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SGLT2i and GLP1RA: Safety and Effectiveness Profiles Evaluation using Real-World Patient Data

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Scientific Posters:

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António Cabral Lopes, Olga Lourenço, Sandra Morgado, Andreia Gaspar, Idalina Freire, Inês Eusébio, João Ribeiro, Mafalda Silva, Marta Mendes, Olímpia Fonseca, Rute Duarte, Ema Paulino and Manuel Morgado - Dapagliflozin short-term use: Effects on Renal function and Electrolyte balance. 82nd International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences in Cape Town, South Africa – Pharmacy Education (2024) 24(7) 263 – 264 https://doi.org/10.46542/pe.2024.247.211294 263-264

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Resumo Alargado

A diabetes é uma doença crónica responsável por elevadas taxas de morbilidade e mortalidade, cuja prevalência está associada a maus hábitos alimentares, inatividade física, consumo de álcool, tabagismo, fatores genéticos e ao aumento da esperança média de vida. Em 2021, a Federação Internacional de Diabetes (IDF) estimava que cerca de 537 milhões de adultos (20-79 anos) viviam com diabetes, um número que poderá atingir os 700 milhões até 2045. Apesar dos avanços no diagnóstico e tratamento, ainda é considerada uma doença subdiagnosticada. Possui um cariz multifatorial, complexo e heterogéneo, sendo que a diabetes do tipo 2 (T2DM) representa cerca de 90% dos casos, estando intimamente associada ao risco de doenças cardiovasculares (CV), acidente vascular cerebral isquémico, retinopatia, nefropatia e amputações dos membros inferiores.

A prevalência da T2DM tem vindo a aumentar nas últimas décadas, especialmente na Europa Ocidental, devido ao envelhecimento demográfico, ao crescimento de grandes centros urbanos, pelo desenvolvimento económico e alterações dos padrões alimentares, agudizados por estilos de vida sedentários. O desenvolvimento de medicamentos inovadores como os inibidores do co-transportador de sódio-glucose 2 (SGLT2i) e os agonistas do recetor do peptídeo-1 semelhante ao glucagon (GLP1RA), surge numa perspetiva de dar resposta a esta tendência, permitindo uma nova abordagem farmacoterapêutica. Para além de contribuírem para o controlo eficaz dos níveis de glicémia, oferecem benefícios CV, renais e ainda promovem a perda de peso em doentes obesos.

Os SGLT2i, como a dapagliflozina e a empagliflozina, atuam pelo bloqueio da reabsorção renal de glucose e promoção da sua excreção urinária, com benefícios na redução da necessidade de hospitalização por insuficiência cardíaca (IC) descompensada e eventos CV. Estudos como o DAPA-CKD e EMPA-KIDNEY demonstraram também efeitos protetores renais em doentes com doença renal crónica (DRC), independentemente da presença de T2DM.

Os GLP1RA promovem o aumento da secreção de insulina e diminuem a secreção de glucagon em resposta aos níveis de glucose, contribuindo para um melhor controlo glicémico, tendo ainda um papel importante na redução de peso, com efeitos cardioprotetores adicionais. Estes fármacos também têm sido alvo de investigação no tratamento da esteatose hepática não alcoólica.

Existem cada vez mais medicamentos cujo potencial terapêutico não se esgota na ou nas principais indicações terapêuticas para as quais foram inicialmente aprovados. O

reposicionamento de medicamentos, ou seja, a adição de novas indicações terapêuticas a fármacos com utilização prévia noutras condições, tem demonstrado benefícios inegáveis na abordagem farmacoterapêutica de patologias complexas, explorando o máximo potencial de cada molécula. Este foi o princípio aplicado quer aos SGLT2i quer aos GLP1RA, para os quais foram recentemente aprovadas novas indicações, para além do tratamento da T2DM, em consequência dos benefícios demonstrados em diversos ensaios clínicos. No entanto, o reposicionamento contribui para o aumento da utilização desses medicamentos em diferentes populações-alvo, exigindo uma revisão contínua dos respetivos perfis de efetividade e de segurança. Deste modo, a realização de estudos de investigação clínica, utilizando dados de doentes num contexto real de utilização desses medicamentos, assume extrema importância.

O objetivo principal desta tese de doutoramento consiste em avaliar os perfis de segurança e de efetividade dos SGLT2i e GLP1RA em contexto real, através da realização de estudos retrospetivos que focam os três níveis principais de prestação de cuidados hospitalares: serviço de urgência, internamento e consulta de especialidade. Além disso, dados de segurança dos medicamentos em investigação e obtidos a partir da base de dados EudraVigilance (EV) foram incluídos de modo a conferir maior robustez aos resultados obtidos.

Em doentes internados e sem utilização prévia de qualquer SGLT2i, a dapagliflozina demonstrou eficácia na redução dos níveis de glicémia desde os primeiros dias sob tratamento no entanto e de um modo geral, constatou-se que os níveis de creatinina aumentaram significativamente após o início da sua administração. Nas mesmas condições, também se verificaram alterações eletrolíticas (hiponatremia e hipercalemia) significativas. Estes resultados relevam a necessidade de uma monitorização minuciosa da função renal e dos níveis séricos de eletrólitos, nomeadamente durante as primeiras semanas de tratamento, de modo a prevenir potenciais riscos de eventos adversos, sobretudo em populações mais vulneráveis.

A análise efetuada na base de dados da EV das reações adversas medicamentosas suspeitas (RAM) notificadas para o semaglutido revelou que os efeitos gastrointestinais foram os mais frequentes, enfatizando a necessidade de intervenções para minimizar a sua ocorrência, dado o seu impacto significativo na adesão ao tratamento e por conseguinte no sucesso terapêutico.

Em doentes seguidos na consulta hospitalar de diabetologia, os SGLT2i e os GLP1RA demonstraram benefícios significativos para além do controlo glicémico, nomeadamente ao nível da função renal, na redução da pressão arterial sistólica, na perda de peso e ainda na diminuição do risco CV. Os resultados obtidos vão ao encontro dos obtidos nos ensaios clínicos controlados realizados, reforçando a importância dos SGLT2i e GLP1RA

como componentes essenciais no tratamento da T2DM e de outras patologias intimamente relacionadas. Além disso, a análise dos casos individuais de segurança de suspeita de RAM notificados na base de dados EV mostrou que, durante o período em estudo, não foram registadas notificações que sugerissem problemas de segurança relacionados com lesão renal aguda (LRA), eventos cardiovasculares ou acidentes cerebrovasculares, o que é coerente com o perfil de segurança favorável destes fármacos. Os SGLT2i e os GLP1RA devem ser considerados numa abordagem terapêutica mais diversificada em pacientes com T2DM, nomeadamente naqueles com maior risco para doenças CV ou renais.

Palavras-chave

Agonistas do recetor do peptídeo-1 semelhante ao glucagon; Diabetes Mellitus Tipo 2; Equilíbrio Eletrolítico; Farmacovigilância; Função Renal; Inibidores do co-transportador de sódio-glucose 2; Insuficiência Cardíaca; Obesidade; Perturbações Gastrointestinais; Reações Adversas Medicamentosas; Risco Cardiovascular.

Abstract

Type 2 Diabetes Mellitus (T2DM) is a highly prevalent chronic disease associated with substantial morbidity and mortality, largely driven by cardiovascular (CV) complications, chronic kidney disease (CKD), and obesity. The global burden of T2DM continues to rise, fueled by aging populations, urbanization, and lifestyle-related risk factors. In this context, newer therapeutic classes such as sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) have transformed the management of T2DM by providing benefits that extend far beyond glycemic control. Robust evidence demonstrates that these agents reduce the risk of major adverse cardiovascular events (MACE), slow CKD progression, promote weight loss, and improve metabolic parameters. As a result, both drug classes have been increasingly repositioned and approved for new clinical indications, broadening their use to diverse and often complex patient populations.

Despite substantial evidence from randomized controlled trials, real-world data on the safety and effectiveness of SGLT2i and GLP1RA remain essential, particularly in older individuals, polymedicated patients, and those with multiple comorbidities—groups often underrepresented in clinical trials. Post-marketing safety signals, including genitourinary infections with SGLT2i and gastrointestinal adverse effects with GLP1RA, underscore the need for continued pharmacovigilance. Understanding how these medicines perform in routine care settings is critical to optimizing therapeutic strategies and supporting clinical decision-making.

This doctoral thesis aimed to evaluate the safety and effectiveness profiles of SGLT2i and GLP1RA using real-world data from hospital settings and pharmacovigilance reports. Retrospective observational studies were conducted across emergency departments, inpatient hospitalizations, and outpatient consultations, complemented by an analysis of adverse drug reaction (ADR) reports from the EudraVigilance (EV) database.

Key findings highlight the effectiveness of SGLT2i in improving renal function, reducing systolic blood pressure, and lowering hospitalization rates for heart failure (HF). GLP1RA were particularly effective in achieving significant weight loss and reducing CV risk scores. Both drug classes demonstrated substantial reductions in glycated hemoglobin (HbA1c), consistent with clinical trial data. Safety analyses revealed low incidences of acute kidney injury (AKI) and major CV events, with gastrointestinal side effects being the most frequently reported ADRs for GLP1RA.

These results underscore the critical role of SGLT2i and GLP1RA in comprehensive T2DM management, particularly for high-risk populations with multiple comorbidities. The findings also emphasize the need for ongoing pharmacovigilance and tailored

therapeutic strategies to optimize patient outcomes. Future research should focus on mitigating adverse effects and validating these findings across diverse populations and healthcare settings.

Keywords

Adverse Drug Reactions; Cardiovascular Risk; Electrolytic balance; Gastrointestinal disorders; Glucagon-like peptide-1 receptor agonists; Heart Failure; Obesity; Pharmacovigilance; Renal function; Sodium-glucose cotransporter-2 inhibitors; Type 2 Diabetes Mellitus.

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List of Abbreviations

ACEis	Angiotensin-Converting Enzyme inhibitors
ACKD	Acute Chronic Kidney Disease
AMP	Cyclic-3'5' -adenosine monophosphate
ADRs	Adverse Drug Reactions
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
ARBs	Angiotensin II Receptor Blockers
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
DHF	Decompensated Heart Failure
DPP4	Dipeptidyl peptidase-4
DPP4i	Dipeptidyl Peptidase-4 inhibitor
EEA	Economic European Area
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EV	EudraVigilance
FDA	U.S. Food and Drug Administration
GIP	Gastric inhibitory polypeptide
GLP1	Glucagon-like peptide-1
GLP1R	Glucagon-like peptide-1 receptor
GLP1RA	Glucagon-like peptide-1 receptor agonist
GLUT	Glucose Transporters
GPCRs	G protein-coupled receptors
GTIs	Genitourinary infections
HbA1c	Glycated hemoglobin
HBP	High Blood Pressure
HF	Heart Failure

HFrEF	Heart Failure with reduced Ejection Fraction
HDL	High-density lipoprotein
HU	Hyperuricemia
ICSRs	Individual Cases Safety Reports
IDF	International Diabetes Federation
KDIGO	Kidney Disease: Improving Global Outcomes
LHUCB	Local Health Unit of Cova da Beira
LHUG	Local Health Unit of Guarda
LDL	Low-density lipoprotein
MACE	Major Adverse Cardiovascular Events
MASH	Metabolic-associated steatohepatitis
NAFLD	Non-alcoholic Fatty Liver Disease
PE	Pulmonary Embolism
SBP	Systolic Blood Pressure
SGLT	Sodium-glucose cotransporters
SGLT1	Sodium-glucose cotransporter-1
SGLT2	Sodium-glucose cotransporter-2
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
SNAC	Synthetic N-acylated amino acid derivative of salicylic acid
SOC	System Organ Classes
T2DM	Type 2 Diabetes Mellitus
TGF	Tubuloglomerular Feedback
UTIs	Urinary Tract Infections

Thesis Overview

The primary goal of this doctoral thesis is to evaluate the safety and effectiveness profiles of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) in a real-world context. This is achieved through an integrated analysis focusing on the following objectives:

- **Assessment of clinical and pharmacological profiles:** Examining patients with type 2 diabetes mellitus (T2DM) admitted to the emergency department to identify how their clinical condition upon admission is influenced by pre-existing comorbidities and prior use of antidiabetic medications.

