Initiation of SGLT2 inhibitors and GLP-1 receptor agonists according to level of frailty in people with type 2 diabetes and cardiovascular disease in Denmark: a cross-sectional, nationwide study

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Summary

Background Whether frailty influences the initiation of two cardioprotective diabetes drug therapies (ie, SGLT2 inhibitors and GLP-1 receptor agonists) in people with type 2 diabetes and cardiovascular disease is unknown. We aimed to assess rates of initiation of SGLT2 inhibitors and GLP-1 receptor agonists according to frailty in people with type 2 diabetes and cardiovascular disease.

Methods For this cross-sectional, nationwide study, all people with type 2 diabetes and cardiovascular disease in Denmark between Jan 1, 2015, and Dec 31, 2021, from six Danish health-data registers were identified. People younger than 40 years, with end-stage renal disease, with registered contraindications to SGLT2 inhibitors or GLP-1 receptor agonists, or with previous use of either drug therapy were excluded. The Hospital Frailty Risk Score was used to categorise people as either non-frail, moderately frail, or severely frail. Cox proportional hazards models were used to analyse the association between frailty and initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist.

Findings Of 119 390 people with type 2 diabetes and cardiovascular disease, 103 790 were included. Median follow-up time was 4·5 years (IQR 2·7–6·1) and median age across the three frailty groups was 71 years (64–79). 65 959 (63·6%) of 103 790 people were male and 37 831 (36·5%) were female. At index date, 66 910 (64·5%) people were non-frail, 29 250 (28·2%) were moderately frail, and 7630 (7·4%) were severely frail. Frailty was associated with a significantly lower probability of initiating therapy with an SGLT2 inhibitor or a GLP-1 receptor agonist than in people who were non-frail (moderately frail hazard ratio 0·91, 95% CI 0·88–0·94, p<0·0001; severely frail 0·75, 0·70–0·80, p<0·0001). This association persisted after adjustment for age, sex, socioeconomic status, year of inclusion, duration of type 2 diabetes, duration of cardiovascular disease, polypharmacy, and comorbidity.

Interpretation In people with type 2 diabetes and cardiovascular disease in Denmark, frailty was associated with a significantly lower probability of SGLT2-inhibitor or GLP-1 receptor-agonist initiation, despite their benefits. Formulating clear and updated guidelines on the use of SGLT2 inhibitors and GLP-1 receptor agonists in people who are frail with type 2 diabetes and cardiovascular disease should be a priority.

Funding Department of Cardiology, Herlev and Gentofte University Hospital.

Introduction

Frailty is a dynamic clinical condition that is characterised by decreased physiological reserve and increased vulnerability to internal and external stressors. It is associated with an increased risk of adverse health outcomes, such as hospital admission, impaired quality of life, and premature death.[1–3] Clinicians are hesitant to introduce new drug therapies in people who are frail due to concerns that they might be less effective and safe because of the decreased physiological reserves and the altered pharmacokinetics and dynamics. Furthermore, poor adherence has been mentioned as a challenge in individuals who are frail due to other factors, such as cognitive impairment and physical limitations. The lack of clear guidance or pathways to help health-care professionals manage the care of these people could be exacerbating the issue of underprescribing new drug therapies in individuals who are frail.[4]

No previous study has clarified whether frailty influences the initiation of two cardioprotective diabetes drug therapies (ie, SGLT2 inhibitors or GLP-1 receptor agonists) in a real-world population of people with type 2 diabetes and cardiovascular disease, so we aimed to do so. The additional advantages and few side-effects of these therapies were shown in a large network meta-analysis published in 2021, including for heart failure, chronic kidney disease, and obesity. This finding is of particular importance as these conditions often coexist in

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For the Danish translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

There is increasing evidence that SGLT2 inhibitors and GLP-1 receptor agonists are potential drugs to treat frailty for people with type 2 diabetes due to their broad and multisystemic effects. Initially approved for the treatment of type 2 diabetes, these drugs have shown convincing beneficial effects in other conditions, such as heart failure, chronic kidney disease, atherosclerotic cardiovascular diseases, and obesity. Because of the additional advantages and relatively few side-effects shown in a large network meta-analysis published in 2021, clarifying and understanding the real-world applications of these drugs for individuals who are frail is crucial. We searched PubMed from database inception to June 23, 2023, to identify literature published in English only examining the use patterns of SGLT2 inhibitors or GLP-1 receptor agonists among people who are frail (including initiation, adherence, and discontinuation). We used the search terms ("discontinuation" [Mesh] or "persistency" [Mesh] or "adherence" [Mesh] or "discontinuation" [tiab] or "persistency" [tiab] or "adherence" [tiab]) and ("sodium-glucose transporter 2 inhibitors" [Mesh] or "sodium-glucose cotransporter-2" [tiab] or "sglt2" [tiab] or "glucagon-like peptide 1"[Mesh] or "glp1" [tiab] or "glp1-ra" [tiab] or "glucagon-like-peptide-1" [tiab]) and ("diabetes" [tiab] or "diabetes mellitus, type 2"[Mesh]) and ("frailty" [tiab] or "frail"[tiab]). Our research revealed that no previous study has investigated the association between frailty and the initiation of SGLT2 inhibitors or GLP-1 receptor agonists.

