + SGLT2 + GLP-1, which explains the inconclusive results. For all regimens, except for MET + DPP-4 + SU, a statistically significant reduction in all-cause mortality compared with MET + SU is observed. The greatest reductions are observed for users of MET + SGLT2 and MET + SGLT2 + GLP-1. People treated with MET + GLP-1 + BASAL have a lower risk of all-cause mortality than users of MET + BASAL. Table 4 shows results of subgroup analysis. The CIs for the group at risk have increased (as compared with results in Fig. 2) due to the reduced sample size, but the estimates have also changed, and the only statistically significant change is now for MET + GLP-1. The estimate for MET + SGLT2 is higher than MET + SU for people at risk for cardiovascular disease but not statistically significant.

CONCLUSIONS

The main findings of this study are as follows. People treated with MET + SU had the highest risk of MACE, severe hypoglycemia, and all-cause mortality, except for people treated with MET + BASAL, who had a higher risk of severe hypoglycemia. People treated with MET + GLP-1 + BASAL had a lower risk of severe hypoglycemia compared with MET + SU and a lower risk of all three end points compared with people on MET + BASAL. People on MET + SGLT2 had a low risk of severe hypoglycemia and all-cause mortality, but for MACE, the highest reductions were seen for people on regimens including GLP-1. The lowest risks were, in general, seen for people on MET + SGLT2 + GLP-1.

The general high risk of severe hypoglycemia and all-cause mortality for MET + SU users observed in this study has been confirmed in other studies, but the risks differ significantly among compounds (17–20), and, especially, glibenclamide has been associated with higher mortality risk (18). Only 17% of the patients treated with MET + SU in this study were on glibenclamide, whereas 59% were on glimepiride; nevertheless, it cannot be excluded that the increased mortality risk is driven by glibenclamide. Furthermore, the group of patients on MET + SU in this study was among the oldest, was less educated, and had the lowest income, and although the models were adjusted for socioeconomic factors, the direct association between low socioeconomic status and shorter life expectancy (21) should be taken into account in the interpretation of these results. Azoulay and Suissa (22) recently demonstrated that SUs are associated with increased cardiovascular events from a meta-regression analysis of observational studies, confirming the observation in this study. The slightly lower risks of MACE and all-cause mortality for people treated with MET + BASAL compared with MET + SU might seem surprising. In a study by Roumie et al. (23) comparing MET + SU and MET + BASAL, risk of a composite outcome of acute myocardial infarction, stroke, or all-cause mortality was increased for insulin users (HR 1.30 [95% CI 1.07–1.58]). However, this risk increase was primarily driven by all-cause mortality, and another end point comparable to MACE in this study was not increased for insulin users. An interesting observation in this study is that people treated with MET + GLP-1 + BASAL have a much lower risk of MACE than people treated with MET + BASAL, and the risk of severe hypoglycemia and all-cause mortality is twofold lower. The reduced

Table 4—Adjusted HRs, 95% CIs, and *P* values for antihyperglycemic dual and triple type 2 diabetes therapies stratified in people at risk for cardiovascular disease or not at risk

Models	HR (95% CI)	*P*
Time to MACE for people at high cardiovascular risk		
MET + DPP-4	1.03 (0.80–1.31)	0.8391
MET + SU	1	—
MET + SGLT2	1.13 (0.66–1.95)	0.6503
MET + GLP-1	0.58 (0.39–0.85)*	0.0057
MET + BASAL	1.06 (0.88–1.27)	0.5485
MET + DPP-4 + SU	0.85 (0.58–1.26)	0.4215
MET + SGLT2 + GLP-1	1.07 (0.56–2.05)	0.8410
MET + GLP-1 + BASAL	0.82 (0.58–1.17)	0.2702
Time to MACE for people without high cardiovascular risk		
MET + DPP-4	0.71 (0.62–0.81)*	<0.0001
MET + SU	1	—
MET + SGLT2	0.50 (0.41–0.61)*	<0.0001
MET + GLP-1	0.76 (0.69–0.84)*	<0.0001
MET + BASAL	0.91 (0.76–1.10)	0.3452
MET + DPP-4 + SU	0.39 (0.22–0.67)*	0.0007
MET + SGLT2 + GLP-1	0.50 (0.41–0.61)*	<0.0001
MET + GLP-1 + BASAL	0.50 (0.41–0.61)*	<0.0001

People at risk have had a nonfatal MACE before baseline. Reference therapy is MET + SU.
*Statistically significant result ($P < 0.05$).

risk of severe hypoglycemia is partly confirmed, for example, by the results of the DUAL-I trial (24). The lower all-cause mortality might be an effect of the lower risk of severe hypoglycemia (17) and the lower risk of MACE. The risk reduction of MACE seen for users of a regimen with a GLP-1 and users of MET + SGLT2 is in line with the literature (3,4,25). The risk reduction was not as profound for MET + SGLT2 as for MET + GLP-1, but the CI for MET + SGLT2 is also wider due to the relatively low number of users. The subgroup analysis indicates that people at risk for cardiovascular disease do benefit from MET + GLP-1 but not MET + SGLT2 as compared with MET + SU, which contradicts the observed similar risk reductions in the EMPA-REG OUTCOME and LEADER trials (3,4). This might be because 50% of the patients on MET + SGLT2 used dapagliflozin in our study, and in a recent CVOT, dapagliflozin showed noninferiority to placebo with respect to MACE (26). People treated with both SGLT2 and GLP-1 have the lowest overall risk of MACE, severe hypoglycemia (inconclusive but zero episodes occurred), and all-cause mortality. Other regimens, such as MET + SU + GLP-1 or MET + SU + SGLT2, could be interesting because the positive effects of GLP-1 and/or SGLT2 might outweigh some of the negative effects of SU, but because of the current low number of users in Denmark, these regimens were not included in the analyses.