- **Evaluation of real-world effectiveness:** Investigating the impact of SGLT2i and GLP1RA on renal function, cardiovascular (CV) risk, weight, and glycemic control over a one-year period in a cohort of patients with T2DM followed in a hospital diabetology consultation.

- **Analysis of short-term effects:** Assessing the effects of dapagliflozin on renal function and electrolyte balance in hospitalized patients receiving the drug for the first time.

- **Comparison with adverse event data:** Analyzing adverse event reports from the European EudraVigilance (EV) database to provide a comprehensive understanding of the safety and therapeutic value of these agents in routine clinical practice.

- **Enhancing clinical decision-making:** Incorporating data from older patients with multiple comorbidities and polypharmacy can provide valuable insights into therapeutic strategies in complex real-world populations.

This thesis is organized into eight chapters:

- **Chapter 1:** Provides a literature review covering the mechanisms of action, characteristics, clinical indications, and main Adverse Drug Reactions (ADRs) of SGLT2i and GLP1RA.
- **Chapter 2:** Presents thesis objectives and overall structure.
- **Chapter 3:** Details an analysis of gastrointestinal disorders potentially associated with semaglutide, employing qualitative, quantitative, and comparative methods based on EudraVigilance (EV) Individual Case Safety Reports (ICSRs). The chapter also provides a critical interpretation of the results, situating them within the current body of evidence and examining their potential clinical relevance.

- **Chapter 4:** Details a retrospective observational study assessing the clinical and pharmacotherapeutic profiles of patients with T2DM admitted to a hospital emergency department, including associations between antidiabetic therapy, metabolic parameters, and acute clinical conditions.
- **Chapter 5:** Examines the short-term renal and electrolyte effects of dapagliflozin, combining clinical data with comparisons to ADR profiles reported in the EV database.
- **Chapter 6:** Explores real-world effects of SGLT2i and GLP1RA in patients followed in a hospital diabetology consultation, assessing kidney function, CV risk, metabolic outcomes, electrolyte balance, and comparisons with pharmacovigilance data.
- **Chapter 7:** Provides an integrated general discussion, contextualizing the findings from all studies within the current state of the art and highlighting implications for clinical practice and pharmacotherapy.
- **Chapter 8:** Summarizes the main conclusions, addresses study limitations, and proposes recommendations for future research on SGLT2i and GLP1RA safety and effectiveness.

By addressing the aforementioned objectives, this thesis seeks to expand knowledge about the real-world application of SGLT2i and GLP1RA, providing valuable insights to inform and optimize clinical and therapeutic decision-making across diverse patient populations.

Chapter 1

Introduction

General Introduction

Diabetes is a chronic condition with significant morbidity and mortality rates worldwide. Its prevalence is intricately linked to poor dietary habits, physical inactivity, alcohol consumption, smoking, genetic factors, and the increased life expectancy observed in recent decades [1–3]. According to the International Diabetes Federation (IDF), approximately 537 million adults (20–79 years) were living with diabetes in 2021, a figure projected to rise to 700 million by 2045 (Fig 1.1). Notably, underdiagnosis remains a significant issue, with data suggesting that one in three patients is not diagnosed. [4–6].

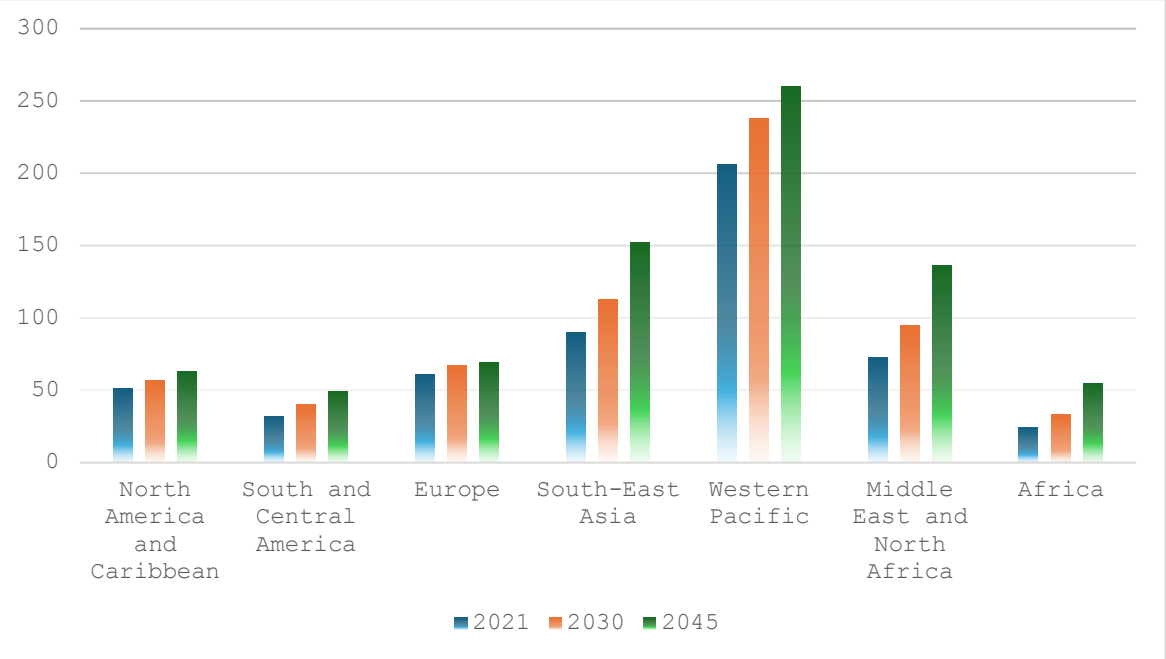

Figure 1.1. Number of people (millions) with diabetes worldwide and per IDF region in 2021, 2030 and 2045 (age 20–79 years). Source: IDF Diabetes Atlas Editions

Diabetes is multifactorial, complex, and heterogeneous, with its pathophysiology involving insulin resistance and hyperglycemia. These factors contribute to the dysfunction of various organs and systems. Among the types of diabetes, T2DM accounts for about 90% of cases [7–9]. T2DM is strongly associated with an increased risk of coronary heart disease, ischemic stroke, retinopathy, nephropathy, diabetic foot, and lower-limb amputations [10–12].

Despite substantial investments in clinical care and pharmaceutical research, the burden of diabetes continues to escalate. Contributing factors include global aging, rapid

urbanization, economic development, and dietary transitions toward high calorie, processed foods. Sedentary lifestyles further exacerbate the problem [1,13,14].

In response, innovative medications like SGLT2i and GLP1RA have been developed. These drug classes not only effectively manage blood glucose levels but also provide CV, renal, and weight-management benefits [15–21].

SGLT2i act by impeding renal glucose reabsorption and promoting urinary glucose excretion, through the inhibition of the glucose high-capacity transporter SGLT2 located in the proximal convoluted tubule. This distinctive mechanism of action operates independently of insulin and depends on blood glucose levels, concurrently enhancing sodium elimination [22–25]. Studies involving dapagliflozin and empagliflozin, have shown significant reductions in hospitalizations due to heart failure (HF), CV events, and mortality. As a consequence, the American College of Cardiology issued the "2020 Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with T2DM", specifically advocating for the use of SGLT2i in patients with or without T2DM, particularly those with HF and reduced ejection fraction (HFrEF) [26,27]. Likewise, DAPA-CKD and EMPA-KIDNEY studies have demonstrated the renal-protective effects of SGLT2i in patients with chronic kidney disease (CKD), regardless of T2DM status, reducing disease progression, prompting the American Diabetes Association and the Kidney Disease Improving Global Outcomes (KDIGO) to provide evidence-based recommendations for its use in CKD management [28–31].

Glucagon-like peptide-1 (GLP1) is an incretin hormone that acts by increasing endogenous insulin levels and decreasing glucagon secretion as a function of glucose levels [32,33]. GLP1RA are approved in the second-line treatment of poorly controlled T2DM and obesity (semaglutide, for example, has been approved by the U.S. Food and Drug Administration (FDA) for weight management and recently to reduce the risk of kidney disease worsening, kidney failure, and death from CV disease in adults with T2DM and CKD), allowing for better glycemic control, weight management, in addition to being associated with a cardioprotective effect [34–36]. Clinical trials are underway to evaluate the effect of semaglutide on the histological and metabolic aspects of non-alcoholic fatty liver disease (NAFLD) [36,37]. Previous studies examining the effects of GLP1RA on the lipid profile of T2DM patients indicated reductions in low-density lipoprotein (LDL) cholesterol, total cholesterol and triglycerides, without affecting high-density lipoprotein (HDL) cholesterol levels [38,39].

CV diseases constitute the leading cause of death in patients with T2DM, but most can be prevented through adopting a healthy lifestyle and using adjunctive medications, including antidiabetic agents [22,23]. Finding new therapeutic uses for existing drugs could lead to safe, affordable and timely new treatment options for most existing chronic diseases,

particularly in patients with multiple comorbidities [40]. Drug repositioning involves changing the indications of the drugs already being used or those in development for the treatment of other diseases or exploring the possibility of new disease treatments [41,42]. Based on the available evidence, after new studies and clinical trials, this was the principle that allowed SGLT2i and GLP1RA to be approved in new indications beyond T2DM treatment. On the one hand, repositioning presents undeniable advantages, expanding the spectrum of therapeutic action of existing drugs, but on the other, it leads to a significant increase in use, namely in different target populations, whose characteristics (such as average age, comorbidities and concomitant drugs, for example) may require a review of safety and effectiveness profiles, which comes to highlight the importance of real-world studies in this domain [43,44].

1.1. Sodium-glucose cotransporter 2 inhibitors

1.1.1. Contextualization and Physiology

Glucose serves as a primary energy source for most living cells, and its blood levels are regulated by insulin. Insulin facilitates glucose uptake in peripheral tissues and regulates glucose production in the liver. Due to its polar nature and large molecular size, glucose cannot pass through cell membranes via simple diffusion. Instead, specialized glucose transporters enable its movement through two primary mechanisms [45]: facilitated diffusion, mediated by the GLUT (glucose transporters) family of transporters, which equalize glucose concentrations across membranes, and active sodium-glucose cotransport, which moves glucose against its concentration gradient using sodium ions. The latter mechanism is facilitated by sodium-glucose cotransporters (SGLT) [46–49].

The GLUT family includes 14 members, each with distinct tissue distribution and kinetics, playing critical roles in glucose metabolism. In peripheral tissues such as skeletal muscle and adipose tissue, GLUT4 is pivotal for insulin-stimulated glucose uptake and homeostasis [50–54].

Within the SGLT family, six isoforms have been identified, with SGLT1 and SGLT2 being the most studied. SGLT1 is primarily located in the small intestine's apical membrane, where it absorbs dietary glucose and galactose. It is also expressed in the proximal renal tubules and cardiac myocytes [55,56]. Is a high-affinity and low-capacity glucose transporter with an apparent 2 Na+:1 sugar coupling stoichiometry [57,58]. In contrast, SGLT2, a low-affinity, high-capacity transporter, is localized in the S1 and S2 segments of the proximal renal tubule, reabsorbing approximately 90% of the filtered glucose load. The remaining 10% is absorbed by SGLT1 in the S3 segment [59–62].

Inhibiting SGLT2 selectively prevents glucose reabsorption in the kidney, increasing urinary glucose excretion. This mechanism forms the basis for SGLT2i, an innovative class of oral antidiabetic drugs designed to manage blood glucose levels effectively in patients with T2DM [62–64].

