Comparative cardiovascular effectiveness of newer glucose-lowering drugs in elderly with type 2 diabetes: a target trial emulation cohort study

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Summary

Background Reducing risk of cardiovascular disease is crucial in managing type 2 diabetes (T2D). This study assessed the comparative cardiovascular effectiveness of newer glucose-lowering drugs in real-world elderly individuals with T2D, and examined how age modified these effects.

Methods We conducted a cohort study using Danish nationwide registries to emulate a three-arm randomized clinical trial. Participants aged ≥70 years were new users of glucagon-like peptide 1 receptor agonists (GLP1-RAs), sodium-glucose cotransporter 2 inhibitors (SGLT-2is), or dipeptidyl peptidase 4 inhibitors (DPP-4is), between 2012 and 2020. We estimated the overall and age-specific incidence rate ratios (IRR) of 3-point major adverse cardiovascular events (3P-MACE) and hospitalization for heart failure (HHF) using Poisson regression models. Summarized weights were used to balance baseline characteristics and treatment adherence.

Findings The study included 35,679 participants (DPP-4is: 21,848 (62%), GLP1-RAs: 5702 (16%), SGLT-2is: 8129 (23%)). In the as-treated analysis, GLP1-RAs and SGLT-2is were associated with significantly reduced rates of 3P-MACE and HHF compared to DPP-4is. The overall IRR for 3P-MACE was 0.68 (95% CI 0.65–0.71) (GLP1-RAs vs. DPP4is) and 0.65 (95% CI 0.63–0.68) (SGLT-2is vs. DPP4is), while for HHF the IRR was 0.81 (95% CI 0.74–0.88) (GLP1-RAs vs. DPP4is) and 0.60 (95% CI 0.55–0.66) (SGLT-2is vs. DPP4is). These effects were predominantly independent of age. No significant difference was observed between SGLT-2is and GLP1-RAs on 3P-MACE, however, SGLT-2is were associated with a significant reduction of HHF, compared to GLP1-RAs, with an overall IRR of 0.75 (95% CI 0.67–0.83), and with age-dependent variations for both outcomes.

Interpretation In the elderly, use of GLP1-RAs and SGLT-2is was associated with reduced rates of 3P-MACE and HHF compared to DPP-4is, independent of age. SGLT-2is were also associated with reduced rates of HHF compared to GLP1-RAs, largely independent of age, in this population of individuals aged 70 years and above. This provides real-world evidence on the comparative cardiovascular effectiveness of the three most recent glucose-lowering medications and may help strengthen implementation of guidelines into clinical practice.

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Keywords: Antidiabetic drugs; 3-Point major adverse cardiovascular events; Hospitalization for heart failure; Target trial emulation study

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Research in context

Evidence before this study

We conducted a PubMed search for studies examining the comparative cardiovascular effectiveness of sodium-glucose cotransporter 2 inhibitors (SGLT-2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase 4 inhibitors (DPP-4is) in elderly individuals with type 2 diabetes mellitus (T2D), published before August 1, 2024. The following search terms were used: "Type 2 Diabetes", "aged", "aged, 80 and over", "older", "elderly", "diabetes medication(s)", "antihyperglycemic(s)", "SGLT2 inhibitors", "GLP-1 receptor agonists", "DPP-4 inhibitors", "cardiovascular", "MACE", and "heart failure" in various combinations, with no language restrictions.

Randomized clinical trials have demonstrated that both SGLT-2is and GLP1-RAsreduce the risk of three-point major adverse cardiovascular events (3P-MACE) and hospitalization for heart failure (HHF) compared to placebo, whereas DPP-4is show a neutral effect on these cardiovascular endpoints. However, elderly populations are often underrepresented in these trials and direct comparisons among the three medication classes are lacking.

Previous observational studies using real-world data in an elderly population have typically been limited to comparisons of only two medication classes per cohort, restricting insights into the broader comparative effectiveness among all three classes. Furthermore, most studies employed 1:1 propensity-score matching to balance baseline characteristics, effectively restricting the analysis to matched pairs and imposing additional selection. Subgroup analyses exploring age-related effects were conducted in some of the studies, but age was treated as a categorical variable, e.g., under or over 75 years, in all but one study, which used four age categories (<65, 65–74, 75–84, and ≥85 years), limiting the nuanced effects of age.

Added value of this study

In this study, we use real-world data from nationwide registers to emulate a three-arm target trial, assessing the comparative effectiveness of the three newest glucose-lowering drug classes (SGLT-2is, GLP1-RAs, and DPP-4is) on the risk of 3P-MACE or HHF. The three-arm approach enables simultaneous, head-to-head comparisons of all three drug classes, providing a comprehensive assessment of their relative effectiveness within an elderly population. The study included 35,679 new users of glucose-lowering medications, comprising 8129 (23%) SGLT-2i users, 5702 (16%) GLP-1RA users, and 21,848 (61%) DPP-4i users, all aged ≥70 years with T2D. We found that GLP1-RAsand SGLT-2is were associated with significant reductions in the rate of 3P-MACE and HHF compared to DPP-4is, regardless of age. Notably, SGLT-2is demonstrated greater reductions in HHF rates compared to GLP-1RAs, with some age-related variations observed. These results confirm the cardiovascular benefits of newer glucose-lowering medications in elderly populations and offer nuanced insights into potential age-modifying effects on these outcomes.

Implications of all the available evidence

Our findings build upon prior observational studies by demonstrating that SGLT-2is and GLP1-RAs are associated with significantly lower rates of 3P-MACE and HHF compared to DPP-4is, regardless of age. Furthermore, they suggest that there may be some age-related modifying effects when comparing SGLT-2is and GLP1-RAs. We found that SGLT-2is were associated with reduced rates of HHF but not 3P-MACE compared to GLP1-RAs and these effects were largely, but not entirely, independent of age. This evidence supports current guidelines and could help strengthen their implementation in clinical practice.

Introduction

The prevalence of elderly with type 2 diabetes (T2D) is increasing worldwide.[1] Diabetes remains a major risk factor for cardiovascular disease (CVD) and a leading cause of morbidity and mortality.[2] Notably, both advanced age and diabetes duration independently predict morbidity and mortality.[3] Reducing CVD risk is therefore a cornerstone of diabetes management, particularly emphasized in the elderly.[4,5]

Since cardiovascular safety assessment for all new glucose-lowering medications became mandatory through cardiovascular outcome trials (CVOTs), results from over 20 CVOTs have been published, evaluating the cardiovascular safety of glucagon-like peptide-1 receptor agonists (GLP1-RAs), sodium-glucose cotransporter-2 inhibitors (SGLT-2is), and dipeptidyl peptidase-4 inhibitors (DPP-4is), primarily compared to placebo.[6,7] GLP1-RAs and SGLT-2is have demonstrated superiority over placebo in reducing major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke (only GLP1-RAs), all-cause mortality, and hospitalization for heart failure (HHF), while DPP-4is have shown neutral effects across these endpoints.[8] This growing evidence of cardiovascular protection has driven guideline updates, recommending SGLT-2is and GLP1-RAs for individuals with T2D and high CVD risk, initially as add-ons to metformin and more recently as first-line treatments.[5]

