Relationship between SGLT2 inhibitor therapy and dementia in older adults with type 2 diabetes

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Dementia is a growing global public health challenge; the number of people affected is estimated to reach 78 million by 2030. As life expectancy increases, so does the socio-economic and health burden of dementia. Type 2 diabetes mellitus (T2DM) is a well-established risk factor and increases the likelihood of developing dementia - including Alzheimer's disease and vascular dementia - by up to 60% [Biessels & Despa, 2018]. The pathophysiological mechanisms linking T2DM to dementia include chronic hyperglycaemia, insulin resistance, cerebrovascular dysfunction, neuroinflammation and oxidative stress - all factors that contribute to cognitive decline [Beeri & Bendlin, 2020]. Despite intensive research, no disease-modifying therapies for dementia exist to date, highlighting the need to identify modifiable risk factors and pharmacological strategies to slow cognitive decline [Livingston et al., 2020].

>> Blood glucose-lowering drugs can influence the risk of dementia, although the effects differ depending on the substance class. SGLT2 inhibitors (sodium-glucose cotransporter 2 inhibitors) have shown potential neuroprotective effects beyond glycaemic control [Low et al., 2022]. Preclinical studies suggest that SGLT2 inhibitors may improve cerebrovascular function, reduce neuroinflammation and increase metabolic efficiency of the brain [Pawlos et al., 2021; Rizzo et al., 2022]. These agents lower blood glucose levels by promoting renal glucose excretion. In addition, some preclinical findings suggest that SGLT2 inhibitors can cross the blood-brain barrier and thus exert direct neuronal effects [Tahara et al., 2016, Gui et al., 2024].

In contrast, DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors), another commonly used class of blood glucose-lowering drugs, show inconsistent effects on cognitive function without convincing evidence of a protective effect against dementia [Biessels et al., 2019; Biessels et al., 2021]. A comparison of SGLT2 with DPP-4 inhibitors is therefore a useful approach to assess potential cognitive benefits.

Summary

This study aimed to assess whether the use of SGLT2 inhibitors (SGLT2i) compared with dipeptidyl peptidase-4 inhibitors (DPP-4i) is associated with a lower incidence of dementia in older adults with type 2 diabetes mellitus (T2DM).

A retrospective cohort study based on the IQVIA™ Disease Analyser database was conducted in Germany. Patients aged ≥60 years with T2DM who received metformin and were newly treated with SGLT2i or DPP-4i between 2012 and 2022 were included.

A 1:1 propensity score matching and Cox proportional hazards models were used to estimate hazard ratios (HR) for dementia over five years. After matching, 38,140 patients were included.

The incidence of dementia was lower in the SGLT2i group (5.4%) than in the DPP-4i group (6.4%) ($p = 0.002$). The use of SGLT2i was associated with a 20% reduced risk of dementia (HR: 0.80; 95% CI: 0.70-0.93; $p = 0.002$), particularly in patients over 80 years of age (HR: 0.75) and in men (HR: 0.77).

Overall, SGLT2i therapy was associated with a lower incidence of dementia in older adults with T2DM, particularly in men and the very elderly.

Keywords

SGLT2 inhibitors, type 2 diabetes mellitus, dementia, real-world evidence, retrospective cohort study

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Observational studies have indicated a possible association between SGLT2 inhibitors and a reduced risk of dementia. For example, an analysis of data from the Korean National Health Insurance Service reported a 35% lower incidence of dementia in SGLT2 inhibitor users compared to DPP-4 inhibitor users [Shin et al., 2024]. However, previous studies focused predominantly on younger populations (40-69 years) and had only short follow-up periods, which limits generalisability [Chuang et al., 2024, Mui et al., 2021].

Whether the newly initiated use of SGLT2 inhibitors is actually associated with a lower risk of dementia remains unclear. The aim of our study is to (i) investigate the incidence of new-onset dementia in older adults (≥60 years) with T2DM using SGLT2 inhibitors compared to users of DPP-4 inhibitors over a five-year period in Germany. In addition, (ii) to examine whether certain

demographic and clinical factors influence the association between SGLT2 inhibitor use and dementia risk.

Methods

The analysis was based on data from the IQVIA™ Disease Analyser database, which contains case-based information from around 3,500 general practitioners and specialists in Germany. Information on patient demographics, drug prescriptions and diagnoses is available. The sampling methodology used to select the medical practices is suitable for ensuring a representative database for general practitioner and specialist practices in Germany [Rathmann et al., 2018].