1.1.2. Mechanisms of action

The discovery of phlorizin, an O-glucoside dihydrochalcone, in 1835 marked the foundation for the development of SGLT2i. Phlorizin demonstrated the ability to block both SGLT1 and SGLT2 but was unsuitable as an antihyperglycemic drug due to its poor bioavailability and gastrointestinal side effects, such as diarrhea and malabsorption. This limitation, caused by its inhibition of SGLT1 in the small intestine, led to the development of phlorizin derivatives with greater selectivity for SGLT2, which effectively minimized these side effects [65–68].
SGLT2i are high-affinity, competitive blockers that act extracellularly in the presence of sodium. They inhibit glucose and sodium reabsorption in the renal proximal tubules, resulting in enhanced glycosuria and natriuresis. This mechanism works independently of insulin, making SGLT2i particularly effective in T2DM management [69–71].
Beyond glucose-lowering effects, SGLT2i have demonstrated significant CV and renal benefits. These include osmotic diuresis, reduced blood pressure through natriuresis, decreased arterial stiffness, and weight loss due to caloric loss from glycosuria. Furthermore, they reduce oxidative stress and uric acid levels, contributing to cardioprotection (Figure 1.2) [64,72–75].

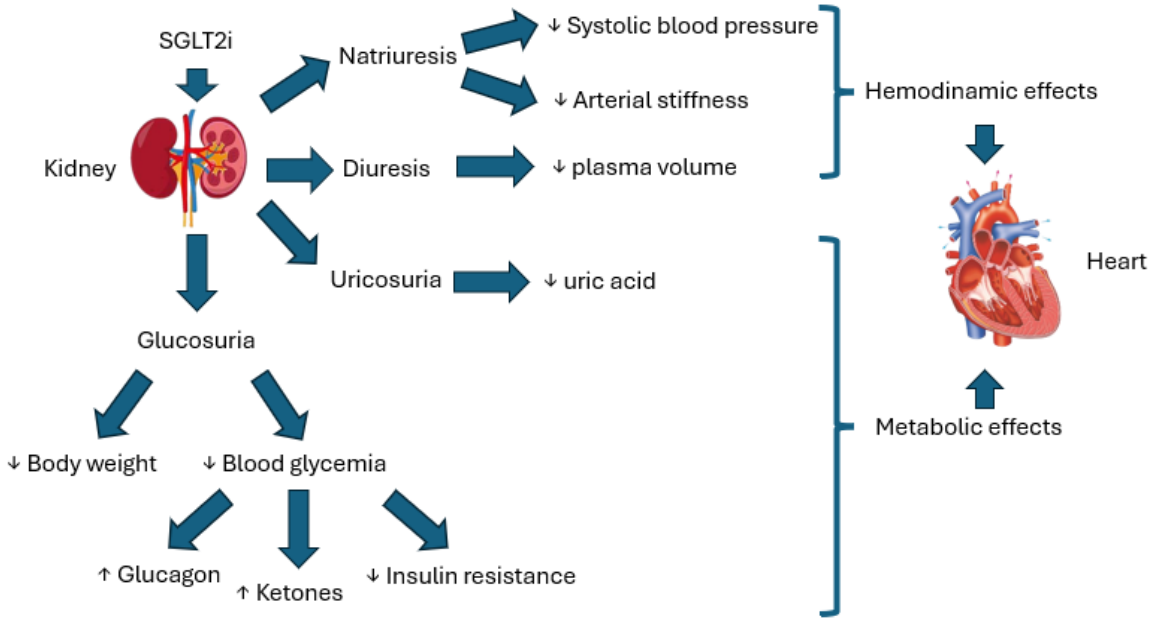

Figure 1.2. SGLT2i mechanisms of action and cardiovascular outcomes (Adapted from Scheen AJ. Cardiovascular Effects of New Oral Glucose-Lowering Agents: DPP-4 and SGLT-2 Inhibitors).

SGLT2i also impact the renal tubuloglomerular feedback (TGF) mechanism. By increasing glucose and sodium levels at the macula densa, SGLT2i promote the release of adenosine triphosphate (ATP) and adenosine, leading to afferent arteriole constriction and

a reduction in intraglomerular pressure. This process underpins the renoprotective effects observed in both diabetic and non-diabetic patients [75–77].

Additionally, SGLT2i influence myocardial metabolism. They increase the hepatic production of ketone bodies, regarded as "superfuels" for the failing heart, enhancing cardiac energy efficiency. This ketogenesis is driven by glycosuria-induced glucagon release and reduced insulin-to-glucagon ratios [76–78].

Overall, SGLT2i have expanded therapeutic applications, addressing hyperglycemia and offering substantial benefits in CV and renal health.

1.1.3. Characterization

The development of SGLT2i was propelled by the characterization of intestinal and renal SGLTs between 1987 and 1992. This discovery led to the creation of a new class of oral antidiabetic drugs [57,79–81]. Early studies by Tsujihara and colleagues evaluated phlorizin derivatives, such as the prodrug T-1095, which promoted renal glucose excretion in animal models [82,83]. These efforts culminated in the synthesis of high-affinity SGLT2i, including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, which received regulatory approval between 2013 and 2018 (Figure 1.3) [84–87].

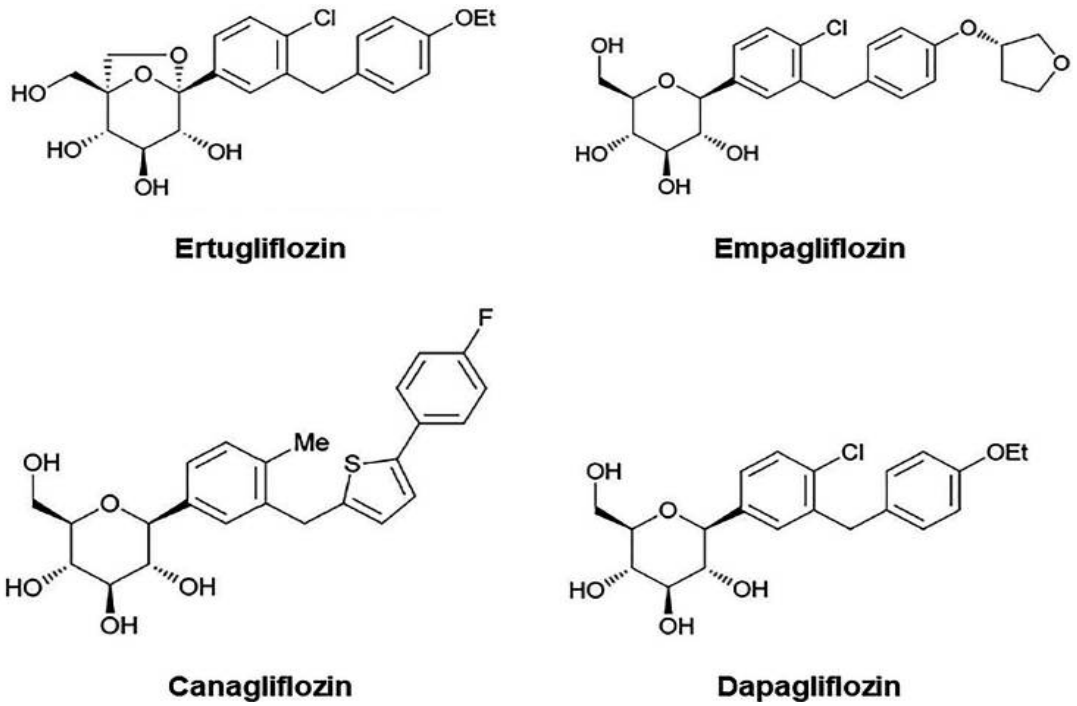

Figure 1.3. Chemical structure of ertugliflozin, empagliflozin, canagliflozin, and dapagliflozin

These agents selectively inhibit SGLT2, preventing the reabsorption of approximately 90% of the filtered glucose load in the kidneys. SGLT1 compensates by reabsorbing 30–40% of the glucose load, partially blunting the glucosuric effect. Despite this, SGLT2i have demonstrated significant clinical benefits [64].

Randomized clinical trials have provided robust evidence supporting their use in patients with T2DM at high CV risk. SGLT2i have been shown to reduce hospitalizations for HF, major adverse CV events (MACE), progression to end-stage renal disease, and CV mortality. These findings have established SGLT2i as a cornerstone in the management of T2DM, particularly in patients with comorbid CV or renal conditions [88,89].

SGLT2i differ in their selectivity for SGLT2 versus SGLT1, which influences their pharmacological profiles and clinical effects. For instance, empagliflozin demonstrates the

highest selectivity (approximately 2,680-fold) for SGLT2 compared to SGLT1, while canagliflozin exhibits weaker selectivity. These differences are reflected in their safety and effectiveness profiles (Table 1.1) [24,55,85,90,91].

Table 1.1. Differences between SGLTi in selectivity for SGLT2 vs. SGLT1 [68,92,93].

SGLT2i	IC50 for SGLT1 (nM)	IC50 for SGLT2 (nM)	Selectivity (SGLT2 vs SGLT1)
Canagliflozin	710	2.7	~260
Dapagliflozin	1,400	1.2	~1,200
Empagliflozin	8,300	3.1	~2,680
Ertugliflozin	1,960	0.87	~2,250

IC50 - Half-maximal inhibitory concentration

From a pharmacokinetic perspective, SGLT2i offer several advantages, including high oral bioavailability, long half-lives that allow for once-daily dosing, and minimal active metabolite excretion. These characteristics reduce the potential for drug-drug interactions and enhance patient compliance (Table 1.2) [24,94,95].

Table 1.2. Pharmacokinetic characteristics of SGLT2i [24,96,97].

	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Absorption	1-2 hours	2 hours	1.5 hour	1 hour
Bioavailability	65%	78%	78%	100%
Fraction bound to protein	99%	91%	86%	93.6%
Volume of distribution (L)	83.5	118	73.8	86
Half-life time (hours)	13.1	12.9	12.4	17
Metabolism	Glucuronidation			
Elimination route	52% feces 33% urine	21% feces 75% urine	41% feces 54% urine	41% feces 50% urine

In summary, the introduction of SGLT2i represents a significant advancement in T2DM therapy. Their effectiveness extends beyond glycemic control, offering substantial CV and renal benefits that have redefined therapeutic guidelines for managing atherosclerotic CV disease (ASCVD) and CKD.

1.1.3.1. Canagliflozin

Canagliflozin was the first SGLT2i approved by the FDA in March 2013. Its approval was based on results from the CANagliflozin Treatment and Trial Analysis (CANTATA) studies, which highlighted its ability to significantly reduce HbA1c levels [98–101]. It is indicated

for adult patients with T2DM to improve blood glucose control in combination with diet and exercise [102,103]. The CANVAS Program demonstrated that canagliflozin offers cardiometabolic benefits, including reduced CV events and improvements in HF and kidney disease outcomes. Phase II trials comparing canagliflozin to a placebo showed significant reductions in blood pressure, body weight, and progression of albuminuria [98,104].
Canagliflozin acts on both SGLT1 and SGLT2 receptors, with lower selectivity for SGLT2 compared to other drugs in this class (Table 1.1) [105,106]. It is available in oral formulations of 100 mg and 300 mg, as well as in combination with metformin. [107,108].

1.1.3.2. Dapagliflozin

Dapagliflozin is a potent, highly selective, reversible, and orally active SGLT2i, approved by the FDA in January 2014. Its approval was supported by 16 clinical trials involving over 9,400 patients with T2DM, demonstrating significant improvements in HbA1c levels. Dapagliflozin exhibits greater selectivity for SGLT2 over SGLT1 than canagliflozin, with a selectivity ratio approximately 1,200-fold higher (Table 1.1) [90,109–111].
Dapagliflozin is associated with substantial CV and renal benefits, including a reduced risk of CV death and hospitalization for HF [112,113]. Studies have shown its effectiveness in lowering the combined risk of worsening HF or CV death among patients with mildly reduced or preserved ejection fraction [113–115]. Furthermore, the DAPA-CKD trial demonstrated that dapagliflozin significantly reduced the risk of sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, or death from renal or CV causes, regardless of diabetes status [28,29].
Currently, dapagliflozin is available in 5 mg and 10 mg oral formulations, as well as combination therapies with metformin or saxagliptin [116–118].