Implementing these guidelines can however be challenging, as reflected by the low initiation rate of these drugs in the elderly.[9] Despite the valuable insights from randomized controlled trials (RCTs) on efficacy in controlled settings, they provide limited information on the effectiveness in routine clinical practice.[10,11] Consequently, in addition to the high cost of these medications, the low prescription rate may partly stem from the

underrepresentation of the elderly population in RCTs and the absence of direct comparisons among these drugs, leading to a lack of evidence specific to this population.[12]

In terms of real-world evidence for this population, prior studies on comparative cardiovascular effectiveness have been limited to comparisons between only two glucose-lowering medications, with none evaluating the class effect of SGLT-2is vs. DPP-4is on MACE. Furthermore, studies assessing the impact of age have typically categorized age as a categorical variable, with the risk of losing nuanced information.[13–15] In this study, we aimed to assess the comparative cardiovascular effectiveness of GLP1-RAs vs. SGLT-2is vs. DPP-4is in an elderly (>70 years) real world population with type 2 diabetes, and examine if and how age modifies these effects.

Methods

Data sources and study design

In this new-user, active comparator, register-based cohort study, we used the target trial framework to design and emulate a three-arm pragmatic randomized clinical trial.[16] In Denmark, access to healthcare is free for all Danish residents and partial reimbursements are provided for most prescription drug expenses.[17] Denmark has a long history of recording administrative and health data on the entire Danish population from birth to death, allowing for large-scale epidemiological studies with a minimum loss to follow-up, made possible by the unique personal identification number assigned to all Danish residents.[17] We used a Danish diabetes register to identify all individuals with a T2D diagnosis and the National Prescription Registry to identify all redeemed prescriptions.[18,19] For the remaining registers used, see Appendix p 3.

Study population

Eligible participants included new users of either GLP1-RAs, SGLT-2is, or DPP-4is, aged 70 years or older, with a T2D diagnosis at the time of treatment initiation, between 1 December 2012 and 31 December 2020. The initiation period was set to ensure all medications were available and to allow for a year of follow-up.[20] New users included first time and previous users with no exposure to the specific medication-class or the comparator classes in the 90 days prior to initiation. Participants were excluded if they had experienced any of the outcomes in the 90 days before initiation, initiated treatment with more than one of the study-drugs at time of initiation, had previously been included in the study population (entails individuals that switch from one medication to another), or had immigrated within the past five years, see Appendix pp 4–5 for a summary of the protocol for the target trial and emulation trial. Both single-agent and combination glucose-lowering medications were included to categorize the medication classes of interest (Appendix p 6). To evaluate the 90-day washout of exposure, we calculated periods in which each person was on sustained use of medication. Sustained use was defined as intervals with a sufficient drug supply, based on the amount purchased, the predicted durability of the purchase (calculated using the Defined Daily Dose [DDD] as defined by the WHO), the date of purchase, and a 90-day grace period. When a period of sustained use ended, a 90-day washout period was subsequently assessed (Appendix p 7).

Follow-up and outcomes

The day of the first redeemed prescription when all eligibility criteria were fulfilled was considered the start of follow-up (i.e., time of initiation). In the main analysis, we adopted an as-treated approach mirroring a per-protocol analysis in an RCT setting. The end of follow-up was defined as discontinuation of the initial treatment, switch to or addon of one or more of the comparator medications, outcome occurrence (first event of 3P-MACE or HHF), emigration, administrative end of data (31 December 2021), which ever came first. In the sensitivity analysis which utilized an as-started approach mirroring an intention-to-treat analysis in an RCT setting, end of follow-up was determined by occurrence of outcome, emigration, or administrative end of data (Appendix p 8). The primary outcomes of interest were 3P-MACE (defined as a composite endpoint of MI, stroke, or all-cause mortality) or HHF (Appendix pp 9–10). Previous studies have determined the positive predictive value (PPV) for identifying MI in Danish registers to range between 92% and 97%, 70–80% for stroke, and 76%–95% for both first-time admissions and readmissions of HHF. Overall, the PPVs have improved over time.[21] Since all non-fatal outcomes are conditions requiring hospitalization, the sensitivity for capturing these outcomes in the national registers is considered high.

Covariates

Comorbidities were primarily identified using International Classification of Diseases (ICD-10) codes. In some instances, comorbidities were also defined through Danish procedure codes and laboratory measurements, employing Nomenclature for Properties and Units codes (Appendix pp 9–10). As for the study medication, other medication classes were classified using Anatomical Therapeutic Chemical (ATC) codes and drug-exposure-periods were calculated, enabling assessment of prior, current (at initiation) and time-varying use (Appendix p 11). Comorbidities and medication use was assessed at baseline and continuously updated during follow-up and used for deriving the summarized weights.

Educational level was determined by the highest education attained, categorized into low (primary and

	DPP-4is 21,848 (61)	GLP1-RAs 5702 (16)	SGLT-2is 8129 (23)
Sex, Women	9687 (44.3)	2472 (43.4)	3159 (38.9)
Age, years	76.4 [72.9–81.5]	74.1 [71.8–77.4]	74.6 [72.1–78.3]
T2D duration, years	9.9 [5.1–15.2]	13.8 [8.1–19.7]	10.5 [5.4–16.6]
Age at T2D diagnosis, years	67.0 [61.2–72.7]	61.1 [55.1–67.1]	64.7 [58.5–70.3]
Follow-up, years[b]			
As treated	1.3 [0.5–2.7]	1.2 [0.5–2.3]	1.0 [0.4–1.9]
As started	3.3 [1.7–5.4]	2.43 [1.4-4.1]	2.23 [1.4–3.6]
Education			
Low	10,789 (49.4)	2555 (44.8)	3456 (42.5)
Medium	8076 (37.0)	2294 (40.2)	3321 (40.9)
High	2983 (13.7)	853 (15.0)	1352 (16.6)
Country of origin[d]			
Denmark	20,487 (93.8)	5366 (94.1)	7487 (92.1)
Non-Western	801 (3.7)	199 (3.5)	399 (4.9)
Western	560 (2.6)	137 (2.4)	243 (3.0)
Comorbidities			
Cardiovascular disease	14,891 (68.2)	4207 (73.8)	5409 (66.5)
Atrial fibrillation	4450 (20.4)	1120 (19.6)	1562 (19.2)
Heart failure[c]	2663 (12.2)	723 (12.7)	972 (12.0)
Hypertensive Disease	12,055 (55.2)	3563 (62.5)	4263 (52.4)
Non-MI Ischemic heart disease	5782 (26.5)	1756 (30.8)	2379 (29.3)
Myocardial Infarction[c]	3775 (17.3)	1146 (20.1)	1682 (20.7)
Stroke[c]	3526 (16.1)	859 (15.1)	1146 (14.1)
Neuropathy	1379 (6.3)	729 (12.8)	578 (7.1)
Retinopathy	570 (2.6)	288 (5.1)	276 (3.4)
Lower limb amputation	375 (1.7)	117 (2.1)	110 (1.4)
Hypoglycemia (ever)	921 (4.2)	304 (5.3)	226 (2.8)
Ketoacidosis (ever)	107 (0.5)	86 (1.5)	47 (0.6)
Albuminuria	7666 (35.1)	2845 (49.9)	3426 (42.1)
Chronic Kidney disease (CKD)	9505 (43.5)	2867 (50.3)	3187 (39.2)
End-stage CKD	356 (1.6)	65 (1.1)	42 (0.5)
Severe CKD	1768 (8.1)	403 (7.1)	203 (2.5)
Moderate CKD	7381 (33.8)	2399 (42.1)	2942 (36.2)
Osteoporosis	408 (1.9)	124 (2.2)	183 (2.3)
Asthma	989 (4.5)	359 (6.3)	415 (5.1)
Chronis obstructive lung disease	2417 (11.1)	642 (11.3)	726 (8.9)
Dementia	751 (3.4)	138 (2.4)	177 (2.2)
In the 12 months before initiation			
Hypoglycemia	251 (1.1)	50 (0.9)	28 (0.3)
Ketoacidosis,	20 (0.1)	12 (0.2)	8 (0.1)
Severe urinary tract infection	35 (0.2)	5 (0.1)	15 (0.2)
Fracture	426 (1.9)	66 (1.2)	75 (0.9)
Pneumonia	90 (0.4)	13 (0.2)	18 (0.2)
Delirium	123 (0.6)	14 (0.2)	10 (0.1)
No. of hospitalizations	1.65 (2.46)	1.34 (2.05)	0.99 (1.79)
Any hospitalizations	12,157 (55.6)	2899 (50.8)	3320 (40.8)
Medication			
First time users of the drug initiate at initiation	19,184 (87.8)	4399 (77.1)	7857 (96.7)

