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Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierj20

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To cite this article: António Cabral Lopes, Olga Lourenço & Manuel Morgado (27 Oct 2024): SGLT2i and GLP1RA effects in patients followed in a hospital diabetology consultation, Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2024.2421872

To link to this article: https://doi.org/10.1080/17512433.2024.2421872

Published online: 27 Oct 2024.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2024.2421872

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ORIGINAL RESEARCH

SGLT2i and GLP1RA effects in patients followed in a hospital diabetology consultation

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ABSTRACT

Background: We aimed to investigate the effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) in patients with type 2 diabetes mellitus (T2DM) in clinical practice.

Research design and methods: A total of 340 patients were included. Data on age, gender, antidiabetic medications, and bioanalytical parameters were collected at baseline and one year later. Were analyzed estimated glomerular filtration rate (eGFR), blood sodium and potassium levels, blood pressure, weight, cardiovascular risk, and glycated hemoglobin (HbA1c).

Results: Patients treated with SGLT2i exhibited a significant improvement in eGFR at the endpoint compared to baseline ($p = 0.006$). Both treatment groups experienced reductions in systolic blood pressure at the endpoint; especially patients treated with SGLT2i ($p = 0.0002$). GLP1RA treatment resulted in a statistically significant weight reduction from baseline to endpoint ($p < 0.0001$), with a higher percentage of patients achieving ≥ 5% weight loss compared to the non-GLP1RA group (33.6% vs. 19.8%). Both SGLT2i and GLP1RA treatments significantly reduced cardiovascular risk scores ($p = 0.004$ and $p = 0.002$, respectively). Additionally, both treatments were associated with a significant reduction in HbA1c levels at the endpoint ($p = 0.010$ and $p = 0.002$, respectively).

Conclusions: Our findings suggest that SGLT2i and GLP1RA offer beneficial effects in patients with T2DM.

ARTICLE HISTORY
Received 22 August 2024
Accepted 23 October 2024

KEYWORDS
Cardiovascular risk; GLP1 RA; HbA1c; obesity; renal function; SGLT2i

1. Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) are two classes of antidiabetic drugs that have gained prominence due to their significant effects on glycemic control and potential cardiovascular and renal benefits in patients with type 2 diabetes mellitus (T2DM) [1–7]. These drug classes act through distinct mechanisms: SGLT2i promote glycosuria by inhibiting glucose reabsorption in the kidneys, while GLP1RA enhances insulin secretion, suppress glucagon release, and slow gastric emptying. Beyond glycemic control, both drug classes have shown promise in addressing complications often associated with T2DM, such as heart failure (HF), chronic kidney disease (CKD), obesity, and hepatic steatosis [1,6,8–12].

Studies such as DAPA-CKD and EMPA-KIDNEY have demonstrated the renal-protective effects of SGLT2i in patients with CKD, regardless of T2DM status, reducing disease progression and cardiovascular mortality [13–16].

The cardiovascular benefits of SGLT2i, particularly in HF with reduced ejection fraction (HFrEF), have led to their endorsement in major guidelines for cardiovascular risk reduction, as recommended by the American College of Cardiology and the European Society of Cardiology. However, while their impact on reducing hospitalization for HF and improving renal outcomes is established, the mechanisms driving these benefits, particularly the role in blood pressure control, are still under investigation [16–21].

GLP1RA, on the other hand, are not only used for glycemic management in T2DM but are also approved for obesity treatment. They have demonstrated favorable effects on lipid profiles, body weight reduction, and emerging evidence suggests their potential in improving liver steatosis. Despite these advantages, more research is needed to understand their long-term cardiovascular benefits and renal effects in real-world settings. Some studies have reported significant weight loss and reductions in LDL cholesterol and triglycerides, with mixed evidence on cardiovascular outcomes [22–25].

While clinical trials have established the efficacy of these agents, translating trial outcomes into routine clinical practice can be challenging. Controlled trials often include carefully selected patient populations, which may not fully reflect the diversity and complexity of real-world patients, particularly those with multiple comorbidities or advanced disease. Real-world studies, therefore, play a critical role in assessing how these drugs perform in broader, more heterogeneous populations.

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In this study, we aim to evaluate the real-world effectiveness of SGLT2i and GLP1RA in a cohort of patients with T2DM followed in a hospital diabetology consultation. The focus will be on the drugs' impact on renal function, cardiovascular risk, weight, and glycemic control over a one-year period. By comparing these outcomes with adverse event reports in the European EudraVigilance database, we hope to provide a comprehensive picture of the safety and therapeutic value of these agents in routine clinical practice.