A limitation of this study is the confounding by indication bias: it is impossible to claim that every indication for the different treatment options has been addressed by model adjustment. However, national coverage minimizes this bias, because indications on a national (or international) level are typically known, and it may be possible to adjust for them. Another concern related to indication bias is that general practitioners who persist to prescribe SU may be associated with less stringent risk factor control with anticipated higher cardiovascular risk for their patients as a result. Lack of knowledge about HbA_{1c}, BMI, blood pressure, smoking status, and cholesterol is a limitation, because these are important in the assessment of the comparability of the treatment groups, which also links to the confounding by indication bias. For example, an indication for using GLP-1 and DPP-4 as antidiabetic treatment is obesity, but BMI was not available in the registries. Adjustment for socioeconomic factors and statin use is anticipated to reduce the plausible skewness caused by smoking and variation in BMI, respectively, though. Patients from two decades were included in the analyses, and thus, a limitation is changes over time in terms of available therapies, treatment strategies, and targets. However, newer users existed in all regimens, and adjustment by treatment start date, therefore, reduces the effect. Furthermore, our adjustment for antihypertensive agents and statin use helps minimize the effect of changes in treatment strategy related to risk factor control. Another limitation is that short life expectancy could contraindicate a switch to newer treatments. The consequence would be that patients on regimens with older products have shorter time to the events of interest. Drug classes with older products, such as SU and BASAL, do contain substantial amounts of new users from the last couple of years, which decreases this skewing effect. Another limitation is lack of surrogate measures for glomerular filtration rate. SGLT2 is indicated for patients with CKD (2), and an overrepresentation of patients with CKD might therefore be present in this group. CKD increases risk of MACE, severe hypoglycemia, and all-cause mortality (27,28). However, an adjustment of history of CKD before baseline was done in all three models, which minimizes the effect of an unequal distribution. The prevalence of CKD is unexpectedly low, which could be explained by the definition of CKD as related to hospitalizations, leading to exclusion of less severe CKD cases and the relatively short diabetes durations associated with lower CKD prevalence. Another limitation is that severe hypoglycemia was defined as episodes leading to hospital admissions. Consequently, the actual incidence of severe hypoglycemia is much higher, as only 19% of severe hypoglycemia leads to hospital admissions (29). Finally, a limitation is the use of prescription data as a surrogate for drug use. Krass et al. (30) summarized in a systematic review that adherence to diabetes medications is reported in most trials and is an ongoing problem. In our study, adherence would probably also differ among types of products due to, for example, route of delivery. The risk of MACE, severe hypoglycemia, and mortality was based on observations of patients on different regimens, in whom the drug doses have been neglected. This makes adherence of less concern, unless the prevalence of low adherence to a particular drug class is systematically

higher, which could be the case, for example, for BASAL.

Strengths of this study are the national coverage with complete follow-up and high validity of outcomes. Furthermore, an advantage compared with the randomized controlled trials is the real-world nature of these data with inclusion of all kinds of patients treated with a variety of combinations of antihyperglycemic dual and triple therapies without any strict inclusion/exclusion criteria and without any considerations about compliance to protocol. These types of data cannot be obtained from randomized controlled trials.

In conclusion, the results of this study show that people treated with MET + SU have the highest risk of MACE, severe hypoglycemia, and all-cause mortality among the treatment regimens investigated, except for people treated with MET + BASAL, who have a higher risk of severe hypoglycemia. People treated with a GLP-1 additionally to MET + BASAL have a significantly decreased risk of all three end points compared with MET + BASAL. In general, the lowest risk for all three end points is seen for users of MET + SGLT2 + GLP-1. Also, MET + SGLT2 users have a very low risk of severe hypoglycemia and all-cause mortality compared with people on other regimens, but for MACE, people on regimens including GLP-1 in general have a lower risk than people on MET + SGLT2, especially in people at risk for cardiovascular disease. Although observational studies are associated with many limitations, we believe clinicians could consider adding GLP-1 and reducing BASAL insulin in patients on MET + BASAL with a tendency toward hypoglycemia. Furthermore, our data on MET + SU do not support that SU should be a second-line treatment choice for patients with type 2 diabetes. It is important to notice that these general recommendations are on a drug class level and should be combined with evidence on differences between individual compounds from other studies. Furthermore, the choice of treatment is a multifactorial process in which many other factors, such as price, efficacy, other side effects, drug delivery technology, patient preferences, etc., should be considered. We acknowledge that data from randomized controlled trials should be the foundation for evidence-based medicine, but we believe that real-world data like those generated from this study should be considered when extrapolating data from the randomized controlled trials to, for example, all patients with type 2 diabetes.

Duality of Interest. M.H.J. is a former employee at Novo Nordisk and holds shares in Novo Nordisk. M.K. holds shares in Novo Nordisk and Novartis. P.V. has received unrestricted grants from Merck Sharp & Dohme and Servier and travel grants from Amgen, Eli Lilly and Company, Novartis, Sanofi-Aventis, and Servier. No other potential conflicts of interest relevant to this article were reported.

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