(Table 1 continues on next page)

lower secondary), medium (upper secondary), and high (short cycle tertiary, bachelor's, or master's degrees, and doctoral), in accordance with the International Standard Classification of Education 2011. Individuals were classified as immigrants if they were born outside Denmark to parents who were not Danish citizens and were also born abroad. Immigrants were further categorized by country of origin, aggregated into categories of western or non-western countries. Income quintiles, where the first quintile represents the lowest income bracket, were calculated annually for the entire Danish population. Marital status was categorized as married, widowed, divorced, or single. The assessment of educational level, country of origin, income, and marital status was conducted within the year before drug initiation. Participants with missing data on any of the socioeconomic covariates at initiation were excluded from the study population (1360 persons corresponding to 3.7%).[22] Laboratory and clinical measurements were assessed within the year before initiation, however, due to significant missingness in most measurements, all but HbA1c were primarily used for descriptives at baseline. An overview over the study design and a flow diagram of the study population is provided in the Appendix pp 12–13.

Statistical analysis

To estimate the comparative effectiveness of the three glucose-lowering treatments on the rates of 3P-MACE or HHF using an as-treated approach, we balanced both baseline characteristics and treatment adherence through summarized weights.[23] Construction of the summarized weights was made in three steps. First, we derived the Inverse Probability Weights (IPW) of treatment assignment, then the stabilized IPW for adherence and lastly constructed the summarized weights. To construct the IPW of treatment assignment, we derived propensity scores (PS) through multinomial logistic regression, where both linear and nonlinear effects of time since initiation were included.[24] All predefined covariates measured at baseline were included in the multinomial logistic regression, except for laboratory and clinical measures (Appendix pp 14–16). Weights for IPW were derived as the inverse of PS and allocated based on treatment exposure, such that IPW_DPP-4i = 1/PS_ DPP-4i for the ones initiating DPP-4i, and 1/(1-PS_ DPP-4i) for the others in the comparator treatment classes. We applied a similar process for GLP1-RAs and SGLT-2is. To mitigate the inflated IPW values (approximately 2.7%), due to small probabilities, we replaced them with a constant value. For the second step, we split follow-up time into 1-month intervals, with updated covariates for each interval, i.e., medication use and comorbidities. The IPW of treatment adherence were derived by employing a pooled logistic regression to estimate the probability of adherence, utilizing all the baseline and time-updated variables, and adjusting for

both linear and nonlinear effects of person-times. This yielded individual adherence probabilities for each person-time and IPW for adherence were derived from the inverse of these probabilities. To stabilize the weights, we divided the probability of adhering to the treatment protocol, conditioned only on baseline variables, while also accounting for linear and nonlinear effects of person-time with the IPW of treatment adherence describe above.[25] Finally, the summarized weights were computed as the product of the IPW for treatment assignment and the stabilized IPW of adherence. Applying the summarized weights is equivalent to analyzing a pseudo-population where the probability of treatment assignment and adherence to the assigned treatment is similar for the three exposure groups.

A multistate model with transitions from initiation to 3P-MACE or HHF was set up, separately for the main-, subgroup-, and all the sensitivity analyses (Appendix p 17). For the main analyses, we also set up a multistate model for transitions from initiation to the individual components of 3P-MACE or HHF. To estimate the overall incidence rate ratios (IRR), time was split up into 1-month intervals and a Poisson regression model assuming proportional hazards was set up, including the appropriate weights, and adjusted for age, time since initiation, calendar time, and diabetes duration, all using natural splines with 4 knots, separately defined for age, time since initiation, calendar time and diabetes duration, and placed at the 12.5th, 37.5th, 62.5th and 87.5th percentiles. For the age-specific incidence rates (IR) and IRR, a similar model was used but further including an interaction term between treatment and age.

We examined the cardiovascular effectiveness across subgroups of individuals with and without manifest CVD at initiation, where CVD was defined as heart failure, MI, ischemic heart disease, hypertensive disease, cerebrovascular disease (stroke and transient cerebral ischemia), and macrovascular atherosclerotic disease (Appendix pp 9–10). To evaluate the robustness of the study design and the success of the emulation, we performed five sensitivity analyses. (1) We used overlap weights instead of IPW in the summarized weights, detailed in the Appendix p 18. (2) We shortened the washout period for non-fatal outcomes from 90 to 14 days. (3) We excluded participants who experienced outcomes within the first 90 days after initiation and move the start of follow-up to 90 days after initiation, as events prior to this were less likely related to the exposure. (4) We excluded the 6% of the main population lacking HbA1c measurements at initiation and included both baseline and time-updated HbA1c measurements as covariates in the summarized weights. (5) In the last sensitivity analysis, we used an as-started approach, emulating the intention-to-treat analysis in an RCT setting, where adherence to treatment was disregarded. Here we only applied the IPW of treatment assignment for balancing baseline characteristics.