2. Methods

2.1. Study design and sampling

This was a retrospective observational study conducted at the hospital diabetology consultation service of the Local Health Unit of Guarda, Portugal, between 1 January 2020, and 31 December 2022. The study aimed to evaluate the pharmacotherapeutic effects of SGLT2i and GLP1RA in patients with T2DM over a one-year period. Ethics approval was granted by the Ethics Committee of the Local Health Unit of Guarda (Approval Reference: SFTSS-REQ-22022), as well as formal authorization by the Institution's Board of Directors. Patient consent was waived because the Ethics Committee of the Local Health Unit of Guarda considered that it would be unnecessary in this retrospective study.

2.2. Sample size calculation

The minimum required sample size was calculated to ensure that the results were statistically significant with a 95% confidence level and a 5% margin of error. Given a population of 1,707 patients receiving care at the hospital diabetology consultation, we used the sample size formula for finite populations. This calculation yielded a minimum sample size of 314 patients.

2.3. Inclusion criteria

- Diagnosis of T2DM.
- Use of SGLT2i or GLP1RA for at least one year with no changes to the antidiabetic regimen during the analysis period.
- Availability of complete baseline and follow-up data on bioanalytical parameters, including estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), blood sodium and potassium levels, weight, and cardiovascular risk scores.

2.4. Exclusion criteria

- Patients with less than one year of follow-up data (±2 months).
- Patients with incomplete or inconsistent information on pharmacotherapeutic regimens.
- Presence of gestational diabetes or type 1 diabetes mellitus.
- Patients with missing bioanalytical parameters at baseline or follow-up.

2.5. Data collection

Data were extracted from the hospital's SClinico® and Modulab® electronic health record systems between 8 April 2023, and 12 May 2023. The following variables were collected at baseline and one year later:

- Demographic variables: Age and gender.
- Pharmacotherapy: Antidiabetic medications, including SGLT2i, GLP1RA, insulin, metformin, dipeptidyl peptidase-4 inhibitors (DPP4i), sulfonylureas, and thiazolidinediones.
- Bioanalytical parameters: HbA1c, serum creatinine, sodium, potassium, total cholesterol, LDL cholesterol, HDL cholesterol.
- Anthropometric data: Weight and body mass index (BMI).
- Hemodynamic data: Systolic and diastolic blood pressure (BP).
- Renal function: eGFR, calculated using CKD-EPI formula.
- Cardiovascular risk: Estimated 10-year cardiovascular risk was calculated using the European Society of Cardiology's HeartScore® tool, adapted for the Portuguese population.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 28 (IBM Corp., Armonk, NY, U.S.A.).

Descriptive Statistics: Continuous variables were summarized as means and standard deviations (SD) for normally distributed data or as medians and interquartile ranges for non-normally distributed data. Categorical variables were presented as absolute and relative frequencies (percentages).

Comparative Analysis:

- The Wilcoxon signed-rank test and paired samples t-test were used to compare continuous variables between baseline and endpoint, depending on the data distribution.
- The Pearson chi-square test was applied to assess associations between categorical variables.
- A statistical significance level of $p < 0.05$ was considered for all analyses.

2.7. eGFR calculation

Renal function at baseline and endpoint was evaluated by calculating the eGFR using the eGFR-App® (eGFR Calculator) based on the CKD-EPI equation. Patients with baseline eGFR values of less than 60 mL/min/1.73 m^2 were classified as having chronic kidney disease (CKD). Changes in eGFR over the study period were compared between patients treated with SGLT2i and those not receiving these agents.

2.8. Cardiovascular risk calculation

Cardiovascular risk was assessed using the HeartScore® tool, which estimates the 10-year risk of fatal and non-fatal cardiovascular events. The tool is based on the SCORE2 algorithm and was used to calculate cardiovascular risk at baseline and endpoint, with a focus on the effects of SGLT2i and GLP1RA treatments on these outcomes.

2.9. Individual case safety reports (ICSRs) from EudraVigilance database

In addition to evaluating clinical outcomes, safety data were obtained from the European EudraVigilance database. We analyzed Individual Case Safety Reports (ICSRs) for SGLT2i (e.g. Jardiance®, Forxiga®), GLP1RA (e.g. Ozempic®, Victoza®), dipeptidyl peptidase-4 inhibitor (DPP4i) (e.g. Januvia®), metformin, and long-acting insulins (e.g. Lantus®, Levemir®) from 1 January 2021, to 31 December 2023. Reported adverse events of interest included acute kidney injury (AKI), acute myocardial infarction (AMI), and cerebrovascular accidents (CVA). Pearson's chi-square test was used to assess differences in adverse event incidence between treatments.