1.1.3.3. Empagliflozin

Empagliflozin is an SGLT2i with the highest selectivity for SGLT2 compared to SGLT1 among its class, offering a selectivity ratio of approximately 2,680-fold higher. This property is particularly advantageous, as it minimizes the risk of SGLT1-associated adverse effects, such as diarrhea and dehydration, which can occur with intestinal glucose absorption inhibition [85,119].
The EMPA-KIDNEY study demonstrated that empagliflozin significantly reduced the risk of disease progression and death from renal or CV causes in patients with CKD, regardless of their T2DM status. Additionally, the EMPEROR-Preserved trial showed that

empagliflozin lowered the combined risk of CV death or hospitalization for HF in patients with HFrEF, irrespective of diabetes status [30,120].
A comparative cohort study using Scandinavian data revealed that empagliflozin and dapagliflozin have similar impacts on CV and renal outcomes, overall mortality, and diabetic ketoacidosis risk [121].
Empagliflozin is available in oral doses of 10 mg and 25 mg and in combination therapies with metformin or sitagliptin [122–124].

1.1.3.4. Ertugliflozin

A phase III clinical trial program (VERTIS) evaluated ertugliflozin efficacy and safety profile. When administered once daily in T2DM patients, either as monotherapy or associated with other antihyperglycemic agents, promoted significant reductions in HbA1c, body weight, and blood pressure, with a favorable safety and tolerability profile [125–128].
Ertugliflozin is a less specific inhibitor of SGLT2 receptors compared to empagliflozin (Fig. 1.2), having a longer half-life and a shorter peak onset of action, resulting in sustained and rapid blood glucose-lowering effects (Table 1.2) [96,129].
The long-term effects of ertugliflozin on CV and renal outcomes were assessed in the Evaluation of Ertugliflozin Efficacy and Safety CV Outcomes Trial (VERTIS CV), with non-superiority of placebo [130]. Ertugliflozin is a relatively recent SGLT2i, so further studies will be needed to determine its real safety and effectiveness profile, particularly in cardiorenal outcomes compared to other SGLT2i.
Ertugliflozin is available in doses of 5 and 10 mg, as well as in combination with metformin or sitagliptin [131–133].

1.1.4. Approved Clinical Indications

Initially developed as anti-hyperglycemic agents, SGLT2i have emerged as critical treatments for HF across the entire spectrum of left ventricular ejection fraction and for slowing the progression of CKD. While the cardiorenal protective effects of SGLT2i are recognized as a class-wide benefit, some differences exist among individual agents [134]. Studies suggest that dapagliflozin may exhibit superior efficacy compared to empagliflozin, canagliflozin, and ertugliflozin in HF patients [135,136]. However, no significant differences in efficacy have been observed among these agents in CKD patients. In populations without CKD, empagliflozin has been associated with a lower risk of CV outcomes than other SGLT2i [136]. Regarding glycemic control, indirect comparisons indicate that ertugliflozin (5 mg) may reduce HbA1c more effectively than dapagliflozin (5 mg) when added to metformin monotherapy. Higher doses of ertugliflozin (15 mg) have outperformed dapagliflozin (10 mg) and empagliflozin (25 mg) in HbA1c reduction when used with diet and exercise or metformin. However, its efficacy was comparable to canagliflozin across all populations [137,138].

Randomized clinical trials have solidified the role of SGLT2i in reducing adverse outcomes in T2DM, HF, and CKD. Notable examples include the EMPA-REG OUTCOME study for empagliflozin, the CANVAS Program for canagliflozin, the DECLARE-TIMI 58 study for dapagliflozin, and the VERTIS CV study for ertugliflozin. These trials have demonstrated significant reductions in MACE, hospitalizations for HF, progression to end-stage kidney disease, and CV mortality (Table 1.3).

International guidelines now recommend SGLT2i as a first-line therapy in T2DM patients at risk of CV or renal events. Furthermore, regulatory approvals have expanded their indications. Dapagliflozin was the first SGLT2i approved for HFrEF in 2020, followed by empagliflozin in 2021. Additionally, canagliflozin, dapagliflozin, and empagliflozin have been approved for CKD management in patients with or without T2DM [127–129,134–136,147–149].

By offering benefits beyond glycemic control, SGLT2i have redefined the management of cardiometabolic diseases, addressing unmet needs in CV and renal protection. Their multifaceted mechanism of action, including natriuretic, hemodynamic, and metabolic effects, further supports their therapeutic relevance in patients with complex comorbidity profiles.

Table1.3. Key cardiovascular and renal outcomes (relative risk reduction) from large-scale SGLT2i randomized studies. [75,112,114,120,130,139–145,145,146].

Study	MACE	CV death	Hospitalization for Heart Failure	Renal endpoint	All-cause mortality
Canvas Program Canagliflozin	↓14%	↓13%	↓33%	↓40%	↓13%
Declare-Timi 58 Dapagliflozin	↓7%	↓2%	↓27%	↓47%	↓7%
EMPA-REG OUTCOME Empagliflozin	↓14%	↓38%	↓35%	↓46%	↓32%
VERTIS-CV Ertugliflozin	↓3%	↓8%	↓30%	↓19%	↓7%
CREDENCE Canagliflozin	↓20%	↓22%	↓39%	↓34%	↓17%
DAPA-CKD Dapagliflozin		↓19%		↓39%	↓31%
SCORED Sotagliflozin	↓33%	↓10%	↓33%	↓29%	↓1%
DAPA-HF Dapagliflozin		↓18%	↓30%	↓29%	↓17%
EMPEROR-reduced Empagliflozin		↓8%	↓31%	↓50%	↓8%
EMPEROR-preserved Empagliflozin		↓9%	↓27%	↓5%	=
SOLOIST-WHF Sotagliflozin	↓28%	↓16%	↓36%	↓	↓18%

Statistically significant relative reduction reported

.

1.1.5. Adverse Drug Reactions

Major clinical trials evaluating SGLT2i have demonstrated their generally favorable safety profiles, with overall ADR rates lower than those of placebo groups [75,114,139]. This safety is attributed to the specific localization of SGLT2 in the renal proximal tubule and, to a lesser extent, in the heart [86,150].

Hypoglycemia is uncommon with SGLT2i due to their glucose-dependent mechanism of action, which reduces urinary glucose excretion as blood glucose levels normalize [150]. However, the glycosuric effect of SGLT2i can predispose patients to specific ADRs [151,152]. The most frequently reported include:

- Genitourinary tract infections (GTIs): Increased glycosuria enhances the risk of genital mycotic infections and urinary tract infections (UTIs), particularly in female patients. Despite some variability in study results, GTIs remain the most common complication associated with SGLT2i use [75,114,139].
- Volume depletion-related symptoms: Increased urinary frequency and nocturia are commonly reported, although significant dehydration is rare [72,153–156].
- Electrolyte imbalances: SGLT2i may heighten susceptibility to conditions such as hyponatremia and hyperkalemia, especially in patients with CKD or those taking angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) [157–160].
- Initial declines in eGFR: A temporary reduction in eGFR is often observed within the first two to four weeks of treatment, followed by partial recovery over time [161,162]. Clinicians are advised to monitor renal function but not discontinue treatment unless the decline is clinically significant [26,163,164].

Comparative safety analyses among SGLT2i have revealed differences in ADR profiles. Dapagliflozin and empagliflozin have been linked to a higher incidence of GTIs and urinary frequency, while no significant differences have been observed for severe ADRs, such as diabetic ketoacidosis, amputation, or severe hypoglycemia [125,165–173].

Figure 1.4 compares SGLT2i safety profile using data from ICSRs reported in EV database from January to December, 2023. The ADRs included, by System Organ Classes (SOC), are UTIs, pollakiuria, GTIs, and AKI.

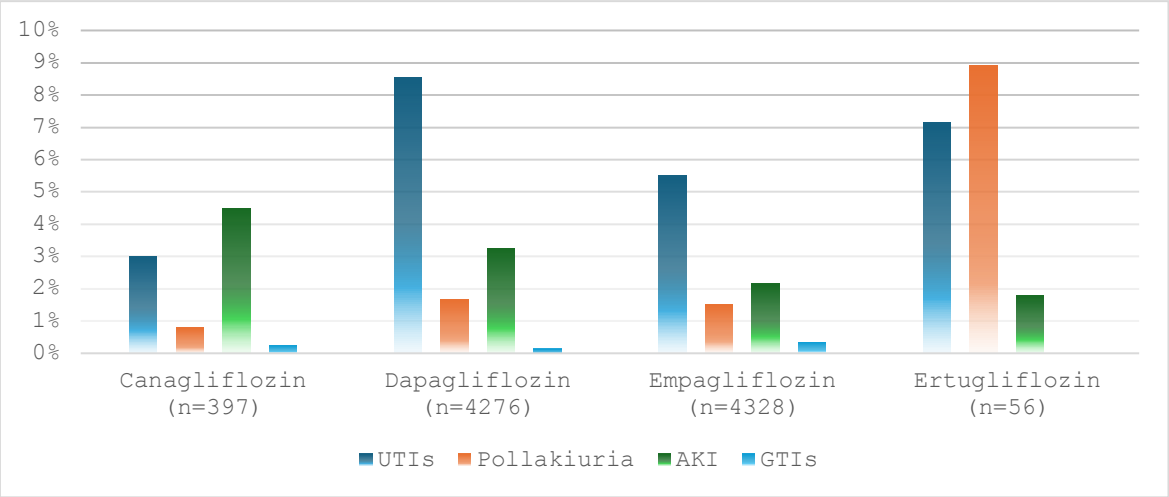

Figure 1.4. ADRs reported for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin by SOC, reported in EV database from January to December, 2023.

Real-world studies are increasingly essential in defining the safety profile of SGLT2i, especially in older adults and patients with polypharmacy. Such data will provide critical insights for optimizing treatment in diverse patient groups.

1.2. Glucagon-like peptide-1 receptor agonists

1.2.1. Contextualization and Physiology

Glucagon-like peptide-1 receptors (GLP1R) belong to the family of G protein-coupled receptors (GPCRs), which are integral to numerous physiological processes and represent key targets for many drugs. These receptors are expressed on various cell types and are widely distributed across multiple organs and tissues. By binding to the hormone GLP1, GLP1R plays a crucial role in regulating blood glucose levels and lipid metabolism [174–179].

GLP1 enhances glucose homeostasis by stimulating insulin secretion, reducing glucagon release, and promoting weight loss through increased satiety. Knockout studies have shown that GLP1R disruption leads to pancreatic dysfunction, hormonal imbalances, and impaired glucose regulation [176,180].

Incretin hormones, including GLP1 and glucose-dependent insulinotropic polypeptide (GIP), mediate the body's insulin response to nutrient intake. These gut-derived peptides are released in response to carbohydrate, fat, and protein ingestion, amplifying insulin secretion from pancreatic β-cells. However, GIP alone has limited therapeutic potential in T2DM, as its insulinotropic effect is reduced in these patients. Conversely, GLP1 exhibits strong and consistent effects on glucose-dependent insulin secretion and is a key target for T2DM treatment [181–188]. Table 1.4 summarizes some differences between GLP1 and GIP mechanisms of action.

Table 1.4. GIP vs GLP1 effects at the organ/tissue level [189,190].

		GLP1	**GIP**
Central Nervous System	Caloric intake	↓↓	↓
Heart	Heart rate	↑	↑
Pancreas	Insulin secretion	↑↑	↑↑
	Glucagon secretion	↓↓	↑
Stomach and Gut	Gastric emptying	↓↓	↔
	Chylomicron production	↓	
Adipose tissue		↔	Glucose and Triglycerides uptake ↑↑
			Triglycerides storage ↑↑
Kidneys	Sodium excretion (transient)	↓	↔
Bones	Meal-associated bone remodeling	↑	↑↑
		Indirect effects: ↑insulin ↓glucagon	**Indirect effects: ↑insulin ↑glucagon**
Liver		Glucose uptake, glycogen↑ Hepatic glucose production↓ Intrahepatic fat↓	Glucose uptake, glycogen↑ Hepatic glucose production↓

GLP1 secretion is transient due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP4), which reduces its half-life to less than two minutes. This short half-life has necessitated the development of GLP1RA, which mimic the effects of native GLP1 while resisting DPP4 degradation [184,190].