	DPP-4is 21,848 (61)	GLP1-RAs 5702 (16)	SGLT-2is 8129 (23)
(Continued from previous page)			
No. of glucose lowering (excl. study medication)			
0	2312 (10.6)	385 (6.8)	585 (7.2)
1	14,046 (64.3)	2576 (45.2)	5074 (62.4)
2	5065 (23.2)	2191 (38.4)	2186 (26.9)
3	383 (1.8)	515 (9.0)	270 (3.3)
≥4	42 (0.2)	35 (0.6)	14 (0.2)
Metformin	17,483 (80.0)	4239 (74.3)	6924 (85.2)
Sulfonylureas	5002 (22.9)	735 (12.9)	1287 (15.8)
Insulin			
Fast-acting Insulin	541 (2.5)	661 (11.6)	336 (4.1)
Long-acting insulin	1291 (5.9)	1963 (34.4)	1193 (14.7)
Premixed insulin	556 (2.5)	556 (9.8)	311 (3.8)
Intermediate-acting insulin	581 (2.7)	486 (8.5)	263 (3.2)
Acetylic salicylic acid	8215 (37.6)	2280 (40.0)	2864 (35.2)
Receptor P2Y12 antagonist	2292 (10.5)	671 (11.8)	927 (11.4)
Oral anticoagulants	4413 (20.2)	1162 (20.4)	1617 (19.9)
Statins	15,894 (72.7)	4432 (77.7)	6233 (76.7)
Other lipid modifying agents	521 (2.4)	228 (4.0)	340 (4.2)
Angiotensin-converting enzyme inhibitors (ACEi)	8247 (37.7)	2091 (36.7)	3013 (37.1)
Angiotensin receptor II blockers (ARB)	7723 (35.3)	2420 (42.4)	3151 (38.8)
Calcium channel blockers	8617 (39.4)	2403 (42.1)	3261 (40.1)
Thiazides	4003 (18.3)	1159 (20.3)	1478 (18.2)
Beta blockers	8625 (39.5)	2336 (41.0)	3184 (39.2)
Loop-diuretics	6749 (30.9)	1973 (34.6)	1836 (22.6)
Aldosterone antagonists and other potassium sparing agents	1614 (7.4)	538 (9.4)	718 (8.8)
Nitrates	1482 (6.8)	391 (6.9)	588 (7.2)
Antiarrhythmics (Digoxin, Flecainide, Amiodarone)	2039 (9.3)	395 (6.9)	609 (7.5)
Laboratory and clinical measurements			
HbA1c, mmol/mol	60 [53–69]	64 [55–76]	61 [55–71]
Missing HbA1c	1716 (8.0)	232 (4.0)	188 (2.0)
Low-density lipoprotein (LDL), mmol/L	1.9 [1.4–2.5]	1.80 [1.3–2.3]	1.8 [1.3–2.4]
Missing LDL	4574 (21.0)	716 (13.0)	804 (10.0)
High-density lipoprotein (HDL), mmol/L	1.2 [1.0–1.5]	1.1 [0.9–1.4]	1.2 [1.0–1.4]
Missing HDL	4909 (22.0)	738 (13.0)	761 (9.0)
Triglycerides, mmol/L	1.8 [1.3–2.6]	2.0 [1.4–2.8]	1.8 [1.3–2.6]
Missing triglycerides	4394 (20.0)	654 (11.0)	713 (9.0)
Total cholesterol, mmol/L	4.0 [3.4-4.7]	3.9 [3.4-4.6]	3.9 [3.3-4.6]
Missing total cholesterol	4824 (22.0)	739 (13.0)	749 (9.0)
Estimated glomerular filtration rate (eGFR), ml/min/1.73m^2	63.0 [44.0–82.0]	67.0 [49.0–84.0]	75.0 [62.0–86.0]
Missing eGFR	2076 (10)	336 (6)	187 (2)
Systolic blood pressure, mmHg	135 [127–145]	135 [126–145]	135 [127–145]

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	DPP-4is 21,848 (61)	GLP1-RAs 5702 (16)	SGLT-2is 8129 (23)
(Continued from previous page)			
Diastolic blood pressure, mmHg	75 [70–81]	75 [70–80]	76 [70–82]
Missing blood pressure	16,957 (78.0)	3633 (64.0)	5602 (69.0)
Smoking status			
Current smoker	497 (11.1)	146 (8.9)	156 (9.0)
Ex. Smoker	2021 (45.2)	848 (51.9)	880 (50.8)
Never	1958 (43.7)	639 (39.1)	696 (40.2)
Missing	17,372 (80)	4069 (71)	6397 (79)
Body mass index (BMI), kg/m^2	29.0 [26.0–32.5]	32.9 [29.1–36.7]	29.6 [26.6–33.3]
Missing BMI	18,414 (84.0)	4027 (71.0)	6064 (75.0)

DPP-4is = dipeptidyl peptidase 4 inhibitors, GLP1-RAs = glucagon-like peptide 1 receptor agonists, and SGLT-2is = sodium-glucose cotransporter 2 inhibitors. [a]Median (Q1-Q3) was calculated for continuous variables. Percentages were calculated for categorical variables and might not sum to 100 because of rounding. [b]Not assessed at initiation. [c]HHF, MI and stroke diagnosis were assessed before the 90-day washout, as an exclusion criterion was occurrence of outcome in the 90-days prior to initiation. [d]Western countries include EU- countries, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Schweiz, United states of America and the Vatican. Non-western countries include Albania, Bosnia and Herzegovina, Belarus, Yugoslavia, Kosovo, Macedonia, Moldova, Montenegro, Russia, Serbia, Soviet Union, Turkey, Ukraine, and all African, Asian, Oceania countries (except Australia and New Zealand), south and central American countries and stateless.

Table 1: **Selected population characteristic at initiation and before adjustment (n = 35,679).**[a]

R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org) was used for statistical analyses.

Ethics

According to Danish law, ethics approvals and patient consent are not required for registry-based studies. Access and use of the described data were approved by the Danish Data Protection Agency (j-No. VD-2019-197) and the Danish Patient Safety Authority (j-No. 3-3013-2959/1).

Role of the funding source

There was no funding source for this study.

Results

We identified 35,679 new users of DPP-4is (21,848 (61%)), GLP1-RAs (5702 (16%)), and SGLT-2is (8129 (23%)), aged 70 years or older with T2D from the Danish nationwide registers between 1 December 2012 and 31 December 2020. Before adjustments, DPP-4is initiators were older at the time of initiation and T2D diagnosis, had a shorter duration of T2D, and included a higher proportion of women (Table 1 and pp 14–16 in the Appendix). GLP1-RAs had higher baseline HbA1c levels and a greater comorbidity burden, including the use of concomitant medications, compared to the other groups. Follow-up times under the as-treated approach were shorter for the SGLT-2i group, whereas they were similar for the DPP-4i and GLP1-RA groups. Distribution of censoring due to discontinuation of the initial treatment, switch to or addon of one or more of the comparator medications is presented in the Appendix p 19. At initiation, 52.7% of DPP-4i users were prescribed sitagliptin, 53.4% of GLP1-RA users received liraglutide, and 62.3% of SGLT-2i users received empagliflozin (Appendix p 20).

Propensity score distribution per comparator class is illustrated for the unadjusted and adjusted using IPW or overlap weights in the Appendix p 21. In general, a greater overlap was seen after adjustment. Standardized mean differences (SMD) of all covariates, included in the propensity scores, before and after adjustments are illustrated in the Appendix pp 22–25. SMD for the pairwise comparison of treatments was predominantly less than 0.1 after adjustment, suggesting a good fit.