This retrospective cohort study included patients aged ≥60 years with a diagnosis of T2DM (ICD-10: E11) who were prescribed either an SGLT2 inhibitor (ATC: A10BK) or a DPP-4 inhibitor (ATC: A10BH) in addition to metformin (ATC: A10BA) for the first time between January 2012 and December 2022 [20]. Individuals with prescriptions for multiple antihyperglycaemic medications on the index date (first prescription of SGLT2 or DPP-4 inhibitors) were excluded. Allocation to the cohorts was based on the earliest prescription date during the study period. People who were receiving both drugs on this index date, were prescribed other antidiabetic drugs at the start of the study or switched between SGLT2 and DPP-4 therapy during the course of the study were also excluded. Participants who died during the follow-up were censored at the time of death. Patients with diagnoses of dementia of any cause (ICD-10: F00, F01, G30), mild cognitive impairment (ICD-10: F06.7), other degenerative diseases of the nervous system (ICD-10: G31) or symptoms/disorders of cognitive function and consciousness (ICD-10: R41) before or on the index date were also excluded. Finally, the study participants were divided into two cohorts: the SGLT2 cohort and the DPP-4 cohort (see Fig. 1).

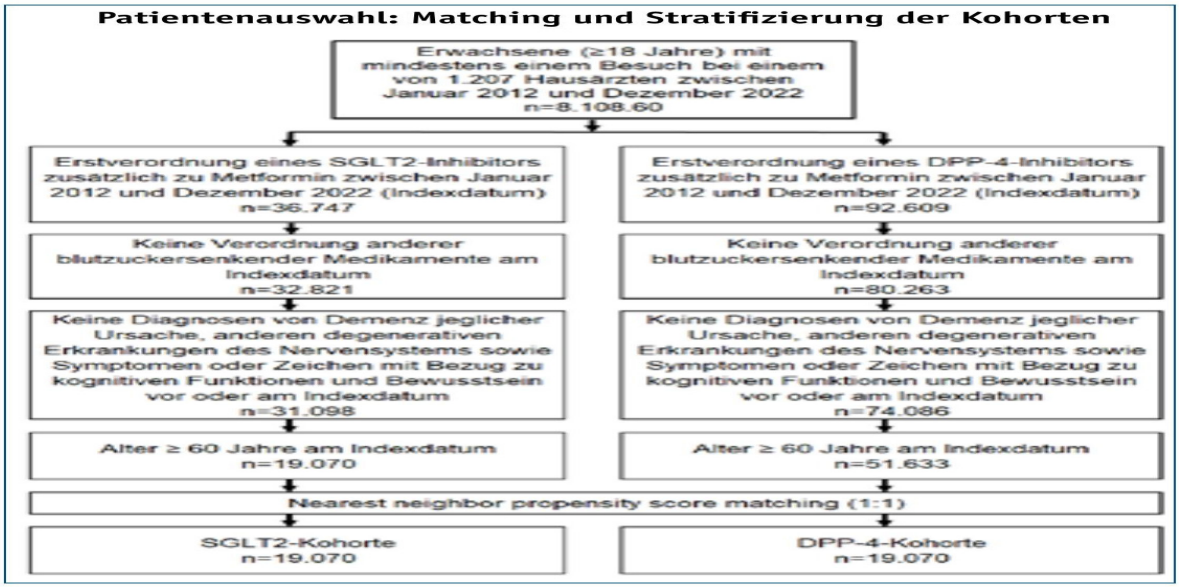


Fig. 1: **Patient selection: Matching and stratification of the cohorts. Own representation.**

The following covariates were taken into account: Age, gender, year of treatment initiation (2012-2022), last HbA1c value within six months prior to or on the index date, and diagnoses within the twelve months prior to the index date that are associated with dementia, including: Hypertension, dyslipidaemia, obesity, chronic obstructive pulmonary disease as a surrogate for smoking (COPD), hearing loss, cerebrovascular disease, intracranial injury, Parkinson's disease, epilepsy, intellectual disability and depression.