The effects of GLP1 extend beyond glycemic control, encompassing delayed gastric emptying, suppression of pancreatic α-cell glucagon secretion, and reduction of β-cell apoptosis. GLP1 also promotes neurohormonal changes that reduce food intake, further contributing to weight loss [191,192].

In summary, GLP1 and its receptor are central to glucose regulation and metabolic health. The therapeutic development of GLP1RA has transformed T2DM management, offering glycemic control with additional benefits in weight management and CV protection.

1.2.2. Mechanism of action

GLP1 is an incretin hormone primarily secreted by L-cells in the intestinal mucosa, α-cells in the pancreatic islets, and neurons in the nucleus of the solitary tract. GLP1 plays a key role in glucose homeostasis, enhancing insulin secretion in response to oral glucose intake. However, its biological activity is short-lived, as DPP4 rapidly degrades GLP1 within 1–2 minutes of its release [193–195].

GLP1RA are synthetic analogs of GLP1, designed with structural modifications to resist DPP4 degradation and prolong their half-life [196,197]. By mimicking GLP1's biological activity, GLP1RA effectively lower blood glucose levels without increasing the risk of hypoglycemia, as their action is glucose-dependent [177].

Mechanistically, GLP1RA bind to GLP1R on pancreatic β-cells, stimulating intracellular AMP (cyclic-3'5' -adenosine monophosphate) production. This leads to enhanced glucose-dependent insulin release, suppression of glucagon secretion from α-cells, and improved glycemic control [198].

The pharmacological effects of GLP1RA extend beyond the pancreas. They delay gastric emptying, reduce food intake through satiety-promoting effects in the hypothalamus, and decrease β-cell apoptosis while promoting β-cell proliferation. Additionally, GLP1RA improve CV and renal outcomes, as demonstrated in numerous clinical trials (Figure 1.5) [21,199–204].

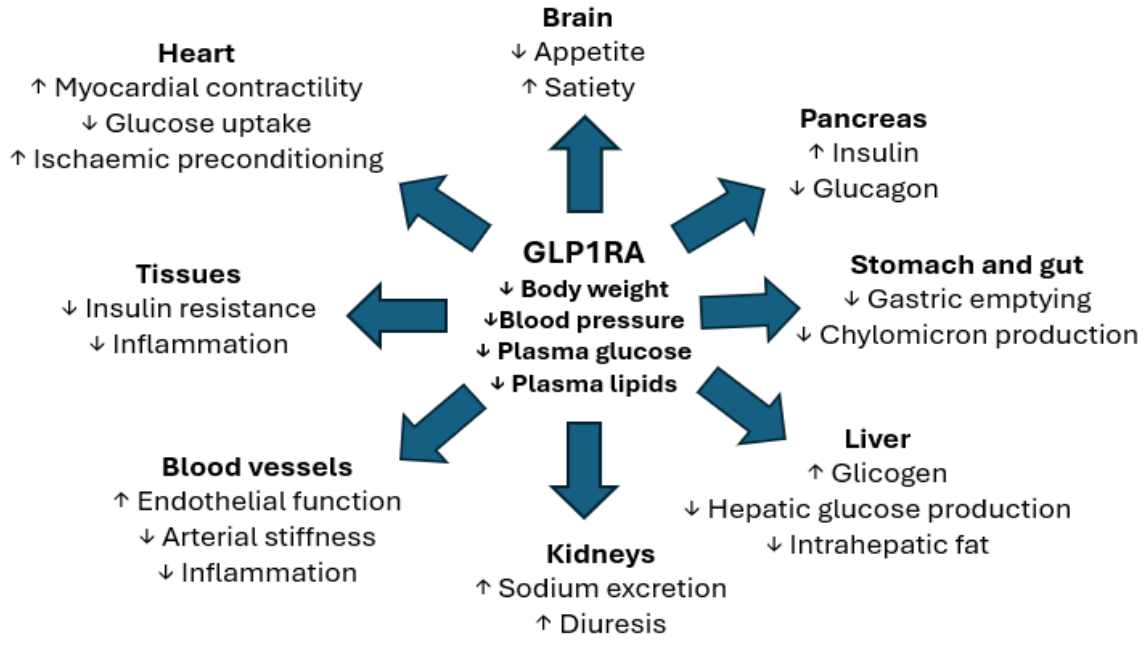

Figure 1.5. GLP1RA mechanisms in different organs and tissues.

Recent studies have shown that GLP1RA exert cardioprotective effects, reducing the risks of myocardial infarction, stroke, CV death, and overall mortality in patients with T2DM.

These benefits are attributed to their ability to reduce oxidative stress, inflammation, and fibrosis while promoting natriuresis [205–210].

In NAFLD, GLP1RA improve hepatic outcomes by increasing adiponectin levels, reducing hepatic fat accumulation, and inhibiting hepatocyte apoptosis caused by endoplasmic reticulum stress (Figure 1.6) [211–214].

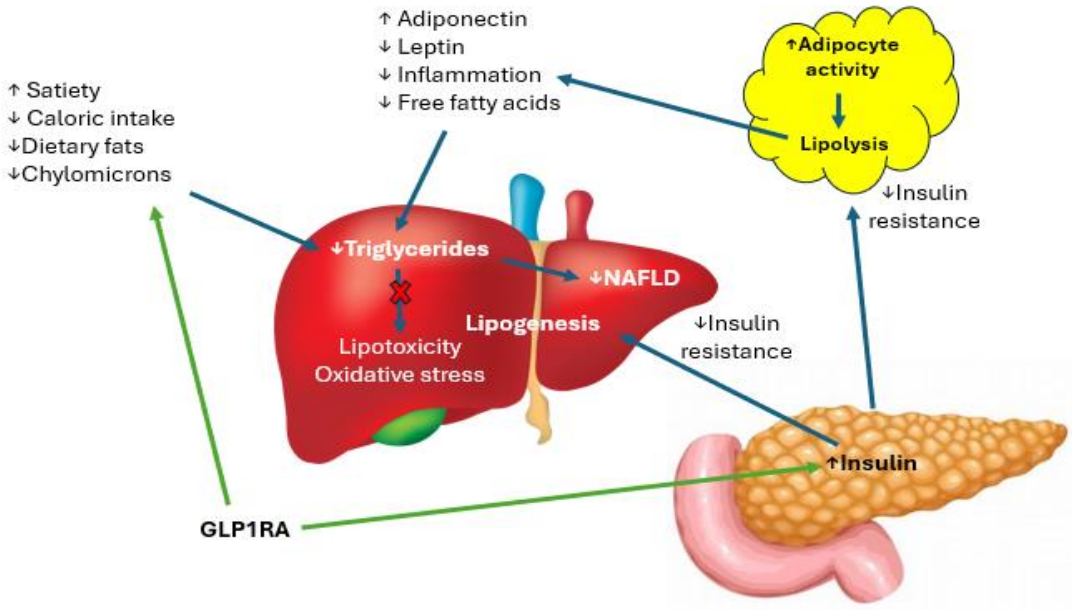

Figure 1.6. Potential targets of GLP1RA in the treatment of NAFLD (Adapted from Seghieri M, Christensen AS, Andersen A, Solini A, Knop FK, Vilsbøll T. Future Perspectives on GLP-1 Receptor Agonists and GLP-1/glucagon Receptor Co-agonists in the Treatment of NAFLD).

By targeting multiple organs and pathways, GLP1RA provide comprehensive metabolic benefits, addressing both glycemic control and associated cardiometabolic risks in T2DM patients.

1.2.3. Characterization

The development of GLP1RA began with the discovery of exenatide in 1992, an analog sharing 53% homology with human GLP1. Unlike native GLP1, exenatide resists degradation by DPP4 and remains active for approximately 12 hours. It was approved for T2DM treatment in 2005, marking the advent of GLP1RA-based therapies [215,216].
Subsequent research focused on creating analogs with greater homology to human GLP1 and extended durations of action. This led to the development of long-acting agents, such as liraglutide, dulaglutide, and semaglutide, as well as the dual GIP/GLP1 receptor agonist tirzepatide (Table 1.5). These agents offer improved glycemic control and additional benefits like weight loss and cardioprotection [217–220].

Table 1.5. Characteristics of Liraglutide, Dulaglutide, Semaglutide, and Tirzepatide [221–225].

GLP1RA	Administration route	Half-life	Dosage and frequency
Liraglutide	Subcutaneous	11-13 hours	0.6 than 1.2 mg daily (maximum dose of 1.8 mg)
Dulaglutide	Subcutaneous	108-112 hours	0.75 or 1.5 mg weekly (maximum dose of 4.5 mg)
Semaglutide	Subcutaneous	6-7 days	0.25 than 0.5 or 1 mg weekly (maximum dose of 2.4 mg)
	Oral	24 hours	3 than 7 or 14 mg daily
Tirzepatide	Subcutaneous	5 days	2.5 than 5mg weekly (maximum dose of 15 mg)

Long-acting GLP1RA generally demonstrate superior glycemic control compared to short-acting agents. Semaglutide, for instance, has a considerably longer half-life, allowing for once-weekly dosing, while its oral formulation provides an alternative to subcutaneous administration. Tirzepatide, approved in 2022, combines GIP and GLP1 receptor agonism, achieving greater reductions in HbA1c and body weight compared to other GLP1RA [192,226–228].
The choice of GLP1RA depends on patient-specific factors, such as dosing preferences, tolerability, and treatment goals. While short-acting agents are primarily used for glycemic control, long-acting GLP1RA also address obesity, CV risk, and renal protection [196,229–231].

1.3.3.1. Liraglutide

Liraglutide shares 97% structural similarity with human GLP1 and is approved for the treatment of T2DM at doses of up to 1.8 mg daily. It is also approved for weight management at a higher dose of 3 mg daily. Its effects are primarily mediated by activation of GLP1R in the hypothalamus, promoting satiety and reducing caloric intake [232–235].

In addition to reducing fasting glucose levels and HbA1c, liraglutide has demonstrated benefits in addressing cardiometabolic risk factors. These include reductions in waist circumference, blood pressure, and inflammatory markers. Modest improvements in fasting lipid levels have also been observed, although their clinical significance remains uncertain [236–238].
Liraglutide's dual role in glycemic control and weight management, coupled with its safety profile, has established it as a versatile agent for managing T2DM and associated comorbidities.

1.3.3.2. Dulaglutide

Dulaglutide is a long-acting GLP1RA approved for once-weekly subcutaneous administration in patients with T2DM. It is indicated as monotherapy for patients who cannot tolerate or have contraindications to metformin, or as an add-on therapy when other glucose-lowering medications, including insulin, fail to achieve adequate glycemic control [239].
Clinical trials and real-world studies have demonstrated that dulaglutide offers effective glycemic control. It has been shown to outperform liraglutide in improving HbA1c levels in some patient populations. Furthermore, dulaglutide's weekly dosing schedule enhances patient convenience and adherence compared to daily GLP1RA options [240–242].
Dulaglutide's safety profile and efficacy make it a valuable option for both initial and combination therapy in T2DM management.

1.3.3.3. Semaglutide

Semaglutide is a long-acting GLP1RA with a significantly extended half-life, allowing for once-weekly subcutaneous administration. It is approved for T2DM treatment and, more recently, has also been authorized by FDA to reduce the risk of MACE in adults with established CV disease and either obesity or overweight, to reduce excess body weight and maintain weight reduction long term, regardless of diabetes status, and to reduce the risk of sustained eGFR decline, end-stage kidney disease and CV death in adults with T2DM and CKD (Table 1.5) [243–248].
Compared to liraglutide, semaglutide demonstrates superior efficacy in HbA1c reduction and weight loss. Clinical trials have shown its efficacy in reducing the risk of clinically significant kidney outcomes and CV events in patients with T2DM and CKD [249–251].
In 2019, an oral formulation of semaglutide was introduced, providing a convenient alternative to subcutaneous injections. This formulation includes sodium N-(8-[2-

hydroxybenzoyl]amino) caprylate (SNAC), which enhances gastric absorption and protects the peptide from enzymatic degradation in the gastrointestinal tract [252].
Overall, semaglutide represents a versatile and effective treatment option for managing T2DM, obesity, and associated complications, with its multiple administration routes enhancing patient accessibility and adherence.