Added value of this study

To our knowledge, our study is the first to investigate the real-world use of SGLT2 inhibitors and GLP-1 receptor agonists in people with type 2 diabetes and cardiovascular disease according to their level of frailty. 103 790 people with type 2 diabetes and cardiovascular disease were included from six Danish nationwide health-data registers between Jan 1, 2015, and Dec 31, 2021. Our results showed significant underprescription of SGLT2 inhibitors and GLP-1 receptor agonists for individuals who were frail compared with individuals who were non-frail. People who were most frail were significantly less likely to receive these treatments compared with people who were non-frail, despite having no registered contraindications. This association did not appear to be driven by other factors, such as age, sex, or socioeconomic status. Furthermore, we observed that individuals who were frail were also less frequently treated with other guideline-recommended preventive cardiovascular drug therapies (eg, renin-angiotensin-system inhibitors, lipid-lowering agents, and aspirin). These findings provide new insights in the real-world prescribing patterns of SGLT2 inhibitors and GLP-1 receptor agonists in a nationwide Danish population and reveal substantial underprescribing among people who are frail.

Implications of all the available evidence

With increasing use of SGLT2 inhibitors and GLP-1 receptor agonists, and increasing evidence of their beneficial effects in older and frail individuals, clarifying the real-world use of these drug therapies in individuals who are frail is important. Data from this study reveal a significant underprescription of SGLT2 inhibitors and GLP-1 receptor agonists in individuals who were frail compared with individuals who were non-frail. This underprescription is of particular concern considering the increased risk of frail individuals having various adverse cardiovascular and diabetes-related events. Although further research on this association is needed, our results should encourage the formulation of clear and updated guidelines on frailty and the use of SGLT2 inhibitors and GLP-1 receptor agonists for people with type 2 diabetes and cardiovascular disease. Future research should prioritise obtaining an increased understanding of the factors that still hinder the prescription of these medications in individuals who are frail despite existing evidence. Moreover, this research should aim to clarify the cost–benefit of these therapies in people who are frail, considering the potential reductions in hospitalisations and possible deprescription of other co-medications.

people who are frail.[5] Furthermore, analyses published in 2022 showed that both drugs were as effective and safe in older people who were frail as they were in people who were not older and not frail, regardless of level of frailty and age.[6,7]

Methods

Study design

This cross-sectional, nationwide study was conducted with data from Jan 1, 2015, to Dec 31, 2021, from six health-data registers in Denmark.

The health-care system in Denmark is universal and most health-care services are financed through national income taxes. For prescribed medication, there is an automatic threshold-based reimbursement system that accounts for the total annual medicine expenditure of a person, with a maximum annual expenditure of €581 for each resident as of January, 2023.[8]

In Denmark, register-based observational studies do not require ethical approval by law. The data access for this study was approved by the Data Responsible Institute in the Capital Region of Denmark (approval number P-2019-191).

Data sources

Danish health data are collected, stored, and managed in national health registers at the Danish Health Data Authority and delivered to Statistics Denmark, through which the data for this study was accessed. We used data from six registers: the Danish Civil Registration System, which contains basic personal information for all people living in Denmark; the Danish National Prescription

Register, which contains information on all dispensed medication prescriptions from Danish pharmacies, classified by the international Anatomical Therapeutic Chemical (ATC) system; the Danish National Patient Register, which contains information on all hospital admissions and outpatient contacts and in which each contact is registered by the date and type of their visit (ie, outpatient, day patient, or overnight stay) with a primary diagnosis at discharge or end of appointment according to the International Classification of Diseases, tenth revision (ICD-10); the Danish Income Statistics Register, which contains complete data on income and transfer payments for all people living in Denmark; the Danish Student Register, which contains information on the education of all people living in Denmark (eg, highest level of education); and the Danish Nationwide Register of Laboratory Results for Research, which contains information on all biomarker analyses at the individual level from public hospital laboratories.[8–10] Data on ethnicity and race were not available for this study.

Study population

From the population of Denmark, we identified all people with type 2 diabetes and cardiovascular disease between Jan 1, 2015, and Dec 31, 2021. Index year was defined as the date of diagnosis of type 2 diabetes or cardiovascular disease, whichever occurred most recently (people with type 2 diabetes and cardiovascular disease diagnosed before 2015 were included with an index date of Jan 1, 2015). People younger than 40 years, with end-stage renal disease, with an estimated glomerular filtration rate (eGFR) below the guideline recommendation at time of identification (a contraindication for SGLT2 inhibitors and GLP-1 receptor agonists), with a history of pancreatitis or thyroid cancer (a contraindication for GLP-1 receptor agonists), or who had redeemed a prescription of an SGLT2 inhibitor or a GLP-1 receptor agonist any time before their index date were excluded. Type 2 diabetes was defined with a diagnosis code (ICD-10 code DE11) or from redeemed prescriptions of non-insulin antihyperglycaemic therapies (ATC code A10B). Cardiovascular disease was defined as a diagnosis of heart failure (ICD-10 code I10), ischaemic heart disease (ICD-10 codes I20–25), stroke or transient ischaemic attack (ICD-10 codes I63–65), or peripheral artery disease (ICD-10 codes I70–74). Comorbidities of interest were defined with primary and secondary inpatient and outpatient ICD-10 diagnosis codes, registered at any time before index date. eGFR, glycated haemoglobin A_{1c} (HbA_{1c}), and albumin were reported at baseline as mean values measured within 1 year before index date. Use of specific concomitant cardiovascular and antihyperglycemic pharmacotherapy was identified with ATC codes and defined by at least one redeemed prescription within 6 months before index date (appendix 2 pp 12–16).