The primary endpoint was the time to the onset of incident dementia. Follow-up time was calculated as the difference between the index date (first prescription of an SGLT2 or DPP-4 inhibitor) and the earliest occurrence of one of the following events: first dementia diagnosis, modification of antidiabetic therapy (initiation of an alternative or additional medication beyond the study therapy), loss to follow-up or end of the observation period (31 December 2023). The follow-up period was specified in years and limited to a maximum of five years per patient.

Nearest-neighbour propensity score matching (1:1) was used to pair patients on SGLT2 inhibitor therapy with those on DPP-4 inhibitor therapy. Age, gender, HbA1c levels, year of therapy initiation and documented comorbidities were taken into account. A standardised mean difference (SMD) of <0.1 was defined as the threshold for adequate covariate balance. The Kaplan-Meier method was used to analyse the cumulative incidence of dementia in both cohorts over up to five years from the start of treatment. A univariate conditional Cox regression was used to analyse the association between SGLT2 therapy (vs. DPP-4 therapy) and dementia risk in the matched cohorts.

Results of Cox regressions were reported as hazard ratios (HR) with associated p-values, using a significance level of $p < 0.01$ to correct for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

After 1:1 propensity score matching, a total of 38,140 patients were included in the analysis, of which 19,070 were in the SGLT2 cohort and 19,070 in the DPP-4 cohort (Fig. 1). Table 1 shows the baseline characteristics of the study population. The mean age in both cohorts was 71.9 years. The proportion of female patients was 39.4% in the SGLT2 group and 42.2% in the DPP-4 group. The HbA1c values were comparable in both cohorts and averaged 7.8%. (Tab. 1).

Over a follow-up period of five years, patients treated with SGLT2 inhibitors showed a significantly lower cumulative incidence of dementia of any cause compared to DPP-4 users ($p = 0.002$) (Figure 2). The cumulative 5-year incidence of dementia was 6.4% in the DPP-4 cohort and 5.4% in the SGLT2 cohort.

Basischarakteristika der 1:1 Propensity-Score-gematchten Studienkohorten			
Variable	**SGLT2 Inhibitor-Anwender**	**DPP-4 Inhibitor-Anwender**	**Standardized Mean Difference**
Anzahl der Patienten	19.070	19.070	
Alter in Jahren (Mittelwert, Standardabweichung)	71,9 (8,1)	71,9 (8,2)	
≤ 70 Jahre	8.609 (45,1)	8.784 (46,1)	0,016
71–80 Jahre	6.529 (34,2)	6.415 (33,6)	
> 80 Jahre	3.932 (20,7)	3.871 (20,3)	
Frauen	7.516 (39,4)	8.048 (42,2)	-0,028
Männer	11.554 (60,6)	11.022 (57,8)	
HbA1c %, (Mittelwert, Standardabweichung)	7,8 (1,5)	7.8 (1,5)	0,000
Jahr des Therapiebeginns: 2012–2015	695 (3,7)	697 (3,6)	0,000
Jahr des Therapiebeginns: 2016–2019	5.591 (29,3)	5.583 (29,3)	
Jahr des Therapiebeginns: 2020–2022	12.784 (67,0)	12.790 (67,1)	
Komorbiditäten			
Hypertonie	13.907 (72,9)	13.472 (70,6)	-0,023
Dyslipidämie	9.313 (48,8)	8.584 (45,0)	-0,038
Adipositas	4.777 (25,1)	4.789 (25,1)	0,000
COPD	2.884 (15,1)	2.501 (13,1)	-0,020
Hörverlust	1.347 (7,1)	1.180 (6,2)	-0,009
Zerebrovaskuläre Erkrankungen	3.268 (17,1)	2.802 (14,7)	-0,024
Intrakranielle Verletzung	164 (0,9)	128 (0,7)	-0,002
Morbus Parkinson	225 (1,2)	202 (1,1)	-0,001
Epilepsie	1.549 (8,1)	1.362 (7,1)	-0,010
Intellektuelle Beeinträchtigungen	54 (0,3)	50 (0,3)	0,000
Depression	3.578 (18,8)	3.416 (17,9)	-0,009

Table 1: **Baseline characteristics of the 1:1 propensity score-matched study cohorts: SGLT2 inhibitor vs. DPP-4 inhibitor users. Data are presented as numbers and (percentages) unless otherwise stated. Own representation.**