3. Results

3.1. Sample selection

Initially, a total of 1707 patients were identified for potential inclusion in the study. Following the application of the exclusion criteria (illustrated in Figure 1), 607 patients were included in the final analysis. The reasons for exclusion included: a follow-up period in consultation of less than 1 year (±2 months) ($n = 39$), incomplete information on biochemical parameters during the analysis period ($n = 126$), incomplete or unclear information regarding the patients' pharmacotherapeutic regimen ($n = 70$), as well as cases of gestational diabetes ($n = 18$) and type 1 diabetes mellitus ($n = 14$). After randomization and selection, the final sample included 340 patients.

3.2. Sample characterization

From the initial pool of 1.707 patients, 340 patients were eligible for this study. The cohort consisted of 165 men (48.5%) and 175 women (51.5%), with a mean age of 66.36 years (SD = 11.65). At baseline, 58.2% of the patients were treated with SGLT2i, and 42.1% with GLP1RA. Other commonly prescribed antidiabetic medications included insulin (56.2%), metformin (70.6%), and DPP4i (60.3%). Detailed characteristics of the study population are provided in Table 1.

3.3. SGLT2i's effects on kidney function and systolic blood pressure and GLP1 RA effects on weight

3.3.1. Impact on renal function

Patients treated with SGLT2i exhibited a statistically significant improvement in renal function, as evidenced by an increase in eGFR from baseline (mean rank = 77.11) to endpoint (mean rank = 98.37) ($p = 0.006$). In contrast, no significant change in eGFR was observed in patients not receiving SGLT2i ($p = 0.166$) (See Figure 2). Among patients with a baseline eGFR <60 mL/min/1.73 m^2, no significant difference was found between patients treated with or without SGLT2i in maintaining or improving eGFR ($p = 0.159$) (See Table S1).

3.3.2. Effects on blood pressure

A significant reduction in systolic blood pressure (SBP) was observed in patients treated with SGLT2i, with a mean decrease from 150.2 mmHg at baseline to 144.8 mmHg at endpoint ($p = 0.0002$). Patients not receiving SGLT2i also showed a reduction in SBP, though to a lesser extent ($p = 0.032$) (See Figure 2). No significant changes were observed in diastolic blood pressure (DBP) in either group (See Table S2).

3.3.3. Weight reduction

Patients treated with GLP1RA experienced a statistically significant reduction in weight from baseline to endpoint (mean rank = 73.98 vs. 48.48, $p < 0.0001$), with a mean weight loss of 2.32%. Additionally, 33.6% of GLP1RA-treated patients achieved a ≥ 5% weight reduction compared to 19.8% in the non-GLP1RA group ($p = 0.0006$) (See Figure 2).

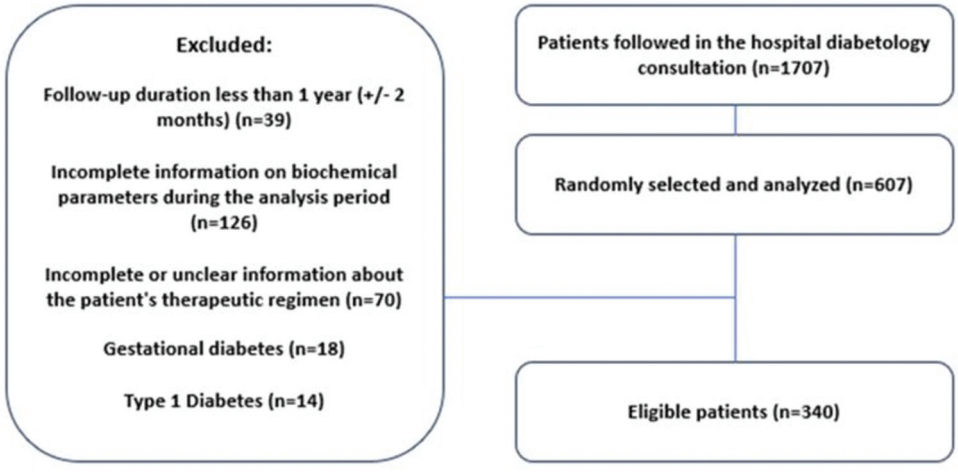

Figure 1. Sample selection.

Figure 2. SGLT2i effects on kidney function and systolic blood pressure and GLP1 RA effects on weight.

Table 1. Sample characterization.