Procedures

Frailty was assessed with the Hospital Frailty Risk Score, an approach for frailty risk stratification based on ICD-10 diagnosis codes obtained from administrative health registers.[11] The Hospital Frailty Risk Score was validated internally and externally in the UK and found to be comparable to other clinical measures of frailty in terms of performance, including the Fried and Rockwood scale and the Rockwood Frailty Index.[12] The Hospital Frailty Risk Score has also been used in previous studies outside the UK.[12,13] In this study, we categorised all people with type 2 diabetes and cardiovascular disease into three subgroups at their date of index depending on their frailty risk score, which was estimated from the hospital admissions and registered ICD-10 codes of each person within 10 years before their index date. The three subgroups were non-frail (0–4 points), moderately frail (5–15 points), and severely frail (>15 points; appendix 2 pp 16–25).

To investigate the association between frailty and socioeconomic factors that might be related to the initiation of SGLT2 inhibitors and GLP-1 receptor agonists in subanalyses, we obtained data on education and income quartile in the 1 year before index date for all people who were included. Education was defined according to the International Standard Classification of Education (ISCED); people were categorised into either basic education (ISCED level 0–2), secondary school or vocational education (ISCED level 3), or higher education (including short-term higher education, bachelor's degree, master's degree, or doctoral-level degree; ISCED level 4 or higher).[14] Income was categorised into quartiles based on the mean income within the past 3 years from the index date of people who were included. Income was assessed via equivalised disposable income, which was measured by the total household income divided by a weighted number of household members (household income and household members are registered for all people living in Denmark in the Danish Income Statistics Register), according to the

See Online for appendix 2

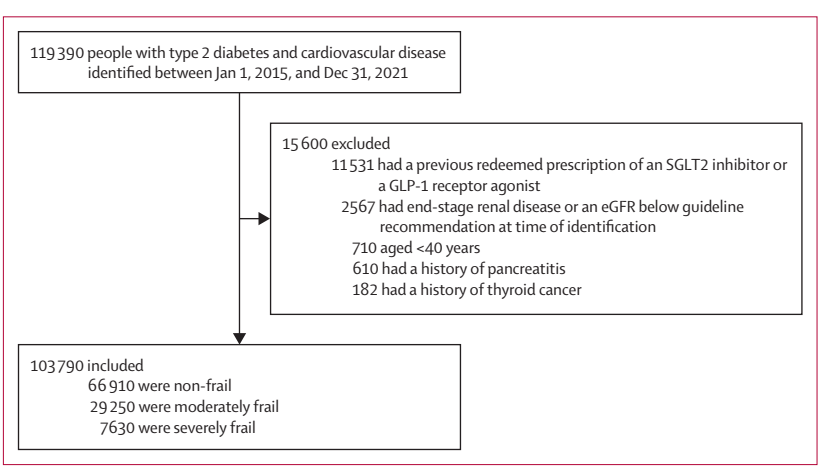

Figure 1: **Flow diagram of patient selection**
eGFR=estimated glomerular filtration rate.

Organisation for Economic Co-operation and Development modified scale.[15] This process was done to ensure comparability between the income of a person living alone and the income of a large family. Income was adjusted for inflation to the year 2015. Data on sex were obtained from the Danish Civil Registration System, in which sex is registered by a medical doctor at birth (ie, male or female) for all people living in Denmark. Sex data were self-reported after immigration, with the same options provided.