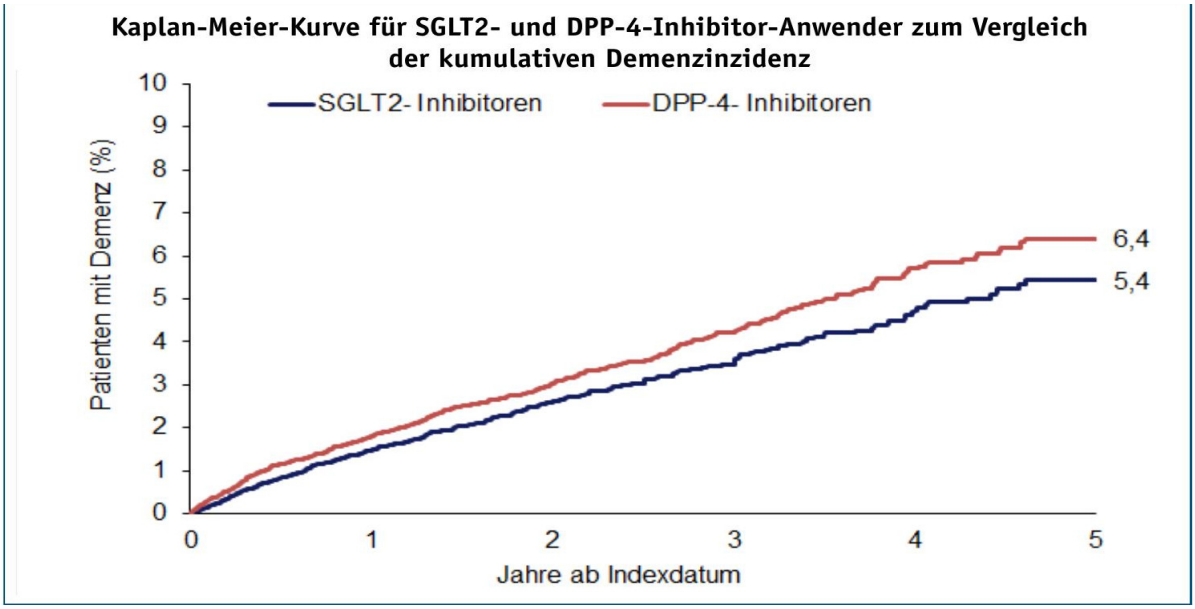


Fig. 2: Kaplan-Meier curve for SGLT2 and DPP-4 inhibitor users to compare the cumulative incidence of dementia over a period of five years after the start of therapy Own illustration.

Relationship between SGLT2 therapy and risk of dementia of any cause

The Cox regression analysis (Table 2) showed that the use of SGLT2 inhibitors was associated with a significantly lower incidence of dementia in the overall population (HR: 0.80; 95% CI: 0.70 - 0.93; p = 0.002). The association was particularly pronounced in patients over 80 years of age (HR: 0.75; 95% CI: 0.61 - 0.91) and in male patients (HR: 0.77; 95% CI: 0.64 - 0.93). There was also a trend towards an association in patients aged ≤70 years (HR: 0.66; 95% CI: 0.45 - 0.98) (p = 0.041).

Discussion

The results of our study show a longer dementia-free survival in older adults with T2DM treated with SGLT2 inhibitors. Compared to DPP-4 inhibitors, treatment with SGLT2 inhibitors was associated with approximately 20% lower risk of dementia - most significantly in those over 80 years of age and in men. These results add to the growing body of evidence pointing to potential neuroprotective effects of SGLT2 inhibitors and their importance for dementia prevention.

Our findings are consistent with previous observational studies suggesting an association between SGLT2 inhibitors and reduced dementia incidence [Jaiswal et al., 2024]. For example, a population-based study from Canada reported a 20% lower incidence of dementia in people over 60 [Wu et al., 2022]. Previous prospective studies suggest that the cognitive benefits of SGLT2 inhibitors only manifest after about three years of use [Low et al.,

2022]. Our data support this assumption by showing a robust association with longer dementia-free survival in older adults.

Zusammenhang zwischen Demenzinzidenz und SGLT2- vs. DPP-4-Inhibitoren		
Kohorten	**Hazard Ratio (95% KI)**	**P-Wert**
Alle Patienten	0,80 (0,70–0,93)	0,002
≤70-Jährige	0,66 (0,45–0,98)	0,041
71–80-Jährige	0,88 (0,71–1,10)	0,263
› 80-Jährige	0,75 (0,61–0,91)	0,005
Frauen	0,87 (0,71–1,07)	0,192
Männer	0,77 (0,64–0,93)	0,006

Tab. 2: Relationship between dementia incidence and SGLT2 vs. DPP-4 inhibitors. Own presentation.