1.3.3.4. Tirzepatide

Tirzepatide is a dual agonist of GIP and GLP1 receptors. Engineered from the native GIP sequence, tirzepatide exhibits equivalent affinity for GIP receptors and approximately five times weaker affinity for GLP1R compared to native GLP1 [253,254]. This dual mechanism of action results in substantial reductions in HbA1c levels and body weight, outperforming other GLP1RA in clinical trials. The SURPASS trial program established tirzepatide as a highly effective agent for glycemic control and weight management, which led to its approval for T2DM treatment in 2022 [227,255–258].
Tirzepatide has also demonstrated significant benefits in reducing the risk of all-cause mortality, MACE, AKI, and negative kidney outcomes in T2DM patients when compared to other GLP1RA. Its unique dual agonist action provides synergistic effects, enhancing its therapeutic potential in metabolic diseases [259–261].
Tirzepatide is administered subcutaneously once weekly, with an initial dose of 2.5 mg titrated up to a maximum of 15 mg, based on patient tolerability and treatment goals (Table 1.5).

1.3.4. Approved Clinical Indications

Initially developed to improve glycemic control, GLP1RA have emerged as key therapies for CV risk reduction in patients with T2DM. While these agents are recognized for their beneficial effects on glycemic control, their ability to reduce MACE has become a cornerstone of their clinical utility in T2DM management. Notably, these agents have been shown to reduce the incidence of MACE in patients with T2DM, a population at high risk for CV complications, which remain the leading cause of death in this group (Table 1.6) [262].

Table 1.6. GLP1RA outcomes in patients with or at high risk for CV disease [33,204,259,263–273].

	HbA1C decrease	CV outcomes ASCVD/HF	Nephropathy	CV/Overall mortality
Liraglutide	-0.8 to -1.5	Benefit/Neutral	Benefit	Benefit/Benefit
Dulaglutide	-1 to -1.5	Benefit/Neutral	Benefit	Benefit/Benefit
Semaglutide (SC)	-1.5 to -2	Benefit/Benefit	Benefit	Benefit/Benefit
Semaglutide (oral)	-0.7 to -2	Neutral/?	Benefit	Benefit/Benefit
Tirzepatide	-2 to -2.5	Benefit/Benefit	Benefit	Benefit/Benefit

The American Diabetes Association, the American Association of Clinical Endocrinology, and other professional organizations have updated their clinical practice guidelines to recommend GLP1RA for T2DM patients with established CV disease, irrespective of HbA1c levels, and have even suggested them as a first-line treatment option for certain individuals. GLP1RA CV outcome trials, such as LEADER, REWIND, and SUSTAIN-6, have demonstrated significant reductions in MACE, highlighting the CV benefits of this class, particularly in those with or at risk for ASCVD (Table 1.6) [263,264].

The SURPASS program on tirzepatide further supports these findings, with pooled analyses from trials like SURPASS-1, -2, -3, and -4 providing additional evidence of the agents' efficacy in reducing CV events in patients with T2DM. These studies solidify the role of GLP1RA in managing both glycemic control and CV risk in T2DM patients (Table 1.6) [274].

The expanding use of GLP1RA for chronic weight management in individuals without diabetes has also drawn attention to their potential CV benefits in this population. The SELECT trial demonstrated that semaglutide 2.4 mg, when used in patients with ASCVD but without diabetes, led to a 20% relative risk reduction in MACE and a 19% relative risk reduction in all-cause mortality over a mean follow-up of 3.3 years. As a result, the FDA approved semaglutide for reducing CV events in individuals with CV disease and overweight or obesity in March 2024 [248,275,276].

Recent regulatory approvals of semaglutide for CKD and metabolic-associated steatohepatitis (MASH) have been catalyzed by pivotal data from the FLOW and ESSENCE trials, respectively. In FLOW, a phase 3b, randomized, double-blind study in patients with T2DM and CKD, weekly semaglutide (1.0 mg) reduced the composite risk of ≥50% decline in eGFR, kidney failure or death from renal or CV causes by ~24% versus placebo. Likewise, the ESSENCE trial, showed that once-daily subcutaneous semaglutide achieved MASH resolution without fibrosis worsening in up to 59% of patients (0.4 mg arm) versus 17% in placebo. These trials support the emerging role of GLP1RA as disease-modifying therapies in renal and hepatic metabolic pathologies [277-280].

Beyond weight reduction and glucose modulation, GLP1RA exert anti-inflammatory, anti-fibrotic, and cardiometabolic benefits, supporting their expanding role in multisystem metabolic disorders. Collectively, these approvals underscore the growing recognition of GLP1RA as disease-modifying therapies across diverse metabolic and renal pathologies.

1.3.5. Adverse Drug Reactions

The most commonly reported adverse effects associated with GLP1RA are upper gastrointestinal symptoms, including diarrhea, nausea, and vomiting [250,281–283]. These gastrointestinal adverse events appear to be dose-dependent and likely represent a class-wide effect [191,192]. They are typically transient, mild to moderate in severity, and tend to occur primarily during the initiation and dose-escalation phases of treatment. In contrast, constipation may persist longer than other gastrointestinal side effects, reflecting the more chronic nature of this condition [246,284].

The exact cause of gastrointestinal ADRs associated with GLP1RA remains unclear, with multiple factors likely contributing, depending on both the drug and patient characteristics. One potential factor is the duration of action of the GLP1RA. Short-acting agents, which are currently used only for the treatment of T2DM, are often linked to a higher incidence of nausea and vomiting, while longer-acting agents, used for both T2DM and weight management, tend to cause more diarrhea [285,286]. Nausea is thought to arise from direct effects on the central nervous system, mediated by GLP1R in the area postrema, a medullary structure in the brain that controls vomiting [287]. Additionally, gastrointestinal effects such as delayed gastric emptying and alterations in intestinal motility and transit time may contribute to the development of these side effects [192,286,288].

Figure 1.7 compares the main GLP1RA gastrointestinal ADRs reported in the EV database from January to December 2023.

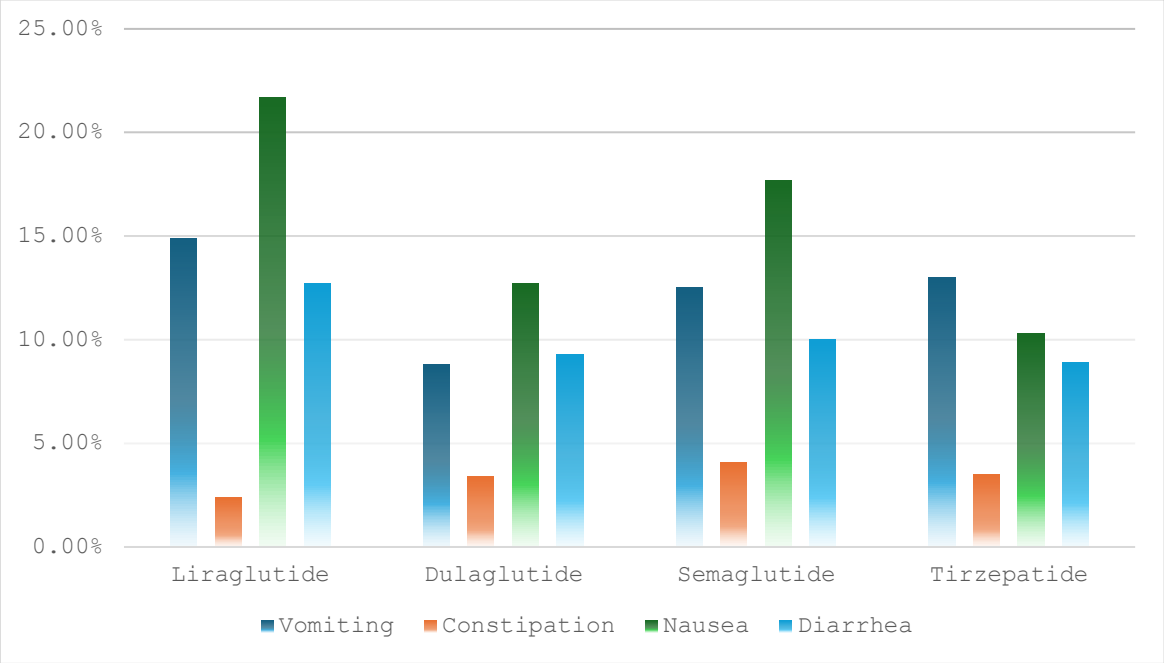

Figure 1.7. ADRs reported for liraglutide, dulaglutide, semaglutide (sc), and tirzepatide by SOC, reported in EV database from January to December, 2023.

The ADRs, categorized by SOC, include vomiting, constipation, nausea, and diarrhea. The safety and tolerability of oral semaglutide are comparable to those of the subcutaneous formulations. A phase 2 study found that patients who began treatment with a low dose of oral semaglutide experienced fewer instances of nausea, while the frequency of gastrointestinal ADRs was highest during the dose-escalation phase [252,289,290]. This highlights the importance of careful dose escalation when initiating semaglutide therapy.
Real-world studies report a variable incidence of gastrointestinal side effects, with some showing rates similar to those in clinical trials, while others indicate lower rates. Despite this variability, gastrointestinal ADRs remain the most common reason for patient discontinuation of treatment [291–293]. More long-term real-world studies are needed to better understand the full safety profile of GLP1RA.

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Chapter 2

Thesis Objectives and Overall Structure

This dissertation aims to evaluate the safety and effectiveness profiles of SGLT2i and GLP1RA using real-world patient data. To accomplish this, retrospective studies were conducted, focusing on three key levels of hospital care: emergency department visits, hospitalizations, and outpatient consultations. Additionally, safety data for the drugs under investigation, sourced from the EV database, were incorporated to enhance the analysis (Fig. 2.1).

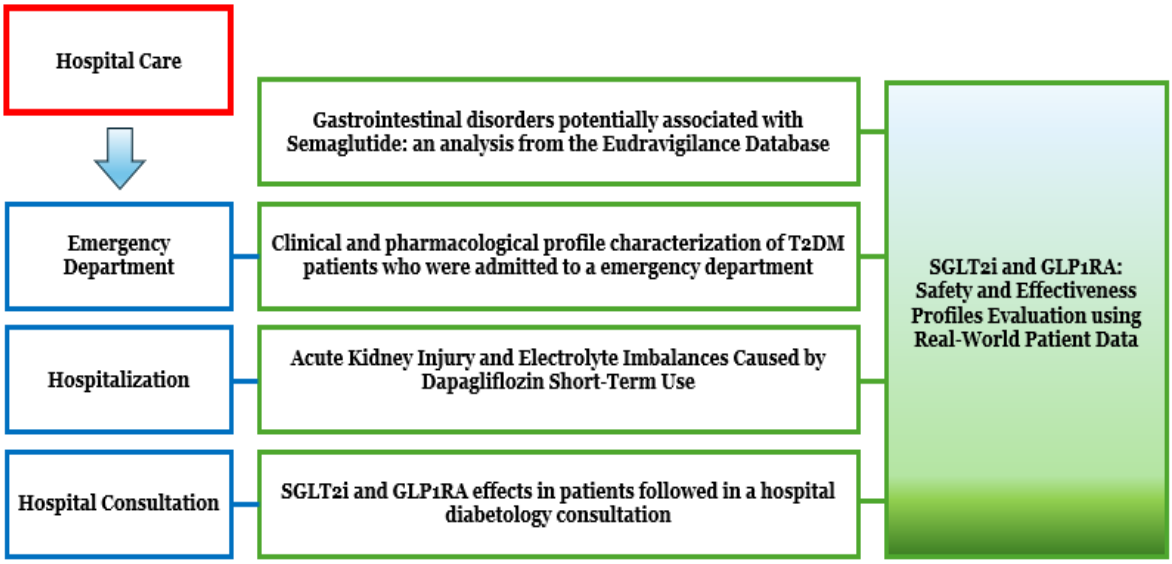

Figure 2.1. General Organization of the Thesis

2.1. Semaglutide Safety Profile: an analysis from the EudraVigilance Database

Studies utilizing EV ICSRs are crucial for understanding the safety profiles of drugs and ensuring patient safety in clinical practice. ICSRs provide real-world data that help identify potential ADRs that may not have been detected during clinical trials. They include detailed information about the nature of suspected adverse reactions, patient demographics, drug dosing, and other relevant factors, such as concomitant medications and underlying conditions. This comprehensive data allows for a thorough evaluation of drug-related risks [1,2].