	Non-frail (n=66 910)	Moderately frail (n=29 250)	Severely frail (n=7630)
Demographics			
Age, years	70 (62–77)	74 (66–81)	77 (70–84)
Male	44 584 (66·6%)	17 278 (59·1%)	4097 (53·7%)
Female	22 326 (33·4%)	11 972 (40·9%)	3533 (46·3%)
Index year			
2015–18	52 191 (78·0%)	23 248 (79·5%)	6416 (84·1%)
2019–21	14 719 (22·0%)	6002 (20·5%)	1214 (15·9%)
Education			
Basic education (eg, primary school)	29 928 (44·7%)	14 584 (49·9%)	4053 (53·1%)
Secondary school or vocational education	27 005 (40·4%)	10 861 (37·1%)	2683 (35·2%)
Higher education	9977 (14·9%)	3805 (13·0%)	894 (11·7%)
Income quartile			
First (ie, lowest)	15 996 (23·9%)	7884 (27·0%)	2067 (27·1%)
Second	14 985 (22·4%)	8244 (28·2%)	2719 (35·6%)
Third	16 673 (24·9%)	7341 (25·1%)	1934 (25·4%)
Fourth (ie, highest)	19 256 (28·8%)	5781 (19·8%)	910 (11·9%)
Comorbidities			
Duration of type 2 diabetes, years	5·6 (5·9)	6·4 (6·5)	8·0 (7·0)
Duration of cardiovascular disease, years	8·5 (8·3)	8·8 (8·3)	9·6 (8·5)
Ischaemic heart disease	41 764 (62·4%)	16 447 (56·2%)	3942 (51·7%)
Myocardial infarction	18 011 (26·9%)	7080 (24·2%)	1650 (21·6%)
Stroke or TIA	11 061 (16·5%)	10 624 (36·3%)	4075 (53·4%)
Peripheral artery disease	6115 (9·1%)	3894 (13·3%)	1414 (18·5%)
Heart failure	10 632 (15·9%)	6849 (23·4%)	2396 (31·4%)
Atrial fibrillation or flutter	10 279 (15·4%)	7622 (26·1%)	2709 (35·5%)
Hypertension	35 298 (52·8%)	16 463 (56·3%)	4155 (54·5%)
Hypercholesterolaemia	20 388 (30·5%)	11 405 (39·0%)	3308 (43·4%)
Chronic kidney disease	3964 (5·9%)	4854 (16·6%)	2193 (28·7%)
Chronic obstructive lung disease	6028 (9·0%)	5297 (18·1%)	2009 (26·3%)
Liver disease	2191 (3·3%)	1560 (5·3%)	678 (8·9%)
Malignancy	8378 (12·5%)	5442 (18·6%)	1540 (20·2%)
Dementia	110 (0·2%)	324 (1·1%)	352 (4·6%)
Laboratory samples			
eGFR, mL/min per 1·73 m^2	78·1 (19·4)	70·3 (22·8)	63·8 (25·2)
Missing eGFR	19 248 (28·8%)	7960 (27·2%)	1759 (23·1%)
HbA_{1c}, mmol/mol	53·0 (13·8)	52·0 (12·8)	51·8 (13·0)
Missing HbA_{1c}	45 763 (68·4%)	20 164 (68·9%)	5464 (71·6%)
Plasma albumin, g/L	38·4 (13·8)	36·9 (5·10)	34·9 (5·3)
Missing plasma albumin	33 919 (50·7%)	17 694 (60·5%)	5293 (69·4%)

(Table continues on next page)

Outcomes

The primary outcome of this study was initiation of either an SGLT2 inhibitor or a GLP-1 receptor agonist (composite outcome), defined as first redeemed prescription from a Danish pharmacy and assessed in all people with type 2 diabetes and cardiovascular disease who were included. Secondary outcomes were initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist individually, discontinuation of SGLT2 inhibitors or GLP-1 receptor agonists, and all-cause mortality. Redeeming a prescription of liraglutide was not considered an outcome as, in Denmark, it is only approved for chronic weight management in people with obesity and not for the treatment of type 2 diabetes.

Statistical analysis

This study was designed and reported in accordance with the STROBE guidelines.[16] Cox models adjusted for age, sex, year of inclusion, socioeconomic status, duration of type 2 diabetes, duration of cardiovascular disease, polypharmacy (ie, ≥5 co-medications), and comorbidity were used to assess time-to-event data. Cumulative incidence curves with 95% CIs were used to show the association between frailty and initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist, with the Aalen-Johansen estimator to account for competing risk of death, emigration, or end of study period.[17]

Discontinuation of SGLT2 inhibitors or GLP-1 receptor agonists according to frailty was also investigated for people who had initiated drug therapy during the study period. In this analysis, discontinuation was defined as an absence of medication supply for at least 90 consecutive days at any point during the study period. People were considered to be in drug therapy until 90 days after the estimated medication coverage period of the last refilled prescription to avoid considering future events. Predefined stratification analyses by year of inclusion and socioeconomic factors (ie, education and income) were also conducted. All people who were included were followed up from index date until emigration, death, or end of study period (ie, Dec 31, 2021), whichever occurred first.

For the sensitivity analyses, cumulative incidence curves with 95% CIs were used to show the association between frailty and initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist, with the Aalen-Johansen estimator to account for competing risk of death, emigration, or end of study period.

Any missing data were reported and handled by pairwise deletion.

Data management and statistical analyses were done in SAS version 9.4 and R version 2023.03.0+386.

Role of the funding source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication.

Results

Of 119 390 people with type 2 diabetes and cardiovascular disease between Jan 1, 2015, and Dec 31, 2021, who were identified, 103 790 were eligible for inclusion. Median follow-up time was 4·5 years (IQR 2·7–6·1) and median age across the three frailty groups was 71 years (64–79). 65 959 (63·6%) of 103 790 people were male and 37 831 (36·5%) were female. At index date, 66 910 (64·5%) people were non-frail, 29 250 (28·2%) were moderately frail, and 7630 (7·4%) were severely frail (figure 1; table).

Compared with people who were non-frail, people who were moderately frail or severely frail were older, had less education, and were in a lower income quartile. Furthermore, they had more comorbidities, except for ischemic heart disease and myocardial infarction. People who were severely frail were less likely to receive therapy with guideline-recommended cardiovascular preventive medications (including renin-angiotensin-system (RAS) inhibitors, lipid-lowering agents, and aspirin), than people who were non-frail. However, people who were severely frail were more frequently treated with insulin, loop diuretics, and anticoagulants than people who were non-frail. Few people were initiated on SGLT2 inhibitors or GLP-1 receptor agonists on the same date they were diagnosed with type 2 diabetes or cardiovascular disease (table; figures 2, 3; appendix 2 p 7).