Gender	Male (n;%)		Female (n;%)			
	165 (48.5%)		175 (51.5%)			
	Mean		Min-Max		SD	
Age	66.36		30-91		11.654	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**
HbA1c (%)	7.61	7.51	5.10-15.59	4.77-12.72	1.42	1.32
Creatinine (mg/dL)	1.08	1.10	0.53-7.54	0.55-8.12	0.60	0.74
Sodium (mmol/L)	138.96	139.23	125-145	123-149	2.76	2.80
Potassium (mmol/L)	4.67	4.67	3.5-6.0	3.5-6.7	0.43	0.47
Total cholesterol (mg/dL)	155.67	154.81	60-290	73-287	36.49	36.56
HDL cholesterol (mg/dL)	45.05	45.23	14-109	22-94	11.80	11.53
LDL cholesterol (mg/dL)	95.14	93.50	17-225	25-220	34.18	33.23
Weight (kg)	78.72	77.90	40-141	26-140	16.36	16.49
Systolic blood pressure (mmHg)	151.26	147.00	96-249	78-229	21.17	22.66
Diastolic blood pressure (mmHg)	75.14	73.60	48-106	44-101	9.78	10.40
Antidiabetic drug		**Male (n;%)**		**Female (n;%)**		**Total (n;%)**
SGLT2i		101 (51.0%)		97 (49.0%)		198 (58.2%)
GLP1 RA		72 (50.3%)		71 (49.7%)		143 (42.1%)
Insulin		86 (45.0%)		105 (55.0%)		191 (56.2%)
Metformin		119 (49.6%)		121 (50.4%)		240 (70.6%)
DPP4i		107 (52.2%)		98 (47.8%)		205 (60.3%)
Sulfonylurea		26 (48.1%)		28 (51.9%)		54 (15.9%)
Thiazolidinedione		21 (46.7%)		24 (53.3%)		45 (13.2%)

3.4. SGLT2i and GLP1 RA effects on cardiovascular risk

Both treatment groups (SGLT2i and GLP1RA) showed significant reductions in cardiovascular risk scores. For patients treated with GLP1RA, cardiovascular risk scores decreased from a mean of 10.59 (SD = 7.05) at baseline to 10.08 (SD = 6.94) at endpoint ($p = 0.002$). Similarly, patients treated with SGLT2i saw reductions in cardiovascular risk scores ($p = 0.004$). Patients not receiving either treatment also exhibited significant cardiovascular risk reductions, though to a lesser extent ($p = 0.010$) (See Table 2).

3.5. SGLT2i and GLP1 RA effects on HbA1c

Among patients with baseline HbA1c ≥ 7.0% ($n = 212$), both SGLT2i and GLP1RA treatments were associated with

Table 2. GLP1 RA and SGLT2i effects on cardiovascular risk.

	Baseline		Endpoint		
	Mean	SD	Mean	SD	*p*-value
GLP1 RA ($n = 143$)	10.59	7.05	10.08	6.94	0.002*
SGLT2i ($n = 198$)	11.36	7.57	10.94	7.39	0.004*
Without GLP1 RA and/or SGLT2i ($n = 103$)	13.94	9.36	13.37	9.13	0.010*

*Wilcoxon signed-rank test.

Table 3. SGLT2i and GLP1 RA effects on HbA1c after 1 year of treatment.

	Baseline		Endpoint			
HbA1c at baseline ≥ 7.0%	Mean	SD	Mean	SD	mean variation	*p*-value
GLP1 RA ($n = 94$)	8.41	0.98	8.13	1.25	−0.28	0.010**
SGLT2i ($n = 135$)	8.21	1.15	7.91	1.20	−0.30	0.002*
Total ($n = 212$)	8.36	1.27	8.05	1.31	−0.31	0.0001*

*Wilcoxon signed-rank test.
**Paired samples *t*- test.

significant reductions in HbA1c levels after one year. Patients treated with GLP1RA had a mean HbA1c reduction of −0.28% ($p = 0.010$), while those treated with SGLT2i showed a mean reduction of −0.30% ($p = 0.002$). The overall reduction for all patients in this group was −0.31% ($p = 0.0001$) (See Table 3).

3.6. SGLT2i's effects on blood sodium and potassium levels

No significant differences were found between the use of SGLT2i and the occurrence of hyponatremia ($p = 0.712$) or hyperkalemia ($p = 0.358$) at the endpoint, suggesting that long-term use of SGLT2i is safe in this regard (Table S3).

3.7. Comparisons with adverse drug reaction profiles reported in the EudraVigilance database

From 1 January 2021, to 31 December 2023, 15573 ICSRs were reported in the European EudraVigilance database for SGLT2i and 16,121 for GLP1 RA. The adverse events analyzed included acute kidney injury (AKI), acute myocardial infarction (AMI), and cerebrovascular accidents. The incidence of AMI was significantly lower for GLP1 RA (0.06%, $p < 0.0001$) compared to other treatments. Both SGLT2i and GLP1 RA demonstrated a low incidence of AKI and cerebrovascular accidents ($p < 0.0001$) (See Table 4).