In our main analysis, using the as-treated approach, both GLP1-RAs and SGLT-2is were associated with reduced overall rates of 3P-MACE (IRR 0.68 [95% CI 0.65–0.71] and 0.65 [95% CI 0.63–0.68]) and HHF (IRR 0.81 [95% CI 0.74–0.88] and 0.60 [95% CI 0.55–0.66]) compared to DPP-4is (Table 2). We found no significant difference in the rates of 3P-MACE when comparing SGLT-2is with GLP1-RAs (IRR 0.96 [95% CI 0.91–1.01]). However, SGLT-2is were associated with reduced overall rates of HFF compared to GLP1-RAs (IRR 0.75 [95% CI 0.67–0.83]). We found that the age-specific IR of 3P-MACE and HHF increased with age across all treatments, particularly for DPP-4is (Fig. 1A and B). The age-specific IRR showed that GLP1-RAs and SGLT-2is were associated with reduced rates of 3P-MACE for all ages compared to DPP-4is, with some variation in effect size for GLP1-RAs vs. DPP-4is (Fig. 2A). Compared to GLP1-RAs, SGLT-2is were associated with increased rates of 3P-MACE until the age of 80 years whereafter SGLT-2is were associated with reduced rates (Fig. 2A). SGLT-2is were associated with reduced rates of HHF independent of age, while GLP1-RAs were associated with reduced rates of HHF for most ages, both compared to DPP-4is (Fig. 2B). Compared to GLP1-RAs, SGLT-2is were associated with reduced rates of HHF until the age of 84 years, whereafter SGLT-2is were associated with increased rates of HHF compared to GLP1-RAs (Fig. 2B). Age-specific IR of 3P-MACE and HHF were slightly higher with a diabetes duration of 5 and 15 years, compared to 10 years, across treatments, however the age-specific IRR remained the same (Appendix p 26–29).

Analyses of the individual components of 3P-MACE showed that both GLP1-RAs and SGLT-2is were associated with reduced overall rates of both all-cause mortality (IRR 0.55 [95% CI 0.52–0.59] and 0.56 [95% CI 0.53–0.60]) and stroke (IRR 0.81 [95% CI 0.74–0.88] and 0.74 [95% CI 0.68–0.80]) compared to DPP-4is (Table 2). SGLT-2is were also associated with a reduced rate of MI 0.89 (95% CI 0.80–0.99). We found no significant difference in the overall effectiveness of the individual

Outcome	Person years of follow-up			Number of events			Crude incidence rate per 100 person years of follow-up			Incidence rate ratios (95% CI)		
	GLP1-RAs	SGLT-2is	DPP-4is	GLP1-RAs	SGLT-2is	DPP-4is	GLP1-RAs	SGLT-2is	DPP-4is	GLP1-RAs vs. DPP-4is	SGLT-2is vs. DPP-4is	SGLT-2is vs. GLP1-RAs
3P-MACE	9668.0	10766.0	41374.9	617	666	4288	6.4	6.2	10.4	0.68 (0.65–0.71)	0.65 (0.63–0.68)	0.96 (0.91–1.01)
HHF	9668.0	10766.0	41374.9	187	141	1023	1.9	1.3	2.5	0.81 (0.74–0.88)	0.60 (0.55–0.66)	0.75 (0.67–0.83)
Individual components of 3P-MACE												
All-cause mortality	9668.0	10766.0	41374.9	273	318	2651	2.8	3.0	6.4	0.55 (0.52–0.59)	0.56 (0.53–0.60)	1.02 (0.95–1.10)
Myocardial infarction	9668.0	10766.0	41374.9	142	133	544	1.5	1.2	1.3	0.97 (0.87–1.08)	0.89 (0.80–0.99)	0.92 (0.82–1.03)
Stroke	9668.0	10766.0	41374.9	202	215	1093	1.5	2.0	2.6	0.81 (0.74–0.88)	0.74 (0.68–0.80)	0.91 (0.83–1.00)

Results are presented for the main analysis using the as-threated approach. GLP1-RAs = glucagon-like peptide 1 receptor agonists, SGLT-2is = sodium-glucose cotransporter 2 inhibitors, and DPP-4is = dipeptidyl peptidase 4 inhibitors.

Table 2: **Overall incidence rate ratios of 3-point major adverse cardiovascular events (3P-MACE), hospitalization of heart failure (HHF), and individual components of 3P-MACE.**

components of MACE with SGLT-2is compared to GLP1-RAs. The age-specific IRs showed increased rates of all-cause mortality and stroke with increasing age and a relatively stable IR of MI for all treatments (Appendix p 30). GLP1-RAs and SGLT-2is were associated with reduced rates of all-cause mortality independent of age compared to DPP-4is (Fig. 3A). However, SGLT-2is were associated with increased rates of all-cause mortality until the age of 80 years, after which SGLT-2is were associated with reduced rates, compared to GLP1-RAs. SGLT-2is were associated with reduced rates of MI in the older ages, compared to DPP-4is (Fig. 3B). Compared to DPP-4is, SGLT-2is were associated with reduced rates of stroke at most ages while GLP1-RAs effect were more age dependent. SGLT-2is were only associated with reduced rates of stroke after the age of 85 years, compared to GLP1-RAs (Fig. 3C).

In the subgroup analyses, we found that GLP1-RAs were associated with lower rates of 3P-MACE compared to DPP-4is in individuals both with and without manifest CVD at initiation, with no significant difference between these subgroups (Appendix, pp. 31–30). However, while GLP1-RAs were associated with reduced rates of HHF in individuals with CVD at initiation (IRR 0.77 [95% CI 0.70–0.84]), they were associated with an increased rate of HHF in those

