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Clinical paper

Glucagon-like peptide-1 receptor agonist use is associated with reduced risk of out-of-hospital cardiac arrest in women with type 2 diabetes: A nationwide nested case-control study

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ABSTRACT

Objective: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve cardiovascular outcomes in patients with type 2 diabetes, but few studies have studied the risk of out-of-hospital cardiac arrest (OHCA). We investigated whether GLP-1 RA use reduce OHCA risk in type 2 diabetes when compared to dipeptidyl peptidase-4 inhibitor (DPP-4i) use.
Methods: We identified all patients having a redeemed prescription of a glucose-lowering drug between 1995 and 2019 and excluded patients with a first-time redeemed prescription consisting of insulin. Within this cohort, we nested a case-control population comprising all OHCA-cases from presumed cardiac causes between 2013 and 2019. OHCA-cases were matched 1:5 to non-OHCA controls of the same sex and age on the date of OHCA. The odds ratios (ORs) and corresponding 95% confidence intervals (95%-CIs) of OHCA were reported comparing GLP-1 RAs versus DPP-4is.
Results: We identified 3,618 OHCA-cases from presumed cardiac causes and matched them to 18,090 non-OHCA controls. GLP-1 RAs were used by 269 (7.44%) cases and 1297 (7.17%) controls, and conferred no increase in the overall odds of OHCA compared with DPP-4i use (OR:0.89, 95%-CI 0.74–1.07). However, stratification according to sex revealed that OHCA risk was significantly reduced in women (OR:0.59, 95%-CI 0.40–0.86) but not in men (OR:1.01, 95%-CI 0.82–1.26, P-value interaction:0.0093). The OR of OHCA did not vary significantly when stratifying for age, duration of diabetes, chronic kidney disease, or presence of cardiovascular disease.
Conclusion: Our findings indicate that GLP-1 RA use is not associated with a reduced risk of OHCA in Danish individuals with type 2 diabetes when compared to DPP-4is.

Introduction

Out-of-hospital cardiac arrest (OHCA) is one of the most common causes of death in Europe where the incidence of treated OHCA has been reported to be between 17 and 53 per 100,000 person-years [1]. Previous studies have shown that individuals with diabetes have an increased risk of OHCA compared to the general population [2–4].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are second or higher line drugs commonly used in the treatment of type 2 diabetes or as an adjunct for weight management in obese patients. They induce direct activation of the GLP-1 receptor, which stimulates pancreatic insulin secretion in a glucose dependent manner, while also inhibiting glucagon secretion [5]. A recent study has demonstrated that GLP-1 RAs prolong the ventricular action potential duration even in the presence of an increase in heart rate [6] Although an increased action potential duration can be pro-arrhythmic (generating Torsade de Pointes), it may also act in an anti-arrhythmic (e.g., class III anti-arrhythmic drugs) fashion in the setting of re-entrant arrhythmias [7]. The use-dependent effect of GLP-1 RAs is particularly relevant to prevent re-entrant tachyarrhythmia like ventricular fibrillation. GLP-1 RAs also lead to weight loss [5]. Since the hearts of women contain more subepicardial fat than that of men, weight loss may affect women more than men [8]. It has

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been shown that secretome of subepicardial fat causes myocardial ion channel remodelling conducive to re-entrant arrhythmia [9]. We therefore hypothesized that GLP1-RA use leads to a reduced risk of OHCA, especially in women.

In this nationwide study, we investigated whether the use of GLP-1 RAs was associated with a decreased risk of OHCA in patients with type 2 diabetes when compared with the use of dipeptidyl peptidase-4 inhibitors (DPP-4is). We used DPP-4is as the active comparator group since they are common second-to-third line drugs for the treatment of type 2 diabetes and expected not to have a relationship with OHCA.

Methods

Ethics

The present study is approved by the Danish Data Protection Agency (Ref.no. 2007–58-0015, local ref.no. GEH-2014–017, I-Suite 0.2735). In Denmark, no additional approvals are needed to conduct retrospective studies where patients remain anonymous.

Study design and population

The study setting, described previously [10], was a nested case-control design by extracting data from the Danish registries. First, we assembled a cohort of patients having a redeemed prescription of a glucose-lowering drug between 1995 and 2019. We excluded patients with a first-time redeemed prescription consisting of insulin because such patients were regarded as having type 1 diabetes. Within this base cohort, we nested a case-control population comprising all OHCA cases from presumed cardiac causes (excluding obvious non-cardiac causes) between 2013 and 2019. OHCA cases were matched in a 1:5 ratio to non-OHCA controls of the same sex and age through incidence density sampling on the date of OHCA defined as index-date. The same study population of OHCA cases and their matched controls has been previously used by us [10]. Characteristics of the cases and their matched controls are described in our previous report [10].