4. Discussion

This study evaluated the real-world effects of SGLT2i and GLP1RA on key clinical parameters in patients with T2DM. Our findings confirm the substantial benefits of these drug classes in improving renal function, blood pressure, weight reduction, cardiovascular risk scores, and HbA1c levels. Additionally, safety data from the European EudraVigilance database further support their favorable adverse event profiles compared to other antidiabetic therapies, such as metformin and long-acting insulins.

4.1. Renal function

We observed a significant improvement in eGFR among patients treated with SGLT2i. This aligns with previous studies such as the DAPA-CKD and EMPA-KIDNEY trials, which demonstrated the renoprotective effects of SGLT2i in patients with chronic kidney disease (CKD), irrespective of T2DM status [9,26]. The improvement in eGFR is particularly relevant as it suggests that SGLT2i can slow the progression of renal impairment in T2DM patients [27,28]. Our results also showed that among patients with baseline eGFR <60 mL/min/1.73 m^2, no significant difference was found between SGLT2i and non-SGLT2i users. This finding could be attributed to the already compromised renal function in this subset of patients, indicating that further investigation is required to fully understand the nephroprotective benefits in patients with advanced CKD [29].

4.2. Blood pressure reduction

Recent evidence has shown that SGLT2i can significantly improve BP in patients with T2DM, in addition to their cardioprotective effects in patients with HF [30–33]. Our study

Table 4. Individual cases safety reports analysis from 1 January 2021 to 31 December 2023.

	Total ICSRs	AKI	AMI	Cerebrovascular accident
SGLT2i	15573	375 (2.41%)	38 (0.24%)	271 (1.74%)
DPP4i	2295	15 (0.65%)	3 (0.13%)	69 (3.0%)
GLP1 RA	16121	188 (1.17%)	10 (0.06%)	208 (1.30%)
Metformin	9786	675 (6.90%)	24 (0.25%)	105 (1.07%)
Long-acting insulin	9186	19 (0.21%)	8 (0.09%)	285 (3.10%)
p-value		p < 0.0001***	p < 0.0001***	p < 0.0001***

***Pearson's chi-square test.

showed a significant reduction in SBP in patients treated with SGLT2i, supporting previous evidence of their antihypertensive effects. SGLT2i promote natriuresis and osmotic diuresis, which contribute to blood pressure reduction [4].

Notably, while the reduction in SBP was more pronounced in the SGLT2i group, DBP did not significantly change, consistent with other reports [34]. This highlights the potential of SGLT2i as a multifaceted treatment option for T2DM patients, particularly those with hypertension or high cardiovascular risk.

4.3. Weight reduction

The weight reduction associated with GLP1RA was significant, with 33.6% of patients achieving ≥ 5% weight loss, which is consistent with other studies. GLP1RA has gained approval for the treatment of obesity, and our findings further reinforce its role in weight management in patients with T2DM [35]. Weight reduction is critical in preventing the progression of T2DM and mitigating cardiovascular risks. The higher proportion of patients achieving significant weight loss underlines the real-world efficacy of GLP1RA, although achieving such outcomes may depend on patient adherence and other factors [36–39].

4.4. Cardiovascular risk

Both SGLT2i and GLP1RA treatments resulted in significant reductions in cardiovascular risk scores, a finding that complements existing literature on the cardiovascular benefits of these drugs. SGLT2i have been widely recognized for reducing heart failure hospitalizations and major adverse cardiovascular events (MACE), particularly in patients with HFrEF [40–44]. GLP1RA have also shown promise in reducing cardiovascular events, as demonstrated by trials such as LEADER and SUSTAIN-6 [45,46]. These findings are especially important considering the elevated cardiovascular mortality risk in patients with T2DM. By lowering cardiovascular risk, these treatments address a critical need in this population, offering benefits beyond glycemic control.

4.5. Glycemic control (HbA1c)

Our results showed significant reductions in HbA1c in both SGLT2i and GLP1RA-treated patients. These reductions are consistent with those reported in previous meta-analyses [47,48]. The modest improvement in HbA1c observed in our study compared to clinical trials may reflect the complexities of real-world practice, where patients often present with multiple comorbidities and adherence issues. Nevertheless, the reductions in HbA1c demonstrate the potential of SGLT2i and GLP1RA to achieve glycemic targets in routine clinical settings. [49,50].

4.6. Safety profile and adverse events

The analysis of adverse events from the EudraVigilance database confirmed the favorable safety profiles of both SGLT2i and GLP1RA.

This real-world evidence aligns with controlled trial data and provides reassurance regarding the long-term safety of these agents [11,12,51,52]. The lower rates of cardiovascular and renal events in patients treated with SGLT2i and GLP1RA support their use in reducing cardiovascular risk in T2DM populations, particularly those with preexisting cardiovascular conditions [7,51].