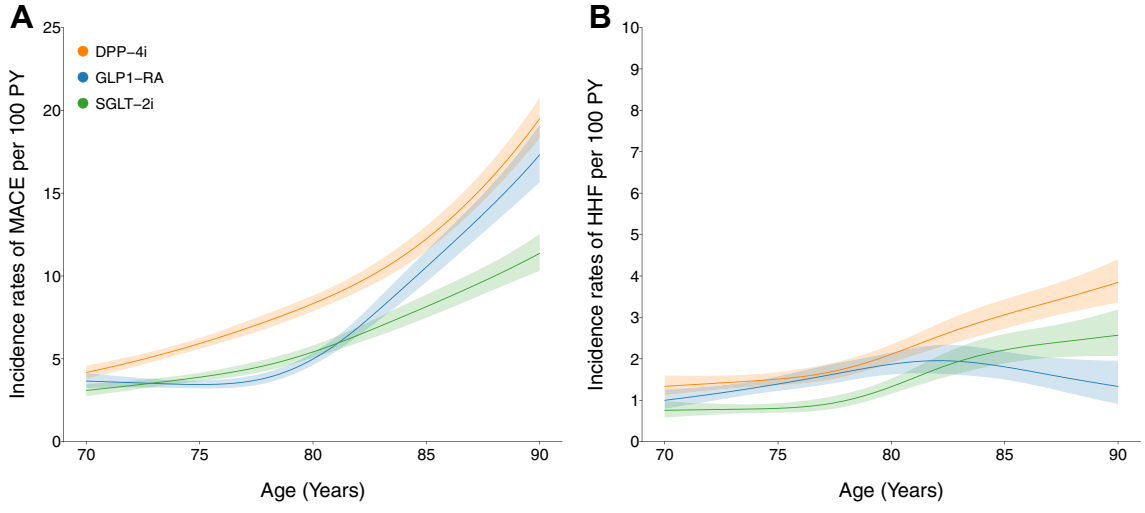


Fig. 1: **Age-specific incidence rates (IR) of 3-point major adverse cardiovascular events (3P-MACE) and hospitalization for heart failure (HHF) per 100 persons years (PY) for glucagon-like peptide 1 receptor agonists (GLP1-RAs), sodium-glucose cotransporter 2 inhibitors (SGLT-2is), and dipeptidyl peptidase 4 inhibitors (DPP-4is) using the as-treated approach. A)** IR of 3P-MACE, **B)** IR of HHF. The age-specific IRs are shown for 1 year since initiation, with the initiation of medication in 2018 and a diabetes duration of 10 years. Figures are based on a Poisson regression model with an interaction between treatment and age, adjusted for time since initiation, calendar year, and diabetes duration. The model includes summarized weights based on inverse probability weighting (IPW) of treatment assignment and IPW of adherence. The shaded area represents the 95% confidence interval (CI).

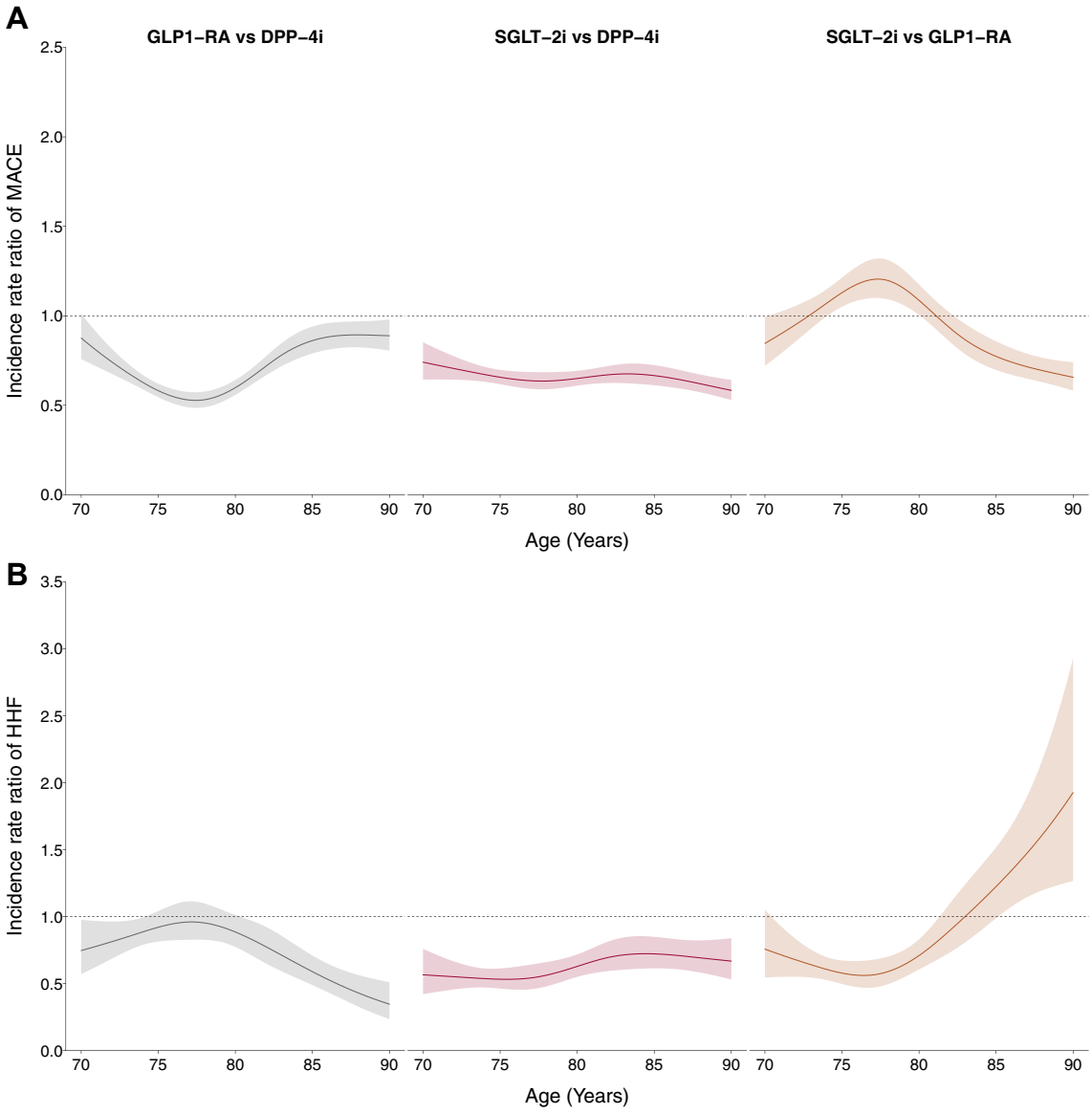
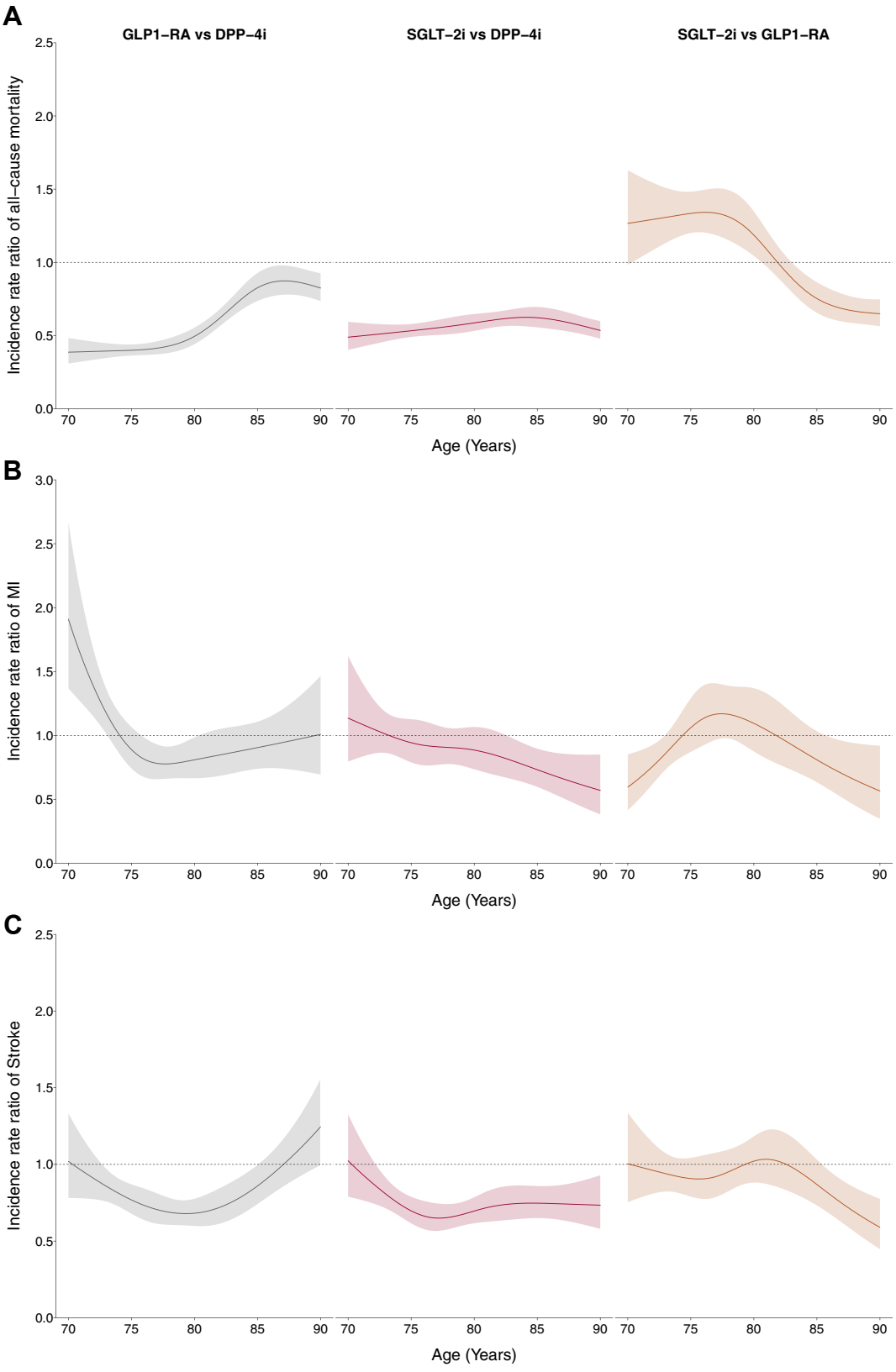