The probability of initiating therapy with either an SGLT2 inhibitor or a GLP-1 receptor agonist was significantly lower for people who were moderately frail or severely frail compared with people who were non-frail (figures 2–4). This association persisted after adjustment for age, sex, year of inclusion, socioeconomic status, duration of type 2 diabetes, duration of cardiovascular disease, polypharmacy, and comorbidity (figure 4; appendix 2 pp 25–26). The association between frailty and a reduced probability of initiating therapy was also present when examining SGLT2 inhibitors and GLP-1 receptor agonists separately (figure 3; appendix 2 pp 4–5). For initiation of an SGLT2 inhibitor, the hazard ratio (HR) for people who were moderately frail was 0·86 (0·84–0·89) and for people who were severely frail was 0·65 (0·60–0·71). By contrast, frailty was not associated with the probability of initiating a GLP-1 receptor agonist, with an HR of 0·97 (0·93–1·01) for people who were moderately frail and of 0·90 (0·82–0·99) for people who were severely frail. The 1-year cumulative incidence of initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist for each year from 2015 to 2021 is provided in appendix 2 (p 7). The probability of being prescribed an SGLT2 inhibitor or a GLP-1 receptor agonist increased over time, whereas the effects of frailty decreased over time (appendix 2 p 7).

Older age (ie, >80 years) was associated with the lowest rate of initiating an SGLT2 inhibitor or a GLP-1 receptor agonist, followed by the second lowest income quartile and polypharmacy (figure 4). Similar patterns were observed for SGLT2 inhibitors and GLP-1 receptor agonists separately (appendix 2 pp 4–5).

Frailty did not significantly modify the risk of discontinuing SGLT2-inhibitor therapy or GLP-1 receptor-agonist therapy during the 1 year after initiation (appendix 2 p 11). The 1-year risk of discontinuing SGLT2 inhibitors was 28% (95% CI 27–29) for people who were non-frail, 30% (28–31) for people who were moderately frail, and 29% (25–34) for people who were severely frail.

	Non-frail (n=66 910)	Moderately frail (n=29 250)	Severely frail (n=7630)
(Continued from previous page)			
Medical therapy			
Polypharmacy (ie, ≥5 co-medications)	38 869 (58·1%)	17 170 (58·7%)	4012 (52·6%)
SGLT2 inhibitor	306 (0·5%)	84 (0·3%)	15 (0·2%)
GLP-1 receptor agonist	129 (0·2%)	61 (0·2%)	15 (0·2%)
Metformin	42 138 (63·0%)	16 066 (54·9%)	3434 (45·0%)
DPP4 inhibitor	3591 (5·4%)	1884 (6·4%)	583 (7·6%)
Sulfonylurea	6642 (9·9%)	2705 (9·2%)	576 (7·6%)
Insulin	8027 (12·0%)	5448 (18·6%)	2013 (26·4%)
RAS inhibitor	37 951 (56·7%)	15 327 (52·4%)	3268 (42·8%)
Hydrochlorothiazide	9574 (14·3%)	3886 (13·3%)	748 (9·8%)
Loop diuretic	10 978 (16·4%)	8685 (29·7%)	3147 (41·2%)
Spironolactone	4206 (6·3%)	2329 (8·0%)	684 (9·0%)
β blocker	27 132 (40·5%)	11 884 (40·6%)	2855 (37·4%)
Calcium-channel blocker	19 366 (28·9%)	8588 (29·4%)	2093 (27·4%)
Digoxin	2919 (4·4%)	2210 (7·6%)	867 (11·4%)
Aspirin	30 896 (46·2%)	11 92 (38·9%)	2364 (31·0%)
Anticoagulant	1619 (2·4%)	1231 (4·2%)	422 (5·5%)
Lipid-lowering agent	42 138 (63·0%)	18 250 (62·4%)	4323 (56·7%)

Data are n (%), median (IQR), or mean (SD). DPP4=dipeptidyl peptidase 4. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. RAS=renin-angiotensin-system. TIA=transient ischaemic attack.

Table: **Baseline characteristics according to frailty**

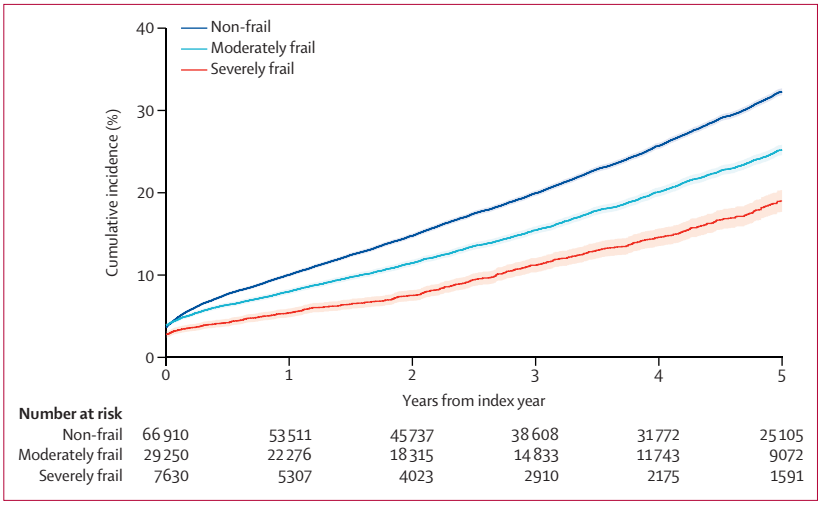

Figure 2: **Initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist (composite outcome) according to frailty**
Shaded areas show 95% CIs.