4.7. Clinical implications

The results of this study underscore the importance of integrating SGLT2i and GLP1RA into the treatment plans of T2DM patients, especially those at high cardiovascular and renal risk. These drug classes offer benefits beyond glycemic control, providing renal protection, cardiovascular risk reduction, and significant weight loss, which are critical for the comprehensive management of T2DM. Given the real-world challenges of managing elderly patients with multiple comorbidities, the findings highlight the practical utility of these therapies in routine clinical practice. However, careful patient selection and monitoring are essential, particularly in those with advanced renal disease or at high risk for adverse events.

5. Conclusions

This study provides valuable real-world evidence on the effectiveness and safety of SGLT2i and GLP1RA in the management of T2DM. Our findings suggest that both drug classes offer significant benefits beyond glycemic control, including improved renal function, reduced SBP, weight loss, and decreased cardiovascular risk. These benefits, observed in routine clinical practice, align with previous results from controlled clinical trials, reinforcing the role of SGLT2i and GLP1RA as essential components of the therapeutic armamentarium for T2DM.

Moreover, the analysis of adverse events from the EudraVigilance database highlights the favorable safety profiles of these agents compared to other antidiabetic therapies, particularly in terms of lower incidence rates of AKI, cardiovascular events, and cerebrovascular accidents. As such, SGLT2i and GLP1RA should be considered for broader use in T2DM patients, especially those with high cardiovascular or renal risk.

While our results underscore the clinical value of SGLT2i and GLP1RA in real-world settings, further prospective studies involving larger and more diverse populations are needed to fully explore their long-term outcomes, particularly in high-risk groups and patients with advanced comorbidities.

6. Limitations

This study has several limitations that should be considered when interpreting the results. First, the retrospective design introduces potential biases, particularly selection bias, as we included only patients with complete and consistent medical records. The exclusion of patients with incomplete data may limit the generalizability of the findings, especially among

patients with well-controlled diabetes or those with fewer comorbidities.

Second, the follow-up period of one year may be insufficient to fully capture the long-term effects of SGLT2i and GLP1RA on cardiovascular and renal outcomes. While short-term improvements were observed, a longer observation period is required to assess the durability of these effects and their impact on major clinical endpoints, such as hospitalization rates for heart failure or the progression of chronic kidney disease.

Third, the lack of data on additional clinical variables, such as microalbuminuria, fasting plasma glucose, and patient adherence to treatment regimens, may have influenced the results. Adherence to antidiabetic therapy is a key determinant of treatment efficacy, and its absence from our analysis represents a notable limitation.

Fourth, our study population consisted primarily of elderly patients with multiple comorbidities, reflecting a high-risk cohort typical of hospital diabetology consultations. While this enhances the relevance of the findings for similar clinical settings, the results may not be directly applicable to younger or healthier populations, particularly those managed in primary care.