Fig. 2: **Age-specific incidence rate ratios (IRR) of 3-point major adverse cardiovascular events (3P-MACE) and hospitalization for heart failure (HHF) for glucagon-like peptide 1 receptor agonists (GLP1-RAs) vs. dipeptidyl peptidase 4 inhibitors (DPP-4is), sodium-glucose cotransporter 2 inhibitors (SGLT-2is) vs. DPP4is and SGLT-2is vs. GLP1-RAs using the as-treated approach. A)** IRR of 3P-MACE, **B)** IRR of HHF. The age-specific IRRs are shown for 1 year since initiation, with the initiation of medication in 2018 and a diabetes duration of 10 years. Figures are based on a Poisson regression model with an interaction between treatment and age, adjusted for time since initiation, calendar year, and diabetes duration. The model includes summarized weights based on inverse probability weighting (IPW) of treatment assignment and IPW of adherence. The shaded area represents the 95% confidence interval (CI).

without CVD (IRR 1.30 [95% CI 1.01–1.67]), compared to DPP-4is. In line with the main analyses, we found that SGLT2is were associated with reduced rates of both 3P-MACE and HHF compared to DPP-4is, as well as reduced rates of HHF compared to GLP1-RAs. These reductions were more pronounced in individuals without CVD at initiation than in those with CVD. Furthermore, consistent with our main findings, there was no significant difference in 3P-MACE rates between SGLT2is and GLP1-RAs in individuals with CVD at initiation. However, among those without CVD at initiation, SGLT2is were associated with a reduced risk of 3P-MACE compared to GLP1-RAs (IRR 0.87 [95% CI 0.78–0.97]). The age-specific IRR of 3P-MACE for both those with and without CVD at initiation and age-specific IRR of HHF for those with CVD were similar


A
GLP1–RA vs DPP–4i
SGLT–2i vs DPP–4i
SGLT–2i vs GLP1–RA
Incidence rate ratio of all–cause mortality
2.5
2.0
1.5
1.0
0.5
0.0
70
75
80
85
90
Age (Years)
B
Incidence rate ratio of MI
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Age (Years)
C
Incidence rate ratio of Stroke
Age (Years)

to the main results. However, the age-specific IRR of HHF for those without CVD showed more variation with age and with wider confidence intervals.

Overall, the five sensitivity analyses yielded similar results as the main analyses (Appendix pp 35–41). The as-started approach yielded less pronounced rate reductions of 3P-MACE and HHF, both for the overall and the age-specific IRR, compared to the as-treated approach. Furthermore, the sensitivity analyses using overlap weight to construct the summarized weights, yielded wider confidence intervals. Finally, both the as-started analysis and the sensitivity analysis with reduced washout period of non-fatal outcomes yielded reduced rates of 3P-MACE with SGLT-2is compared with GLP1-RAs.

Discussion

In this cohort study, we emulated a three-arm randomized pragmatic clinical trial using Danish nationwide registers to assess the comparative effectiveness of the newest available glucose-lowering medication in an elderly (≥70 years) population with T2D. In an as-treated approach, we found that both GLP1-RAs and SGLT-2is were associated with reduced rates of 3P-MACE and HHF compared to DPP-4is, overall and independent of age. Compared to GLP1-RAs, SGLT-2is were associated with reduced rates of HHF but not 3P-MACE, with some age-specific variation. The five sensitivity analyses yielded similar findings showing robustness of the results, with minor variations in point estimates and confidence intervals.

Most previous observational studies on cardiovascular effectiveness in elderly populations have focused on comparing SGLT-2is with DPP-4is or GLP1-RAs, with only one addressing the cardiovascular effectiveness of GLP1-RAs vs. DPP-4is.[14,15,26–33] Consistent with our findings, these studies have shown that SGLT-2is and GLP1-RAs were associated with a reduced risk of MACE, HHF, and all-cause mortality compared to DPP-4is, while results for MI and stroke varied.[13–15] Similar to our study, most have not found differences between SGLT-2is and GLP1-RAs in reducing MACE and all-cause mortality, though all but one reported that SGLT-2is were associated with a lower HHF risk compared to GLP1-RAs.[13,15] Age-specific effects on these outcomes are difficult to compare with previous work due to age being treated as a discrete variable. However, consistent with our findings, Htoo et al. reported no age-modification in the risk reduction of 3P-MACE and HHF when comparing empagliflozin to sitagliptin.[29] In contrast, Han et al. reported that SGLT-2is compared to DPP-4is reduced the risk of HHF, all-cause mortality, stroke, and MI in those under 75 years but not in individuals aged 75 years or older.[26] Similarly, Nakai et al. observed a trend of diminishing HHF risk reduction with increasing age until 85 years, after which the effect size increased among SGLT-2is compared to DPP-4is.[28] Finally, contrary to our findings, two studies examining SGLT-2is vs. GLP1-RAs in elderly individuals found no age-modifying effects on 3P-MACE or HHF outcomes.[29,31]

Based on data from the GLP1-RAs and SGLT-2is CVOTs, a meta-analysis assessing the cardiovascular effect in an elderly (≥65 years) vs. younger (<65 years) population with T2D found results suggesting that the beneficial effect of SGLT-2is on HHF was driven by the elderly population.[34] A result that is difficult to compare to our results as we have excluded persons younger than 70 years. The authors also found a more pronounced effect of GLP1-RAs on MACE in those older than 75 years compared to those younger than 75 years, aligning with our findings. Otherwise, the study found no age-modifying effects on other outcomes.