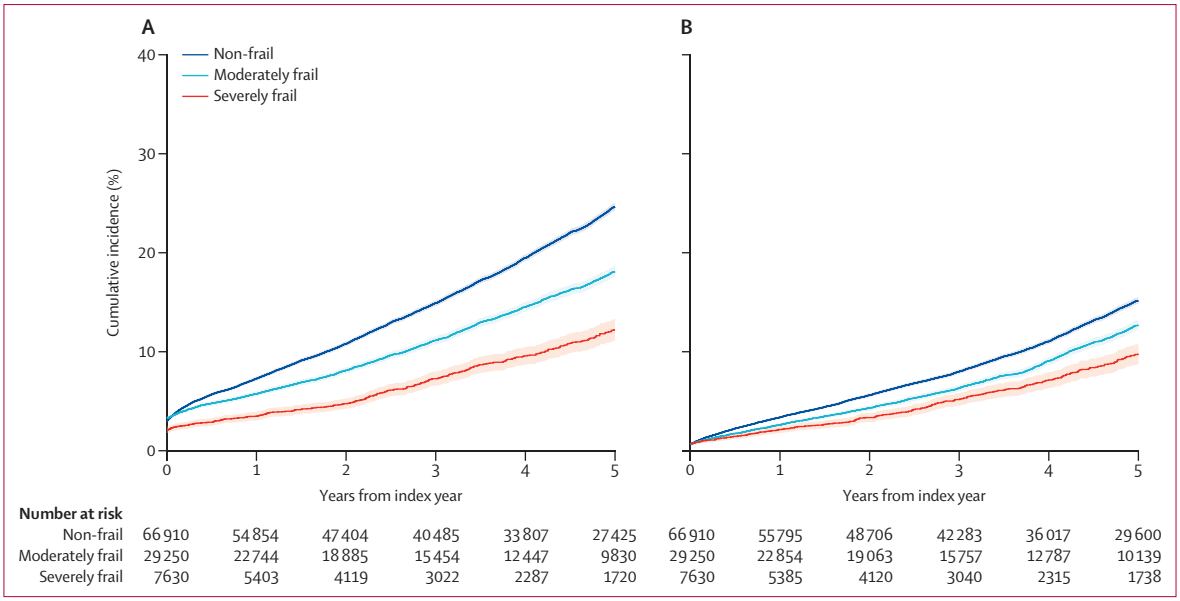

Figure 3: **Initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist according to frailty**
(A) Initiation of an SGLT2 inhibitor. (B) Initiation of a GLP-1 receptor agonist. Shaded areas show 95% CIs.

For GLP-1 receptor agonists, the risk of discontinuing was 24% (23–25) for people who were non-frail, 27% (25–28) for people who were moderately frail, and 27% (23–32) for people who were severely frail.

People who were non-frail had a 5-year risk of all-cause mortality of 24% (95% CI 24–25), people who were moderately frail had a 5-year risk of 45% (44–46), and people who were severely frail had a 5-year risk of 68% (67–69; appendix 2 p 8).

In a sensitivity analysis, we only included patients with a registered eGFR at baseline and examined the effects of frailty on the initiation of SGLT2 inhibitors or GLP-1 receptor agonists (appendix 2 p 9). In another sensitivity analysis, we redefined baseline co-medication as three redeemed prescriptions within 6 months before the index date (data not shown).

Discussion

To our knowledge, this cross-sectional, nationwide study of 103 790 people with type 2 diabetes and cardiovascular disease is the first to investigate the initiation of two cardioprotective diabetes drug therapies (ie, SGLT2 inhibitors and GLP-1 receptor agonists) in relation to frailty. 36 880 (35·5%) of 103 790 people who were included were categorised as frail; these individuals had a higher mortality rate and a lower probability of being prescribed an SGLT2 inhibitor or a GLP-1 receptor agonist than people who were non-frail. People who were the most frail were significantly less likely to receive these treatments compared with people who were non-frail, despite having no registered contraindications. Moreover, this association did not appear to be driven by other factors, such as age, sex, or socioeconomic status.

As well as the underprescription of SGLT2 inhibitors and GLP-1 receptor agonists in individuals who were frail, we also observed that these individuals were less frequently treated with other guideline-recommended preventive cardiovascular drug therapies (eg, RAS inhibitors, lipid-lowering agents, and aspirin) than individuals who were non-frail. However, they were more frequently treated with insulin, loop diuretics, and anticoagulants, which indicates more advanced disease. Underprescription of cardioprotective drug therapies might be of particular concern in people who are frail due to their high risk of adverse cardiovascular-related and diabetes-related events.[18–20]

Several factors have previously been associated with underprescription of drug therapies in older people. Among these factors are fear of adverse drug events, comorbidity, patient complexity, and scarce age-specific evidence from clinical trials. However, regarding SGLT2 inhibitors, 2022 data from a prespecified analysis of the DELIVER trial and a post-hoc analysis of the DAPA-HF trial showed that the beneficial effects of dapagliflozin (an SGLT2 inhibitor) on heart failure and other clinical outcomes compared with placebo were consistent across severity of frailty.[6,7] Improvements in symptoms, physical function, and quality of life were largest in people categorised as the most frail. These analyses also showed that adverse events were not more common in individuals who were frail and randomly assigned to receive dapagliflozin than in individuals who were non-frail or compared with placebo, which emphasises the safety of SGLT2 inhibitors in older people who are frail.