Data sources

All data used for the present study were obtained from Danish nationwide registries. These registries have previously been used by this research group [10–12]. A detailed description of these registries can be found in other reports [10–12]. Each Danish citizen is being provided with a unique personal identification number which makes it possible to link individual-level data across different nationwide clinical registries, thereby allowing to conduct large-scale epidemiologic research with nationwide coverage.

Exposure of interest

Information on GLP-1 RA use was obtained from the National Prescription Registry. A GLP-1 RA user was defined as an individual who redeemed a prescription of GLP-1 RA in a period of 180 days before the index-date. We selected DPP-4 is as the active comparator because they are an alternative second-line drugs used in the treatment of diabetes. DPP-4is were defined similar as GLP-1 RAs. Subjects were then classified into one of the following three mutually exclusive categories: [1] current use of a GLP-1 RA (alone or in combination with other antidiabetic drugs); [2] current use of a DPP-4i (alone or in combination with other antidiabetic drugs) and [3] current use of other antidiabetic drugs. This way of exposure definition has been previously used by us which is described in detail elsewhere [10].

Covariates

Comorbidities were defined as present if any hospital contact was registered within 10 years before the index-date, as we did previously [10–12]. Comorbidities identified for this study are listed in Table 1. Concomitant pharmacotherapy was identified up to 6 months before the index-date, as done previously (listed in Table 1) [10–12]. All the codes used to define comorbidities and concomitant pharmacotherapy in the present study have been used previously by this research group. A detailed overview of these codes can be found in our previous report [10]. In addition, the time between the first antidiabetic drug and index-date was used to assess the duration of diabetes, as we did previously [10] Further, we obtained the most recent measurements of haemoglobin A1c (HbA1c) within 1 year before the index-date, as done previously [10].

Statistical analyses

Conditional logistic regression was used to assess the association between GLP-1 RAs and OHCA. Our models were adjusted for a priori defined well-known risk factors of OHCA such as ischemic heart disease, heart failure, atrial fibrillation, peripheral artery disease, duration of diabetes, dyslipidaemia, obesity and chronic kidney disease. We conducted stratified analyses according to sex, age, diabetes duration (<10 or ≥ 10 years), the presence of chronic kidney disease, and the presence of cardiovascular disease including heart failure and calculated $P_{\text{interaction}}$ using multivariable conditional logistic regression. Finally, the primary analysis was repeated after additionally adjusting for the presence of pacemaker or implantable cardioverter defibrillator (ICD) and for the use of insulin or sodium-glucose cotransporter-2 inhibitors (SGLT-2is). We adjusted for the use of SGLT-2is, since SGLT-2is have

Table 1
Characteristics of out-of-hospital cardiac arrest cases classified into users of GLP-1 receptor agonists and DPP-4 inhibitors.

	GLP-1 receptor agonists ($n = 269$)	**DPP-4 inhibitors** ($n = 323$)	***P*-value**
Age (years), mean [SD]	68.29 [8.91]	75.84 [9.58]	<0.0001
Male sex, *n* (%)	215 (79.93)	228 (70.59)	0.009
Diabetes duration (years), mean [SD]	12.43 [5.79]	10.85 [6.03]	0.001
Haemoglobin A1c level, *n* (%)			0.001
≤53 mmol/mol	54 (20.07)	108 (33.44)	
>53 mmol/mol	140 (52.04)	132 (40.87)	
Unknown	75 (27.88)	83 (25.70)	
Comorbidity, *n* (%)			
Ischemic heart disease[§]	116 (43.12)	134 (41.49)	0.688
Heart failure	96 (35.69)	135 (41.80)	0.129
Atrial fibrillation	83 (30.86)	114 (35.29)	0.254
Peripheral artery disease	39 (14.50)	77 (23.84)	0.004
Chronic kidney disease	45 (16.73)	108 (33.44)	<0.0001
Dyslipidaemia	102 (37.92)	96 (29.72)	0.035
Obesity	94 (34.94)	50 (15.48)	<0.0001
Neuropathy	44 (16.36)	34 (10.53)	0.037
Retinopathy	96 (35.69)	121 (37.46)	0.656
Pacemaker/ICD	17 (6.32)	28 (8.67)	0.283
Medication, *n* (%)			
Beta blockers	100 (37.17)	134 (41.49)	0.285
Calcium channel blockers	106 (39.41)	97 (30.03)	0.017
Antithrombotics	199 (73.98)	239 (73.99)	0.996
Diuretics	206 (76.58)	233 (72.14)	0.219
Renin-angiotensin system inhibitors	204 (75.84)	204 (63.16)	0.001
Nitrates	40 (14.87)	48 (14.86)	0.998
Antiarrhythmic drugs class 1 or 3	9 (3.35)	14 (4.33)	0.535
Lipid-lowering drugs	217 (80.67)	218 (67.49)	<0.001
Metformin	211 (78.44)	164 (50.77)	<0.0001
Sulfonylureas	30 (11.15)	57 (17.65)	0.026
Insulin	157 (58.36)	89 (27.55)	<0.0001
SGLT-2 inhibitors	23 (8.55)	13 (4.02)	0.022