Lastly, the study did not include patients using continuous glucose monitoring (CGM), which could have provided a more detailed analysis of glucose control, including time-in-range metrics. Future studies incorporating CGM data could offer deeper insights into the effects of these drugs on glycemic variability and other clinical outcomes.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Conceptualization: All authors; Methodology: AC Lopes, and M Morgado; Validation: All authors; Formal analysis: All authors; Investigation: All authors; writing original draft preparation: AC Lopes; Writing review and editing: O Lourenço and M Morgado; Supervision: O Lourenço and M Morgado; Project administration: O Lourenço and M Morgado. All authors have read and agreed to the published version of the manuscript.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Local Health Unit of Guarda (SFTSS-REQ-22022). Data were collected anonymously. Patient consent was waived because the Ethics Committee of the Local Health Unit of Guarda considered that it would be unnecessary in this retrospective study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Zhou Z, Zheng M, Zuo Z, et al. Comparison of cardiovascular outcomes of new antihyperglycemic agents in type 2 diabetes mellitus: a meta-analysis. ESC Heart Fail. 2024;11(3):1647–1656. doi: 10.1002/ehf2.14726
2. Mone P, Ciccarelli M, Jankauskas SS, et al. SGLT2 inhibitors and GLP-1 receptor agonists: which is the best anti-frailty drug? The Lancet Healthy Longevity. 2024;5(9):100632. doi: 10.1016/j.lanhl.2024.08.001
3. Forst T, Mathieu C, Giorgino F, et al. New strategies to improve clinical outcomes for diabetic kidney disease. BMC Med. 2022;20(1):337. doi: 10.1186/s12916-022-02539-2
4. Puglisi S, Rossini A, Poli R, et al. Effects of SGLT2 inhibitors and GLP-1 receptor agonists on renin-angiotensin-aldosterone system. Front Endocrinol. 2021;12:738848. doi: 10.3389/fendo.2021.738848
5. Nauck MA, Quast DR. Cardiovascular safety and benefits of semaglutide in patients with type 2 diabetes: findings from SUSTAIN 6 and PIONEER 6. Front Endocrinol. 2021;12:645566. doi: 10.3389/fendo.2021.645566
6. Wang J-Y, Wang Q-W, Yang X-Y, et al. GLP−1 receptor agonists for the treatment of obesity: role as a promising approach. Front Endocrinol. 2023;14:1085799. doi: 10.3389/fendo.2023.1085799
7. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. The Lancet Diabetes Endocrinol. 2021;9(10):653–662. doi: 10.1016/S2213-8587(21)00203-5
8. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. The Lancet. 2022;400(10354):757–767. doi: 10.1016/S0140-6736(22)01429-5
9. Yau K, Dharia A, Alrowiyti I, et al. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney Int Rep. 2022;7(7):1463–1476. doi: 10.1016/j.ekir.2022.04.094
10. Nevola R, Epifani R, Imbriani S, et al. GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. IJMS. 2023;24(2):1703. doi: 10.3390/ijms24021703
11. Oates CP, Santos-Gallego CG, Smith A, et al. SGLT2 inhibitors reduce sudden cardiac death risk in heart failure: meta-analysis of randomized clinical trials. Cardiovasc Electrophysiol. 2023;34(5):1277–1285. doi: 10.1111/jce.15894
12. Santos-Gallego CG, Requena-Ibáñez JA, Picatoste B, et al. Cardioprotective effect of empagliflozin and circulating ketone bodies during acute myocardial infarction. Circ: Cardiovasc Imag [Internet]. 2023 [cited 2024 Sep 29];16(4). doi: 10.1161/CIRCIMAGING.123.015298
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446. doi: 10.1056/NEJMoa2024816
14. Kurata Y, Nangaku M. Dapagliflozin for the treatment of chronic kidney disease. Expert Rev Endocrinol Metab. 2022;17(4):275–291. doi: 10.1080/17446651.2022.2099373
15. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–127. doi: 10.1056/NEJMoa2204233
16. Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Empagliflozin improves quality of life in nondiabetic HFrEF