As for GLP-1 receptor agonists, there is currently no evidence supporting their use in people who are frail.

However, a pooled analysis of the SUSTAIN 1–5 trials revealed that semaglutide (a GLP-1 receptor agonist) had a comparable efficacy and safety profile in older people (aged >65 years) and younger people with type 2 diabetes, with low rates of hypoglycaemia and other side-effects.[21] Because of the association between advancing age and frailty, GLP-1 receptor agonists might also be efficient and safe in individuals who are frail, although more data are needed.

Despite the universal health-care system with low medication costs in Denmark, income was the second most influential factor (after age) associated with initiation of SGLT2 inhibitors or GLP-1 receptor agonists. By contrast, education was only minorly influential. These findings are similar to findings from other observational studies.[22,23] The importance of income as a predictor of SGLT2-inhibitor and GLP-1 receptor-agonist initiation, due to the relatively high cost of medication, has been a long-term concern about equitable access to these treatments. However, when evaluating the cost-effectiveness of these treatments, the overall expenses that are associated with type 2 diabetes and cardiovascular disease should be considered, including the range of related comorbidities, to fully understand their effects on the health-care system which might, to some extent, justify the costs.[24,25]

Clinical trials that have investigated the effect of SGLT2 inhibitors on renal outcomes have shown robust evidence that SGLT2 inhibitors reduce the risk of progression of renal disease.[26,27] Although this effect was not investigated in older individuals or individuals who were frail, a post-hoc analysis of these trials showed data indicating that the renoprotective effect might also include older people (aged >75 years).[28] GLP-1 receptor agonists were also associated with a beneficial effect on renal outcomes in a pooled analysis of the SUSTAIN 6 and LEADER trials.[28] However, to investigate the full effects of GLP-1 receptor agonists on primary renal endpoints, further dedicated trials in people with diabetic renal disease are required.

SGLT2 inhibitors and GLP-1 receptor agonists have shown several other benefits, particularly in older people and people who are frail. A prospective cohort study of older people who were frail with hypertension and type 2 diabetes found that empagliflozin (an SGLT2 inhibitor) led to significant improvements in cognitive function and gait speed after 1 month compared with placebo.[29] The authors suggested that empagliflozin might reduce frailty through its effect on endothelial cells and oxidative stress regulation, which was shown in mechanistic examinations. A matched case-control study also observed beneficial effects of empagliflozin on cognitive and physical impairment in older people who were frail with type 2 diabetes and heart failure after 3 months,[30] and a cohort study observed that empagliflozin caused a modification of some microRNA in a direction that was opposite to what was observed in people with heart failure and preserved ejection fraction, indicating a rescue of endothelial function.[31]

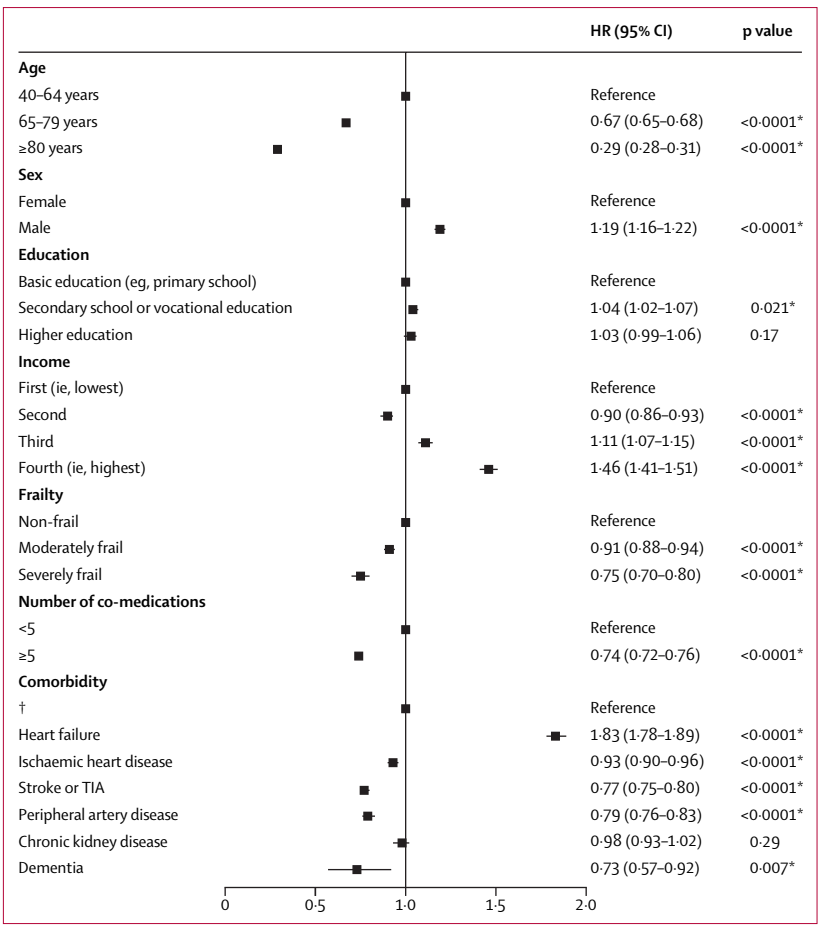

Figure 4: **Age, sex, and demographic factors associated with initiation of an SGLT2 inhibitor or a GLP-1 receptor agonist**
Cox proportional hazards model. HR=hazard ratio. TIA=transient ischaemic attack. *Statistically significant. †Reference is the absence of the condition.