[§] Including acute myocardial infarction

been shown to be associated with reduced risk of OHCA [10,13].

Results

Baseline characteristics

We identified 3,618 OHCA cases from presumed cardiac causes and matched them to 18,090 non-OHCA controls. Among all OHCA cases, 69.0 % were men, and the mean age at time of OHCA was 74 years (SD: 10.98). Characteristics of OHCA cases divided by the use of GLP-1 RAs and DPP-4is are specified in Table 1. Compared with users of DPP-4is, users of GLP-1 RAs were younger with a higher proportion of men, more likely to be obese, had higher HbA1c levels, and a longer duration of diabetes compared with users of DPP-4is. Also, users of GLP-1 RAs had higher prevalence of dyslipidaemia, neuropathy and insulin use, while the prevalence of peripheral artery disease and chronic kidney disease was in general lower compared with users of DPP-4is. Supplementary Table 1 presents the characteristics of users of GLP-1 RAs and DPP-4is for women and men separately. In general, distribution of variables among users of GLP-1 RAs and DPP-4is for women and men was similar. In both women and men, users of GLP-1 RAs were younger, more likely to be obese, had higher prevalence of dyslipidaemia and insulin use, and a longer duration of diabetes, while the prevalence of cardiovascular comorbidities in general and chronic kidney disease was lower compared with users of DPP-4is.

Association between GLP-1 RAs and OHCA

Table 2 presents both the crude and adjusted odds ratios of OHCA according to exposure with GLP-1 RAs and DPP-4is as the reference category. GLP-1 RAs were used by 269 (7.44 %) cases and 1297 (7.17 %) controls and conferred no statistically significant decrease in the overall odds of OHCA compared with use of DPP-4is (OR 0.89, 95 % CI 0.74–1.07). Next, we performed several stratified analysis based on age, sex, duration of diabetes, chronic kidney disease, or presence of cardiovascular disease including heart failure. Our subgroup analysis on sex was one of the six subgroup analyses and revealed that OHCA risk was reduced in women (OR 0.59, 95 % CI 0.40–0.86) but not in men (OR 1.01, 95 % CI 0.82–1.26, P-value interaction: 0.0093). Our sensitivity analyses yielded consistent findings, where the ORs did not vary when we repeated the analyses by adjusting for the presence of pacemaker/ICD and for the use of insulin or SGLT-2is (data not shown). The OR of OHCA did not vary significantly when stratifying on age (Table 2), duration of diabetes, chronic kidney disease, or presence of cardiovascular disease including heart failure (Table 3).

Table 2
Association between the use of GLP-1 receptor agonists and the odds ratio of out-of-hospital cardiac arrest (OHCA): overall and stratified by sex.

	Cases (n = 3,618)	**Controls** (n = 18,090)	**Crude OR** (95 % CI)	**Adjusted OR** (95 % CI)[§]
Overall				
DPP-4 inhibitors	323 (8.93)	1491 (8.24)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	269 (7.44)	1297 (7.17)	0.96 (0.80–1.15)	0.89 (0.74–1.07)
Sex (p-value interaction = 0.0093)				
Male				
DPP-4 inhibitors	228 (9.13)	1061 (8.50)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	215 (8.61)	925 (7.41)	1.09 (0.88–1.34)	1.01 (0.82–1.26)
Female				
DPP-4 inhibitors	95 (8.47)	430 (7.67)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	54 (4.82)	372 (6.64)	0.65 (0.45–0.94)	0.59 (0.40–0.86)
Age (p-value interaction = 0.4425)				
Age ≤ 65 years				
DPP-4 inhibitors	42 (5.24)	273 (6.81)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	93 (11.60)	515 (12.84)	1.17 (0.79–1.73)	1.15 (0.76–1.74)
Age > 65 years				
DPP-4 inhibitors	281 (9.98)	1218 (8.65)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	176 (6.25)	782 (5.55)	0.98 (0.80–1.21)	0.90 (0.72–1.12)