patients. Sub-analysis of the EMPATROPISM trial. Diabetes Metabolic Syndr: Clin Res Rev. 2022;16(2):102417. doi: 10.1016/j.dsx.2022.102417
17. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424. doi: 10.1056/NEJMoa2022190
18. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes. J Am Coll Cardiol. 2020;76(9):1117–1145. doi: 10.1016/j.jacc.2020.05.037
19. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–3726. doi: 10.1093/eurheartj/ehab368
20. Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open. 2012;2(5):e001007. doi: 10.1136/bmjopen-2012-001007
21. Kario K, Ferdinand KC, Vongpatanasin W. Are SGLT2 inhibitors new hypertension drugs? Circulation. 2021;143(18):1750–1753. doi: 10.1161/CIRCULATIONAHA.121.053709
22. Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. Mol Metab. 2021;46:101090. doi: 10.1016/j.molmet.2020.101090
23. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021;384(12):1113–1124. doi: 10.1056/NEJMoa2028395
24. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. Clin Ther. 2015;37(1):225–241.e8. doi: 10.1016/j.clinthera.2014.11.008
25. Ajabnoor GMA, Hashim KT, Alzahrani MM, et al. The possible effect of the long-term use of glucagon-like peptide-1 receptor agonists (GLP-1RA) on Hba1c and lipid profile in type 2 diabetes mellitus: a retrospective study in KAUH, Jeddah, Saudi Arabia. Diseases. 2023;11(1):50. doi: 10.3390/diseases11010050
26. Prandi FR, Barone L, Lecis D, et al. Biomolecular mechanisms of cardiorenal protection with sodium-glucose Co-transporter 2 inhibitors. Biomolecules. 2022;12(10):1349. doi: 10.3390/biom12101349
27. Meraz-Muñoz AY, Weinstein J, Wald R. eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined. Kidney360. 2021;2(6):1042–1047. doi: 10.34067/KID.0001172021
28. Chan Y-H, Chao T-F, Chen S-W, et al. Association of acute increases in serum creatinine with subsequent outcomes in patients with type 2 diabetes mellitus treated with sodium–glucose cotransporter 2 inhibitor or dipeptidyl peptidase-4 inhibitor. Eur Heart J - Qual Care Clin Outcomes. 2022:qcac040. doi: 10.1093/ehjqcco/qcac040
29. De La Flor JC, Villa D, Cruzado L, et al. Efficacy and safety of the use of SGLT2 inhibitors in patients on incremental hemodialysis: maximizing residual renal function, is there a role for SGLT2 inhibitors? Biomedicines. 2023;11(7):1908. doi: 10.3390/biomedicines11071908
30. Li M, Yi T, Fan F, et al. Effect of sodium-glucose cotransporter-2 inhibitors on blood pressure in patients with heart failure: a systematic review and meta-analysis. Cardiovasc Diabetol. 2022;21(1):139. doi: 10.1186/s12933-022-01574-w
31. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia. 2018;61(10):2098–2107. doi: 10.1007/s00125-018-4669-0
32. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Obes Metab. 2021;23(9):2116–2124. doi: 10.1111/dom.14451
33. Landolfo M, Spannella F, Giulietti F, et al. Detecting heart stress using nt-proBNP in patients with type 2 diabetes mellitus and hypertension or high-normal blood pressure: a cross-sectional multicentric study. Cardiovasc Diabetol. 2024;23(1):297. doi: 10.1186/s12933-024-02391-z
34. Zhang Q, Zhou S, Liu L. Efficacy and safety evaluation of SGLT2i on blood pressure control in patients with type 2 diabetes and hypertension: a new meta-analysis. Diabetol Metab Syndr. 2023;15(1):118. doi: 10.1186/s13098-023-01092-z
35. Jensterle M, Rizzo M, Haluzík M, et al. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: a narrative review. Adv Ther. 2022;39(6):2452–2467. doi: 10.1007/s12325-022-02153-x
36. Yeh T-L, Tsai M-C, Tsai W-H, et al. Effect of glucagon-like peptide-1 receptor agonists on glycemic control, and weight reduction in adults: a multivariate meta-analysis. Chiang M-C, editor. PLOS ONE. 2023;18(1):e0278685. doi: 10.1371/journal.pone.0278685
37. Chao AM, Tronieri JS, Amaro A, et al. Semaglutide for the treatment of obesity. Trends Cardiovasc Med. 2023;33(3):159–166. doi: 10.1016/j.tcm.2021.12.008
38. Weiss T, Yang L, Carr RD, et al. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. BMJ Open Diab Res Care. 2022;10(1):e002517. doi: 10.1136/bmjdrc-2021-002517
39. White GE, Shu I, Rometo D, et al. Real-world weight-loss effectiveness of glucagon-like peptide-1 agonists among patients with type 2 diabetes: a retrospective cohort study. Obesity. 2023;31(2):537–544. doi: 10.1002/oby.23622
40. Bailey CJ, Marx N. Cardiovascular protection in type 2 diabetes: insights from recent outcome trials. Diabetes Obes Metab. 2019;21(1):3–14. doi: 10.1111/dom.13492
41. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. doi: 10.1093/eurheartj/ehz486
42. Sharma A, Aziz H, Verma S, et al. Permission to prescribe: do cardiologists need permission to prescribe diabetes medications that afford cardiovascular benefit? Curr Opin Cardiol. 2021;36(5):672–681. doi: 10.1097/HCO.0000000000000892
43. American Diabetes Association Professional Practice Committee. 6. Glycemic targets: standards of medical care in diabetes—2022. Diabetes Care. 2022;45(Supplement_1):S83–96. doi: 10.2337/dc22-S006
44. Marx N, Husain M, Lehrke M, et al. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. Circulation. 2022;146(24):1882–1894. doi: 10.1161/CIRCULATIONAHA.122.059595
45. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–322. doi: 10.1056/NEJMoa1603827
46. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–1844. doi: 10.1056/NEJMoa1607141
47. DeFronzo RA. Combination therapy with GLP -1 receptor agonist and SGLT2 inhibitor. Diabetes Obes Metab. 2017;19(10):1353–1362. doi: 10.1111/dom.12982
48. Scheen AJ. GLP-1 receptor agonists and SGLT2 inhibitors in type 2 diabetes: pleiotropic cardiometabolic effects and add-on value of a combined therapy. Drugs [Internet]. 2024 [cited 2024 Oct 4]. doi: 10.1007/s40265-024-02090-9
49. Kim HS, Yoon T, Jung CH, et al. Clinical efficacy of sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist combination therapy in type 2 diabetes mellitus: real-world study. Diabetes Metab J. 2022;46(4):658–662. doi: 10.4093/dmj.2021.0232
50. Harris KB, McCarty DJ. Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus. Ther Adv Endocrinol. 2015;6(1):3–18. doi: 10.1177/2042018814558242
51. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109–121. doi: 10.1056/NEJMoa2403347
52. Chang RC, Huang J, Hurst J, et al. Benefits of dapagliflozin in chronic kidney disease for US commercial payers: a cost-offset analysis. JMCP. 2024;30(8):834–842. doi: 10.18553/jmcp.2024.30.8.834