The mechanisms underlying the beneficial effects of GLP1-RAs and SGLT-2is are not yet fully understood. However, GLP1-RAs are thought to exert their effects through anti-atherogenic mechanisms, including anti-inflammatory actions, enhancement of endothelial function, and plaque stabilization. In contrast, SGLT-2is are believed to act by reducing tubular-glomerular feedback, improving intra-glomerular hypertension and hyperfiltration, and decreasing cardiac preload and afterload. These differences may explain the specific cardiovascular protective effects observed and the age-specific variations.[35] Finally, the age-specific differences in the effectiveness of for example SGLT-2is vs. GLP1-RAs on HHF beyond the age of 80 should be interpreted with caution due to the low number of events, as reflected by the wide confidence intervals.

In the subgroup analyses, we observed a greater effectiveness among individuals without CVD at baseline across most comparisons, except for the comparison of GLP1-RAs vs. DPP-4is. These findings should be interpreted with caution due to the low number of events and the high proportion with CVD at baseline. Additionally, we could not identify individuals with high CVD risk at baseline, as

Fig. 3: **Age-specific incidence rate ratios (IRR) of the individual components of 3-point major adverse cardiovascular events (3P-MACE) for glucagon-like peptide 1 receptor agonists (GLP1-RAs) vs. dipeptidyl peptidase 4 inhibitors (DPP-4is), sodium-glucose cotransporter 2 inhibitors (SGLT-2is) vs. DPP4is and SGLT-2is vs. GLP1-RAs in an as-treated approach A) all-cause mortality, B) myocardial infarction and C) stroke.** The age-specific IRRs are shown for 1 year since initiation, with the initiation of medication in 2018 and a diabetes duration of 10 years. Figures are based on a Poisson regression model with an interaction between treatment and age, adjusted for time since initiation, calendar year, and diabetes duration. The model includes summarized weights based on inverse probability weighting (IPW)of treatment assignment and IPW of adherence. The shaded area represents the 95% confidence interval (CI).

Danish registers lack sufficient data on smoking status, hypertension, family history of CVD, and BMI.

When prescribing medication to elderly persons, it is essential to consider both the potential benefits and the risk of adverse effects. Side effects of SGLT-2is include genital infections and diabetic ketoacidosis, while GLP1-RAs are associated with gastrointestinal events.[8] Although previous studies have shown no age-related differences in adverse effects with GLP1-RAs or SGLT-2is, the real-world elderly population may have more comorbidities and polypharmacy.[36,37] Therefore, clinical status, life expectancy, and patient preferences should be carefully considered when prescribing. The safety of these medications was not assessed in this study, partly due to incomplete registration of these diagnosis in national registers.

To our knowledge, this is the first three-arm, real-world comparative study to comprehensively analyze the cardiovascular effectiveness of SGLT-2is, GLP1-RAs, and DPP-4is in elderly (≥70 years) individuals with T2D, as well as the first to provide age-specific IRR for these outcomes. Key strengths include the use of a new-user, active comparator design, enhanced by statistical methods aiming to minimize confounding by indication and difference in adherence, and supported by multiple sensitivity analyses. The IPW approach, which includes the entire population rather than excluding unmatched individuals, yields an average treatment effect representative of the entire cohort.[38] Sensitivity analyses confirmed the robustness of the study design in both as-treated and as-started approaches, with the former accounting for non-adherence, a significant issue in real-world settings.[39] The study also benefits from complete, validated nationwide registers and a researcher-initiated diabetes registry, allowing for the distinction between diabetes types and insight into disease duration. The large sample size and relatively long follow-up period ensure highly precise, reliable results.

Limitations include residual confounding due to unmeasured covariates such as laboratory measurements, BMI, smoking, vital signs, reason for discontinuation or switch and addon of medications in comparator class (including side effects), severity of disease, and non-patient related factors driving prescribing behavior, which have changed over time. While the methods used in this study, including propensity score methods, help mitigate confounding by indication, they may not fully eliminate it due to unmeasured confounders. We opted not to use cause-specific death due to diagnostic validity concerns.[40] While dates of death are reliably recorded, cause-of-death diagnoses rely solely on physician reports and low autopsy rates limit the possibility for validation. Furthermore, we relied on redeemed prescriptions which does not guarantee actual medicine intake, and therefore some misclassification of the exposure cannot be ruled out. However, we deem this to have little impact on our results, as recurrent redemptions strengthen the assumption of actual use. We excluded 3.7% of the population due to missing information in the predefined covariates, with a potential risk of selection bias. However, we estimated this risk to be relatively small. Finally, as the Danish population is ethnically homogeneous, with only 7% of the population in this study being born outside of Demark, the generalizability of this study is limited to populations with a similar ethnicity.

In conclusion, in this three-arm comparative real-world study in an elderly (≥70 years) population with T2D, we compared the cardiovascular effectiveness of GLP1-RAs, SGLT-2is, and DPP-4is. We found that both GLP1-RAs and SGLT-2is were associated with reduced risk of 3P-MACE and HHF, compared to DPP-4is and independent of age, and that SGLT-2is were associated with reduced risk of HHF, largely independent of age, compared to GLP1-RAs. These results could help strengthen the implementation of current guidelines into clinical practice.

Contributors

All authors were involved in the conceptualization and the design of the study. VK was responsible for data management and contributed to data acquisition. MP detailed the statistical method for constructing the weights, while VK outlined and performed the remaining analyses. VK and MP had accessed and verified the data. VK wrote the initial draft of the manuscript and was responsible for visualizing the results. All authors contributed to the interpretation of the data and the revision of the manuscript. VK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. All authors have approved the final version of the manuscript.

Data sharing statement

All data are securely stored on Statistics Denmark's servers and are subject to strict confidentiality regulations to protect data privacy. Access to individual-level data requires a formal application and approval from the relevant register authorities. Consequently, the data cannot be made publicly available.

Declaration of interests

VK, MZA, BB, JR and KKS have nothing to declare. SHS, MP, DV and KKBC are employed at Novo Nordisk A/S. DV has received research grants from Bayer A/S, Sanofi Aventis, Novo Nordisk A/S, and Boehringer Ingelheim and holds shares in Novo Nordisk A/S. KKBC holds shares in Novo Nordisk A/S and has received research grants from the Innovation Fund Denmark.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103162.

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