Abbreviations: CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1 RAs, glucagon-like-peptide-1 receptor agonists; OR, odds ratio. Numbers in table are number (%) unless indicated otherwise.
Not included in the figure: cases (%) and controls (%) of nonusers of DPP-4 inhibitors and GLP-1 RAs 180 days before index-date: (overall) 3026 (83.64 %)/15302 (84.59 %), (men) 2054 (82.26 %)/10499 (84.09 %), (women) 972 (86.71 %)/4803 (85.69 %), (age ≤ 65 years) 667 (83.17 %)/3222 (80.35 %), and (age > 65 years) 2359 (83.77 %)/12080 (85.80 %).
[§] Adjusted for cardiovascular disease, duration of diabetes, dyslipidemia, obesity and chronic kidney disease.

Discussion

In this nationwide nested case-control study, we showed that use of GLP-1 RAs was not associated with OHCA when compared to the use of DPP-4is. The association between GLP-1 RAs and OHCA did not vary when stratifying on age, duration of diabetes, chronic kidney disease, or presence of cardiovascular disease. Our subgroup analysis on sex, however, revealed that OHCA risk was reduced in women but not in men.

GLP-1 RAs improve cardiovascular outcomes in both patients with type 2 diabetes [14,15] and in patients without diabetes [16]. Several mechanisms have been proposed regarding these beneficial effects on cardiovascular outcomes. For instance, GLP-1 RAs have been demonstrated to result in reductions in blood pressure [17], and have been associated with improvements in lipid profiles and inflammatory markers [18], thereby providing (indirect) anti-atherosclerotic effects. Despite these beneficial effects, GLP-1 RAs have also been associated with increase in heart rate which appears to be indirect, mediated via increased activity of the sympathetic nervous system [19] or through attenuation of parasympathetic tone [20]. The autonomic nervous system plays an important role in the regulation of cardiac electrophysiology and arrhythmias [21]. Accordingly, increased activity of the sympathetic nervous system may influence cardiac electrophysiology and predispose to cardiac arrhythmias and OHCA [11]. Theoretically, this may place users of GLP-1 RAs at higher risk for the occurrence of OHCA. However, our results provide strong evidence that GLP-1 RAs are not associated with increased risk for OHCA in type 2 diabetes, thereby demonstrating an assuring cardiovascular safety profile. Possible confounding by indication must be considered in our study since diabetes itself is a known risk factor for OHCA [2–4]. In the present study, we noticed that GLP-1 RAs users had a longer duration of diabetes and a significant higher prevalence of insulin use compared with DPP-4i users, which could indicate a higher diabetes severity in GLP-1 RAs users. Nonetheless, despite probably having more advanced stage of diabetes than DPP-4i users, users of GLP-1 RAs had no increased risk of OHCA, providing additional evidence that it is unlikely that GLP-1 RA use is associated with increased OHCA risk. Our finding that GLP-1 RA use was not associated with increased risk of OHCA is supported by previous studies [15,22–24].

While previous studies on GLP-1 RAs have reported to improve cardiovascular outcomes [14–16], the beneficial effects of DPP-4is on cardiovascular diseases have not been established in clinical trials [25,26]. To our knowledge, however, no previous study has investigated the relation between GLP-1 RAs and OHCA versus DPP-4is using an OHCA registry that was specifically designed to study OHCA, like our study. Given the reported beneficial effects of GLP-1 RAs and the neutral effects of DPP-

Table 3
Association between the use of GLP-1 RAs and the odds ratio of out-of-hospital cardiac arrest: stratified according to cardiac disease, heart failure, diabetes duration and chronic kidney disease.