GLP1RA belong to a class of drugs not currently included in the hospital formulary. The aim of the study titled "*Gastrointestinal Disorders Potentially Associated with Semaglutide: An Analysis from the Eudravigilance Database*" was to evaluate the safety profile of semaglutide, offering valuable insights that could not be obtained from data on hospitalized patients.

2.2. SGLT2i and GLP1RA Safety and effectiveness Profile: retrospective studies conducted within the context of hospital healthcare

2.2.1. Emergency Department Care

The Emergency Department serves as the point of entry for patients experiencing acute medical conditions that require immediate attention. Retrospective studies, which analyze pharmacological profiles at the time of patient admission, can provide valuable insights into the interactions between pre-existing treatments and the patient's current condition:

- **Medication-Related Issues:** identification of medication errors, drug-drug interactions, or ADRs that may have contributed to the patient's condition or prolonged recovery.
- **Multiple concomitant drugs:** mainly older adults are admitted to the Emergency Department with complex therapeutic regimens, which increases the risk of ADRs, drug-drug interactions, and contraindications. Retrospective analyses are helpful to identify common patterns of polypharmacy and guide strategies to reduce medication-related complications.
- **Assessing drug appropriateness at admission:** It also enables the evaluation of whether patients are receiving appropriate medications for their conditions upon Emergency Department admission.

The study "*Clinical and Pharmacotherapeutic Profile of Patients with Type 2 Diabetes Mellitus Admitted to a Hospital Emergency Department*" aimed to characterize the clinical and pharmacological profile of T2DM patients admitted to the emergency department of the Local Health Unit of Guarda (LHUG), identifying how their clinical condition, on admission, can be influenced by pre-existing comorbidities and by antidiabetic drugs previously used.

2.2.2. Hospitalization (Inpatient Care)

Retrospective studies are valuable for assessing drug effects in hospitalized patients, as they provide insights into how these drugs influence patient outcomes based on historical data. These studies are especially useful for evaluating the real-world impact of drugs, identifying potential ADRs, and determining treatment effectiveness in specific patient populations:

- To evaluate drug safety and effectiveness profile when used in routine clinical practice. In clinical trials, patient populations are often more homogenous and monitored in controlled environments. Hospitalized patients are generally older,

with multiple comorbidities, and may be on multiple concomitant drugs, which reflects the diversity seen in everyday medical practice.

- To analyze drug performance in different subgroups of hospitalized patients (e.g., those with diabetes, renal failure, or heart disease), identifying whether the drug's effectiveness varies depending on comorbidities or age.
- Helping to identify ADRs that are seen more frequently in hospital settings, where drugs may be used in combination or in patients with underlying health issues.

The study "*Short-term effect of dapagliflozin on renal function and electrolyte balance*" aimed to assess the short-term effects of dapagliflozin on renal function and electrolyte balance in hospitalized patients (LHUG and Local Health Unit of Cova da Beira (LHUCB)) after drug initiation, comparing results to ADRs profiles reported in the EV database.

2.2.3. Hospital Consultation (Specialist Care)

Hospital consultation involves expert input from clinicians for medical conditions that cannot be fully managed by primary care. Retrospective studies are crucial for assessing drug effects in patients undergoing hospital consultations, as they provide valuable real-world data on:

- Drug effectiveness and safety profiles in complex, multi-comorbidity patient populations;
- Identification of ADRs and drug-drug interactions that may be missed in clinical trials;
- Optimizing monitoring strategies and developing more personalized treatment plans for hospitalized patients;
- Assessing the cost-effectiveness of specialized medications and their impact on health system resources.

The study "*SGLT2i and GLP1RA effects in patients followed in a hospital diabetology consultation*" aimed to evaluate the real-world effectiveness of SGLT2i and GLP1RA in a cohort of patients with T2DM followed in a hospital diabetology consultation (LHUG).

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Chapter 3

Gastrointestinal disorders potentially associated with Semaglutide: an analysis from the Eudravigilance Database

3.1. Introduction

GLP1 is an incretin hormone that enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby contributing to physiologic glycemic regulation. GLP1 RA exploit these mechanisms to improve glycemic control in T2DM and are recommended as second-line therapy, either as monotherapy or in combination with other antidiabetic agents or insulin, particularly in patients requiring additional metabolic or cardiometabolic benefit. Beyond their glucose-lowering effects, GLP1RA promote clinically meaningful weight loss and confer CV protection, supporting their approval for both T2DM and obesity management [1-3].

Semaglutide, a long-acting GLP1RA available in weekly injectable and daily oral formulations, has demonstrated robust efficacy and safety. Despite these benefits, GLP1RA are associated with gastrointestinal adverse events and a potential transient worsening of diabetic retinopathy, underscoring the relevance of ongoing pharmacovigilance [4,5].

This study aims to characterize the safety profile of semaglutide by analyzing suspected ADRs reported in the EV database.

3.2. Materials and Methods

3.2.1. Evaluation of semaglutide's safety profile through Individual Case Safety Reports reported in the EudraVigilance database

The EV system is used to manage and analyze information on suspected adverse reactions to medicines that are either authorized or being studied in clinical trials within the European Economic Area (EEA). Managed by the European Medicines Agency (EMA) on behalf of the European Union medicines regulatory network, it plays a key role in monitoring drug safety [6].

- 3.2.1.1. Qualitative and quantitative analysis for the main outcomes of ICSRs was carried out from 1 January to 1 December, 2021.
- 3.2.1.2. A comparison was made between reported ICSRs for semaglutide (GLP1RA), sitagliptin (DPP4i), and empagliflozin (SGLT2i).
- 3.2.1.3. A more detailed analysis was also carried out by selecting all ICSRs with semaglutide as the suspected drug reported in the EV database from 1 October to 1 December 2021 (oral and injectable forms). Information was collected on sex, age group, outcome, number of gastrointestinal events per ICSR, the overall number of suspected ADRs and concomitant medications reported.
- 3.2.1.4. For the statistical analysis IBM SPSS statistics 28 (IBM, Armonk, NY, USA) was used. Categorical variables were described through their respective absolute and relative frequencies (percentages). Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

3.3. Results

3.3.1. Demographic characteristics of ICSRs

Since semaglutide's marketing authorization in the European Union (injectable dosage form: 8 February 2018; oral dosage form: 3 April 2020) until 1 December 2021, 6,584 ICSRs have been reported due to suspected ADRs. Among these, 550 (8.4%) reports were linked to the oral dosage form, and 6,034 (91.6%) to the injectable dosage form. There was no statistically significant association between sex and the dosage form (p=0.204). Of the cases reported, 44.7% involved male patients (n=2,942), 53.0% female (n=3,491), and 2.3% (n=151) did not specify sex. Adults aged 18–64 years constituted the largest proportion of cases (38.6%, n=2,544), followed by those aged 65–85 years (24.2%, n=1,593). Most reports originated from health professionals (67.7%, n=4,455), and 56.4% (n=3,715) occurred within the European Economic Area.

Table 3.1 summarizes the demographic characteristics of ICSRs involving semaglutide.

Table 3.1. Demographic characteristics of ICSRs involving semaglutide reported in the EudraVigilance spontaneous reporting system from 8 February 2018 (injectable form) or 3 April 2020 (oral dosage form) to 1 December 2021.

	Individual Case Safety Reports 6584 (%)			
	Oral dosage form	**Injectable dosage form**	**Total**	
	N=550	**N=6034**	**N=6584**	***p*-value[1]**
Male	246 (44.7)	2696 (44.7)	2942 (44.7)	
Female	262 (47.6)	3229 (53.5)	3491 (53.0)	0.204
Not specified	42 (7.6)	109 (1.8)	151 (2.3)	
Age group				
Pediatrics (<18 Years)	0	6 (0)	6 (0.1)	
Adult (18–64 Years)	171 (31.1)	2373 (39.3)	2544 (38.6)	
Elderly (65–85 Years)	123 (22.4)	1470 (24.4)	1593 (24.2)	
Very Elderly (>85 Years)	6 (1.1)	31 (0.5)	37 (0.6)	
Not Specified	250 (45.5)	2154 (35.7)	2404 (36.5)	
Type of reporter				
Health Care Professional	398 (72.4)	4057 (67.2)	4455 (67.7)	
Non-Health Care Professional	152 (27.6)	1977 (32.8)	2129 (32.3)	
Region				
European Economic Area	193 (35.1)	3522 (58.4)	3715 (56.4)	
Non-European Economic Area	357 (64.9)	2512 (41.6)	2869 (43.6)	
Individual cases reported by system organ classes*				
Total adverse events	1029	11967	12996	
Gastrointestinal disorders	294 (53.5)	3208 (53.2)	3502 (53.2)	
Nervous system disorders	85 (15.5)	817 (13.5)	902 (13.7)	
Metabolism and nutritional disorders	82 (14.9)	926 (15.3)	1008 (15.3)	
Cardiac disorders	41 (7.45)	251 (4.2)	292 (4.4)	
Eye disorders	29 (5.3)	424 (7.0)	453 (6.9)	
Infections and infestations	22 (4.0)	303 (5.0)	325 (4.9)	
Musculoskeletal and connective tissue disorders	24 (4.4)	267 (4.4)	291 (4.4)	
Renal and urinary disorders	30 (5.5)	292 (4.8)	322 (4.9)	
Psychiatric disorders	28 (5.1)	244 (4.0)	272 (4.1)	
Skin and subcutaneous disorders	32 (5.8)	380 (6.3)	412 (6.3)	
Number of individual cases				***p*-value[1]**
Serious	369 (67.1)	3112 (51.6)	3481 (52.9)	<0.00001
Non serious	181 (32.9)	2922 (48.4)	3103 (47.1)	

*10 most reported ADRs were considered (percentages presented by reported cases).
[1]Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% (p<0.05).

Regarding ADRs severity, a significantly higher proportion of serious events were reported for the oral dosage form (67.1%, n=369) compared to the injectable form (51.6%, n=3,112; *p*<0.00001).

3.3.2. Main reported SOCs

The most frequently reported ADRs were gastrointestinal disorders (53.2%, n=3,502). Other notable SOCs included nervous system disorders (13.7%, n=902) and metabolism and nutrition disorders (15.3%, n = 1,008) (Table 4.1). No significant differences were observed in the prevalence of main SOCs between the oral and injectable dosage forms (p>0.05). Table 3.2 provides a detailed breakdown of reported SOCs.

Table 3.2. Main reported SOCs for oral and injectable semaglutide dosage forms from 1 January to 1 December 2021.