Our study is among the first to directly compare SGLT2 inhibitors with DPP-4 inhibitors in a large real-world cohort and to focus exclusively on an older European population (≥60 years) to differentially assess dementia risk over five years. In doing so, we provide important insights into the potential impact of SGLT2 inhibitors in a high-risk group for cognitive decline.

Similar trends have also been described in younger populations. A Korean cohort study found a 35% lower incidence of dementia in 49- to 69-year-olds on SGLT2 inhibitors compared to DPP-4 inhibitors [Shin et al., 2024]. A national study from Taiwan also reported a significant reduction in the incidence of dementia, although the effect sizes varied between subgroups [Chuang et al., 2024].

The observed gender-specific differences are partly consistent with previous findings. While some studies suggest a stronger effect in women, others - like our results - report more pronounced effects in men [Wu et al., 2022]. One possible explanation is the higher prevalence of cardiovascular comorbidities in men, which are key risk factors for dementia [Low et al., 2022]. As SGLT2 inhibitors have pronounced cardioprotective effects, this could have a greater impact on neuroprotection in men [Rivera et al., 2023]. In addition, postmenopausal women lose the neuroprotective influence of oestrogen, which could attenuate the additional effect of SGLT2 inhibitors [Beeri & Bendlin, 2020]. Differences in metabolic profiles, hormone levels and treatment adherence could provide further explanations. Future studies should

systematically investigate these differences with biomarkers and subgroup analyses.

A major advantage of our study is the use of a large, representative database of GP care in Germany. This enables robust real-world evidence on SGLT2 inhibitors and dementia diagnoses. Propensity score matching reduced confounding and ensured balanced comparison groups. However, the observational design remains limiting, as it does not allow any causal conclusions to be drawn. There is also a lack of information on lifestyle and socioeconomic factors, genetic predispositions and detailed cognitive testing. Diagnoses were based on ICD-10 codes recorded in GP practices, where structural barriers can limit diagnostic precision. Competing risks, particularly mortality in older age, may also have influenced the results.

Clinical implications

Our results suggest that SGLT2 inhibitors may have potential neuroprotective effects beyond glycaemic control and may therefore offer benefits for elderly T2DM patients at high risk of dementia. Given their established cardio- and renoprotective effects, their potential contribution to dementia prevention should be further investigated in randomised controlled trials.

Literature

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In addition, population-specific strategies in diabetes management and new pharmacological approaches could be part of a comprehensive strategy to reduce the double burden of diabetes and dementia.

Conclusion

This study provides further evidence for the association between SGLT2 inhibitors and a reduced incidence of dementia in older adults with T2DM. The observed age- and gender-specific effects underline the importance of individualised treatment approaches. Further research is needed to confirm these findings and assess their relevance for dementia prevention strategies in diabetes management. <<

Association between SGLT2 inhibitor therapy and dementia in older adults with type 2 diabetes

This study aimed to assess whether SGLT2i use is associated with a lower incidence of dementia compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in older adults with T2DM. This retrospective cohort study used data from the IQVIA™ Disease Analyser database in Germany.

Patients aged ≥60 years with T2DM, receiving metformin and newly prescribed SGLT2i or DPP-4i (2012-2022), were included. Propensity score matching (1:1) and Cox proportional hazards models were used to estimate hazard ratios (HR) for dementia over five years. After matching, 38,140 patients were included. Dementia incidence was lower in the SGLT2i group (5.4%) than the DPP-4i group (6.4%) (p=0.002).

SGLT2i use was linked to a 20% reduced dementia risk (HR: 0.80; 95% CI: 0.70-0.93; p=0.002), especially in patients >80 years (HR: 0.75) and males (HR: 0.77). SGLT2i therapy was associated with a lower incidence of dementia in older adults with T2DM, particularly in men and the very elderly.

Keywords

SGLT2 inhibitors, type 2 diabetes mellitus, dementia, real-world evidence, retrospective cohort study

Authors' statement

The authors declare that there are no conflicts of interest in connection with this study.

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