	Cases (n = 3,618)	Controls (n = 18,090)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Cardiac disease (P-value interaction: 0.523)[§]				
Absent	1571	12,399		
DPP-4 inhibitors	110 (7.00)	969 (7.82)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	103 (6.56)	875 (7.06)	1.04 (0.78–1.38)	0.92 (0.69–1.23)
Present	2047	5691		
DPP-4 inhibitors	213 (10.41)	522 (9.17)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	166 (8.11)	422 (7.42)	0.96 (0.76–1.23)	0.85 (0.67–1.10)
Heart failure (P-value interaction: 0.137)[§§]				
Absent	2464	16,401		
DPP-4 inhibitors	188 (7.63)	1300 (7.93)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	173 (7.02)	1186 (7.23)	1.01 (0.81–1.26)	0.90 (0.71–1.12)
Present	1154	1689		
DPP-4 inhibitors	135 (11.70)	191 (11.31)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	96 (8.32)	111 (6.57)	1.22 (0.86–1.74)	0.98 (0.68–1.42)
Diabetes duration (P-value interaction: 0.374)[*]				
<10 years	1950	11,491		
DPP-4 inhibitors	161 (8.26)	687 (10.41)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	93 (4.77)	496 (4.32)	0.94 (0.71–1.24)	0.98 (0.74–1.32)
≥10 years	1668	6599		
DPP-4 inhibitors	162 (9.71)	687 (10.41)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	176 (10.55)	801 (12.14)	0.93 (0.74–1.18)	0.87 (0.68–1.11)
Chronic kidney disease (P-value interaction: 0.067)[**]				
Absent	2919	16,457		
DPP-4 inhibitors	215 (7.37)	1214 (7.38)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	224 (7.67)	1148 (6.98)	1.10 (0.90–1.35)	0.95 (0.77–1.18)
Present	699	1633		
DPP-4 inhibitors	108 (15.45)	277 (16.96)	1.0 (reference)	1.0 (reference)
GLP-1 RAs	45 (6.44)	149 (9.12)	0.78 (0.52–1.16)	0.61 (0.40–0.94)

Not included in the table: cases (%) and controls (%) of nonusers of DPP-4 inhibitors and GLP-1 RAs 180 days before index-date: (absent cardiac disease) 1358 (86.44 %)/10555 (85.13 %), (present cardiac disease) 1668 (81.49 %)/4747 (83.41 %), (absent heart failure) 2103 (85.35 %)/13915 (84.84 %), (present heart failure) 923 (79.98 %)/1387 (82.12 %), (diabetes duration < 10 years) 1696 (86.97 %)/10191 (88.69 %), (diabetes duration ≥ 10 years) 1330 (79,74 %)/5111 (77.45 %), (absent chronic kidney disease) 2480 (84.96 %)/14095 (85.65 %), (present chronic kidney disease) 546 (78.11 %)/1207 (73.91 %).

[§] Adjusted for duration of diabetes, dyslipidemia, obesity and chronic kidney disease.

[§§] Adjusted for cardiovascular disease (but not for heart failure), duration of diabetes, dyslipidemia, obesity, obesity and chronic kidney disease.

[*] Adjusted for cardiovascular disease, dyslipidemia, obesity and chronic kidney disease.

[**] Adjusted for cardiovascular disease, duration of diabetes, dyslipidemia and obesity.

By conducting stratified analyses according to cardiac disease, heart failure, duration of diabetes and chronic kidney disease the original matching on age and sex was lost. Therefore, ORs were additionally adjusted for age and sex when we performed stratified analyses.