In diseases such as Alzheimer's disease and Parkinson's disease, insulin resistance has been found to exist in the brain, making it a substantially influential factor on the underlying mechanisms of cognitive impairment and neurodegeneration. Conducting clinical trials that focus on assessing the direct effects of SGLT2 inhibitors and GLP-1 receptor agonists on neurological outcomes while controlling for their hypoglycaemic actions could reveal their potential as therapeutic agents for both diabetes and related neurodegenerative diseases.

Considering the multisystemic effects of SGLT2 inhibitors and GLP-1 receptor agonists, these therapies might be potential agents to treat frailty in older people with type 2 diabetes and cardiovascular disease living with other serious comorbidities. By addressing multiple aspects of the diseases and promoting overall wellbeing, these treatments might reduce the burden of polypharmacy and medication costs in this vulnerable population.

The strengths of this study were a large study population, high-quality data from the Danish nationwide registers, and no losses to follow-up. However, several limitations should be acknowledged. First, this study did not include important clinical measures such as BMI, smoking status, ejection fraction, or blood pressure. These are all factors that might affect treatment decisions (eg, people with low BMI might be less likely to be started on GLP-1 receptor agonists than people with high BMI, people with reduced ejection fraction might be more likely to be started on SGLT2 inhibitors than people with preserved or mid-range ejection fraction, and people with hypertension might be more likely to be started on either an SGLT2 inhibitor or a GLP-1 receptor agonist than people without hypertension). The direction and magnitude of the potential biases from these missing variables are uncertain and should be considered when interpreting the results.

Second, this study used the Hospital Frailty Risk Score to define frailty, which relies solely on the medical history of a person that is recorded in ICD-10 codes.[11] Although this approach has been widely used and validated, it might have led to the exclusion of older individuals who were frail but had few or no past hospital admissions. This limitation could have biased the findings by under-representing specific members of the population, particularly those who were mildly frail but could still benefit from SGLT2 inhibitors or GLP-1 receptor agonists.

Third, variations in documentation and coding practices among health-care institutions might have introduced measurement errors and misclassification in this study, particularly regarding the severity of frailty. The accuracy and consistency of recorded data might have varied, which would affect the reliability of results.

Finally, as with any observational study, there is the possibility of residual confounding despite the efforts to adjust and stratify for known confounders. Unmeasured or unknown factors could still have influenced the association between frailty and initiation of SGLT2 inhibitors or GLP-1 receptor agonists.

Considering the efficacy and safety of SGLT2 inhibitors and GLP-1 receptor agonists, their use should be encouraged in people who are frail. Formulating clear and updated guidelines on frailty and SGLT2 inhibitors or GLP-1 receptor agonists in people with type 2 diabetes and cardivascular disease should be a priority. Future research should prioritise obtaining an increased understanding of the factors that still hinder the prescription of these medications in individuals who are frail despite existing evidence. Moreover, this research should aim to clarify the cost–benefit of these therapies in people who are frail, considering the potential reductions in hospitalisations and possible deprescription of other co-medications.

Contributors

MEM conceptualised the study and methodology, conducted the formal analyses and literature search, visualised and interpreted the data, and wrote the original draft of the Article. MS conceptualised the study and methodology; supervised the work; accessed, validated, interpreted, and verified the data; verified the results; and reviewed and edited the Article. LK conceptualised the methodology, supervised the work, interpreted the data, and reviewed and edited the Article. JES accessed and verified the data and results, interpreted the data, and reviewed and edited the Article. JJVM interpreted the data; conducted the literature search; and reviewed, edited, and proofread the Article. MCP and NS interpreted the data, conducted the literature search, and reviewed and edited the Article. JHB, ACF, JJ, CA, and EF interpreted the data and reviewed and edited the Article. DZ accessed and verified the data and results and reviewed and edited the Article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing

Danish health data are collected, stored, and managed in national health registers at the Danish Health Data Authority, which provided anonymised data to this study (registered at Statistics Denmark; approval number P-2019-191). Researchers who are not based in Denmark can apply for access to the data via an affiliation with an authorised Danish research environment. De-identified patient data, statistical codes, and a data dictionary for this particular study can be made available via this process. The authorised Danish research environment will decide whether or not the request is reasonable, and whether an additional access agreement or restrictions are necessary. The study protocol and statistical analysis plan are available upon

reasonable request, such as for ensuring consistency in other observational studies, to members of the public with a genuine interest in understanding the study, or to educational institutions for academic purposes, via email to the corresponding author. Data will be available between Sept 1, 2023, and Sept 1, 2026.

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