4is on cardiovascular outcomes, we would have expected to find a lower OHCA risk associated with GLP-1 RAs versus DPP-4is. In our study, however, we observed no statistically significant reduced OHCA risk with GLP-1 RAs when compared to DPP-4is in the overall group; reduced OHCA risk with GLP-1 RAs was only present in women. Several mechanisms explaining our observation could be suggested. First, GLP-1 RAs may prevent re-entrant arrhythmia like ventricular fibrillation by impacting on the epicardial adipose tissue (EAT). EAT refers to the visceral adipose tissue located between the myocardium and the epicardium [27]. Its volume depends on body mass index [28]. Adipokines secreted by EAT may modulate cardiac electrophysiology by stimulating fibrosis [9]. EAT is therefore considered an important potential target for prevention of cardiac remodeling and arrhythmias [9]. The observed association between GLP-1 RAs and reduced OHCA in women could therefore be related to the weight reducing effects of GLP-1 RAs [5]. Since the hearts of women contain more subepicardial fat than that of men [8], we speculate that weight loss may affect women more than men and may explain our observation that GLP-1 RAs are associated with more OHCA risk reduction in women than in men. It should be noted, however, that data regarding weight reduction were not available in the present study. Therefore, we acknowledge that more study is needed to confirm our findings; our study may provide the basis for future research. Second, a recent study has demonstrated that GLP1-RAs prolong the ventricular action potential duration even in the presence of an increase in heart rate, which is particularly relevant to prevent re-entrant arrhythmia [6]. Women have smaller repolarization reserve than men due to lower expression of repolarizing channels [29]. Consequently, women using GLP-1 RAs may have longer QT-intervals than men. This may exert a larger class III anti-arrhythmic effect. This may provide an alternative explanation for our observation of reduced OHCA with GLP-1 RA use in women. Regardless of the underlying mechanisms of our epidemiologic findings, our results are of clinical importance given the continues rise of diabetes, and the fact that diabetes is associated with increased OHCA risk [2–4]. To our knowledge, no differential effects of GLP-1 RAs have been reported on cardiovascular outcomes between both sexes in previous studies [30]. In our study, we had relatively low percentage of subjects using GLP-1 RAs or DPP-4is throughout our study, which may have resulted in possibly low statistical power. Moreover, we cannot rule out the possibility of type I error since we could not adjust for all the confounders throughout our study. Furthermore, it should be noted that our subgroup analysis on sex was one of the six subgroup analyses; this subgroup analysis should be considered as hypothesis generating rather than a definitive finding itself. Therefore, a potential relation between GLP-1 RAs and lower OHCA risk in women and the mechanisms involved warrants future replication studies in other settings.

In our study, we used DPP-4is as the active comparator category since they are common second-to-third line drugs for the treatment of type 2 diabetes and expected not to have a relationship with OHCA. We have not selected users of first-line antidiabetic drugs (i.e., metformin) as the reference category as users of first-line antidiabetic drugs only are probably in a less advanced stage of diabetes than users of GLP-1 RAs. This might lead to confounding due to time lag bias and could limit the generalizability of our findings. Similarly, we have not selected users of insulin as the reference group as users of insulin are probably in a more advanced stage of diabetes than users of GLP-1RAs, thereby leading to confounding. Further, we have not selected users of other second-to-third line antidiabetic drugs such as SGLT-2 inhibitors as the reference category as we have already investigated the relationship between SGLT-2 inhibitors and OHCA in our previous study [13]. Other second-line antidiabetic drugs such as thiazolidinediones and sulfonylurea drugs are not so often used anymore in Denmark.

Strengths and limitations

Inclusion data from nationwide databases provided valid and individual level information which strengthens the generalizability of our

results. Another strength is our active comparator design in which GLP-1 RAs were compared with DPP-4is, thereby minimizing possible confounding by indication. Nonetheless, some limitations apply. First, although we have adjusted for all the relevant cardiovascular comorbidities, we cannot rule out the possibility of residual confounding and the risk of type I error since the registers do not contain data on disease severity, left ventricular ejection fraction and lifestyle variables Another limitation is that data on HbA1c was not registered for all the individuals. We attempted to reduce the impact of residual confounding by performing several subgroup analyses and by controlling for a wide range of potential confounders. Our main results were confirmed in these subgroup analyses. However, as this is a nonrandomized, observational study, we could only detect associations and not causation. Second, not all the comorbidities in the Danish registries have been validated. However, most of the included comorbidities in this study have previously been shown to have a high positive predictive value [31]. Third, we had relatively low percentage of subjects using GLP-1 RAs and DPP-4is throughout our study. Hence, our analyses was based on small sample sizes, which may have resulted in possibly low statistical power. Therefore, the potential relation between GLP-1 RAs and lower OHCA risk in women and the mechanisms involved warrants future studies with higher sample size. Finally, no information was available regarding compliance, since data on pharmacotherapy was based on drug-dispensing records without further information on actual drug intake which may lead to misclassification of the exposure. However, possible misclassification arising from this was probably equally distributed between OHCA cases and non-OHCA controls.

Conclusion

Our study suggest that GLP-1 RA use is not associated with a reduced risk of OHCA in Danish individuals with type 2 diabetes when compared to DPP-4is. The association between GLP-1 RAs and OHCA did not vary when stratifying on age, duration of diabetes, chronic kidney disease, or presence of cardiovascular disease including heart failure. Our subgroup analysis on sex, however, revealed that OHCA risk was reduced in women but not in men.

CRediT authorship contribution statement

Talip E. Eroglu: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Ruben Coronel:** Writing – review & editing, Conceptualization. **Fredrik Folke:** Writing – review & editing. **Gunnar Gislason:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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