SOC		Individual Case Safety Reports (%)				*p*-value[1]
		Oral dosage form Total (N=266)		Injectable dosage form Total (N=1246)		
Gastrointestinal disorders	Vomiting	133 (50.0)	40 (30.1)	588 (47.2)	153 (26.0)	0.40534
	Pancreatitis		35 (26.3)		126 (21.4)	
	Nausea		31 (23.3)		161 (27.4)	
	Diarrhea		20 (15.0)		134 (22.8)	
Metabolism and nutritional disorders	Diabetes inadequate control	40 (15.0)	6 (15.0)	236 (18.9)	6 (2.5)	0.13467
	Dehydration		10 (25.0)		75 (31.8)	
	Decreased appetite		15 (37.5)		75 (31.8)	
	Diabetic Ketoacidosis		6 (15.0)		21 (8.9)	
Eye disorders	Visual impairment	20 (7.5)	5 (25.0)	99 (7.9)	18 (18.2)	0.81453
	Blindness		2 (10.0)		2 (2.0)	
	Diabetic retinopathy		2 (10.0)		11 (11.1)	
	Vision blurred		2 (10.0)		9 (9.1)	
Renal and urinary disorders	Acute kidney injury	21 (7.9)	12 (57.1)	113 (9.1)	40 (35.4)	0.54072
	Renal failure		0		16 (14.2)	
	Nephropathy		0		3 (2.7)	
	Chronic kidney disease		3 (14.3)		11 (9.7)	
Cardiac disorders	Angina pectoris	27 (10.2)	0	88 (7.1)	6 (6.8)	0.08461
	Atrial fibrillation		7 (25.9)		10 (11.4)	
	Tachycardia		2 (7.4)		6 (6.8)	
	Myocardial infarction		8 (29.6)		15 (17.0)	

[1]Pearson's Chi-Square test

3.3.3. Comparative analysis between semaglutide, sitagliptin, and empagliflozin

From 1 January to 1 December 2021, semaglutide was associated with a higher proportion of gastrointestinal ADRs (47.7%) compared to sitagliptin (34.7%) and empagliflozin (9.8%; p<0.00001). Similarly, semaglutide reports showed a higher prevalence of eye disorders (7.9%) compared to sitagliptin (4.2%) and empagliflozin (0.8%; p<0.00001). Pearson's Chi-

Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p<0.05$).

Figure 3.1 highlights these comparative findings.

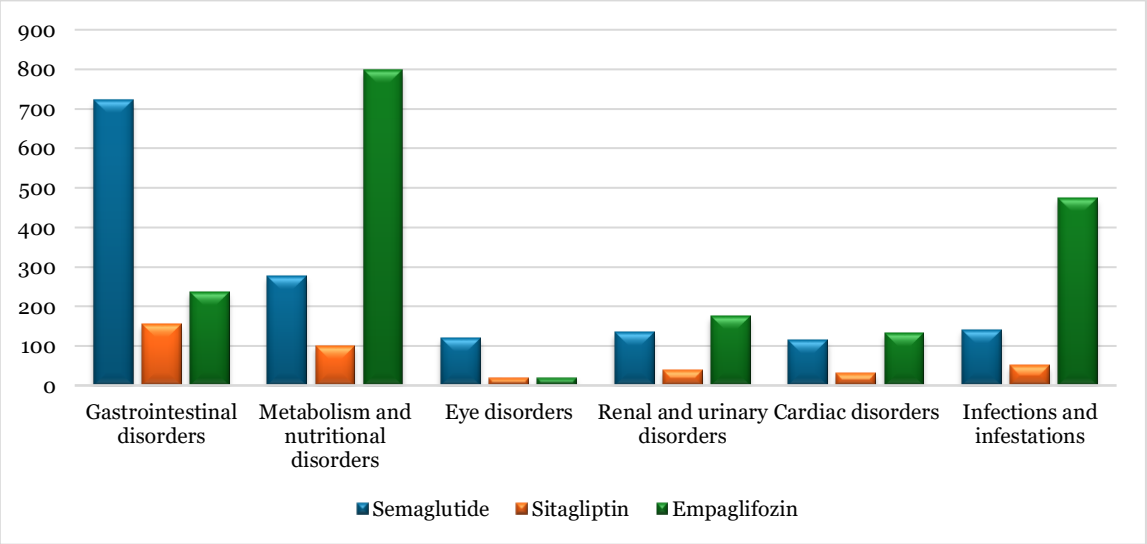

Figure 3.1. Comparative analysis for the main reported system organ classes (SOCs) adverse events for semaglutide, sitagliptin and empagliflozin from January 1st to December 1st, 2021.

3.3.4. Characteristics of ICSRs which include gastrointestinal disorders

Table 3.3. Characteristics of individual cases reported for patients treated with semaglutide (oral and injectable forms) which include gastrointestinal disorders, over 2 months (from 1st October to 1st December 2021).

Gastrointestinal disorders ICSR (N = 164)	
Sex (%)	
Male	69 (42.1)
Female	93 (56.7)
Unknown	2 (1.2)
Age group (%)	
18–64 Years	69 (42.1)
65–85 Years	50 (30.5)
>85 Years	6 (3.7)
Not Specified	39 (23.8)
Outcome (%)	
Fatal	3 (1.8)
Not Recovered/Not Resolved	29 (17.7)
Recovered/Resolved	52 (31.7)
Recovering/Resolving	8 (4.9)
Unknown	72 (43.9)
Number of gastrointestinal disorders per ICSR (%)	
1	85 (51.8)
2	35 (21.3)
3	21 (12.8)
4	15 (9.1)
5 or more	8 (4.9)
Global analysis of reported suspected ADRs	
Total number	745
Median per ICSR	3
Other drugs	
Total number	379
Median per ICSR	4
Other drugs used chronically to treat gastrointestinal disorders	
Yes	14 cases reported (18 drugs mentioned)

Within a two-month observation period, 164 ICSRs reported at least one gastrointestinal ADR associated with semaglutide. Females accounted for a higher proportion of these reports (56.7%) than males (42.1%). The most reported gastrointestinal ADRs included nausea, vomiting, and diarrhea.

Table 3.3 details the characteristics of these ICSRs.

3.4. Discussion

Semaglutide has emerged as a highly effective treatment for T2DM, significantly reducing HbA1c levels and promoting weight loss with a relatively low incidence of ADRs [7,8]. It is used as monotherapy or in combination with other antidiabetic medications for both primary and secondary prevention [9,10].

Analysis of the EV database revealed 6,584 ICSRs for semaglutide, predominantly from healthcare professionals. The majority of reports involved female patients, a trend likely influenced by sex-specific factors, including hormonal differences and variations in pharmacokinetics [11,12]. The injectable form of semaglutide, favored for its weekly dosing schedule, enhances adherence and offers convenience, while also demonstrating effectiveness in reducing CV events and slowing renal disease progression [13–20].

The most reported ADRs were gastrointestinal disorders (53.2%), followed by metabolic disturbances (15.3%) and nervous system disorders (13.7%). Gastrointestinal ADRs, such as nausea, vomiting, and diarrhea, were more severe at higher doses, underscoring the importance of a gradual dose-escalation strategy [21–25].

Comparative analysis indicated that semaglutide was associated with a higher prevalence of gastrointestinal ADRs compared to sitagliptin and empagliflozin. Despite these side effects, semaglutide tolerability and pharmacoeconomic advantages make it a viable option for patients with inadequately controlled T2DM and weight management. Effective management of ADRs, including dietary adjustments and dose escalation, can enhance patient outcomes and satisfaction [26–28].

Pharmacovigilance remains critical for early ADRs detection, promoting safer drug use, and improving patient quality of life while reducing healthcare system burdens.

3.5. Main Conclusions

- ✓ Gastrointestinal disorders represent the most frequently reported adverse drug reactions and warrant targeted clinical attention.
- ✓ The higher proportion of gastrointestinal adverse events reported for semaglutide compared with sitagliptin and empagliflozin underscores class-specific tolerability issues associated with GLP1RA.
- ✓ Most ADRs occurred in adult and elderly populations, with relatively few fatal outcomes, though a substantial proportion of reports lacked complete outcome data.
- ✓ Management strategies such as dose-escalation protocols and dietary modifications may help mitigate gastrointestinal intolerance in clinical practice.
- ✓ Continued pharmacovigilance is essential to identify patient subgroups at higher risk of serious ADRs and to optimize the safe and effective use of semaglutide in real-world settings.

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Chapter 4

Clinical and Pharmacotherapeutic Profile of Patients with Type 2 Diabetes Mellitus Admitted to a Hospital Emergency Department

4.1. Introduction

T2DM results from a combination of insulin resistance and impaired pancreatic insulin secretion. Its prevalence has increased due to urbanization, lifestyle changes, and poor diet, with risk factors including obesity, physical inactivity, aging, hypertension, dyslipidemia, and family history. Treatment options range from classic drugs such as insulin, metformin, and sulfonylureas to newer agents, including SGLT2i and GLP1RA, which improve glycemic control and provide cardiorenal benefits, though potential adverse effects must be monitored [1-3].

This study aims to characterize the clinical and pharmacological profiles of T2DM patients admitted to the emergency department of the LHUG, assessing the influence of comorbidities and prior antidiabetic therapy on their clinical condition at admission.

4.2. Materials and Methods

4.2.1. Study Design and Sampling

A retrospective study was conducted on 420 T2DM patients admitted to the LHUG emergency department between June 2019 and September 2022. Ethics approval from LHUG Ethics Committee was obtained, as well as formal authorization by the Institution's Board of Directors. Patient consent was waived, as the Ethics Committee of the LHUG deemed it unnecessary for this retrospective study, once the data has been irreversibly anonymized.

About 140 patients are admitted to the LHUG emergency department per day, of which about 60% have a known diagnosis of T2DM. Our study includes 39 months of analysis, which amounts to approximately 163,800 admissions episodes in that period (approximately 98,280 patients with a previously known diagnosis of T2DM). This means 383 or more measurements are needed to achieve a 95% confidence level, ensuring that the true value lies within ±5% of the measured value.

Patients with the following characteristics were randomly selected:

- ✓ Diagnosis of T2DM before admission to the emergency department;
- ✓ At least 65 years of age;
- ✓ At least one antidiabetic drug included in the chronic treatment plan before admission;
- ✓ Complete and objective information described in the clinical diary regarding chronic medication, clinical history, and reason(s) for admission to the Emergency Department;
- ✓ Complete information regarding the analytical parameters included in the study upon admission;
- ✓ After applying these criteria, a sample of 613 patients was obtained, from which 420 were randomly selected.

4.2.2. Data Collection

Data on patients with T2DM were obtained from the SClinico® and Modulab® platforms. The following variables were analyzed:

- ✓ Age, gender, and condition (autonomous, family support, or institutionalized);
- ✓ Bioanalytical parameters at admission: blood glycemia; creatinine; hemoglobin; aspartate aminotransferase (AST), and alanine aminotransferase (ALT);

- ✓ Personal pathological history: T2DM; high blood pressure (HBP); HF; atrial fibrillation (AF); acute myocardial infarction (AMI); dyslipidemia; CKD; hyperuricemia (HU); stroke, obesity; chronic liver disease; oncological disease; chronic obstructive pulmonary disease (COPD); alcoholism; chronic anemia;
- ✓ Diagnosis that justifies admission: decompensated heart failure (DHF); acute chronic kidney disease (ACKD); AKI; UTI; pulmonary embolism (PE); stroke; AMI; respiratory tract infection (RTI); hydroelectrolytic disorders (HED); bleeding; gastroenteritis; acute chronic liver disease; pancreatitis; hypoglycemia; respiratory failure; sepsis;
- ✓ Antidiabetic drugs included in the therapeutic plan before admission: insulin; SGLT2i; DPP4i; GLP1RA; metformin and sulfonylureas.

4.2.3. Statistical Analysis

For the statistical analysis, IBM SPSS statistics 28 (IBM, Armonk, NY, USA) was used. Categorical variables were described through their respective absolute and relative frequencies (percentages). Pearson's Chi-Square, Fisher's exact test, and linear regression tests were used with a statistical significance level of 5% ($p < 0.05$).

4.3. Results

4.3.1. Sample Characterization

A total of 420 patients with T2DM were included in this analysis (Figure 4.1). The mean age was 80.59 ± 7.92 years, with a roughly equal distribution between males (n = 204) and females (n = 216). High blood pressure (84.3%), dyslipidemia (42.8%), CKD (37.2%), and HF (41.6%) were among the most prevalent comorbidities.

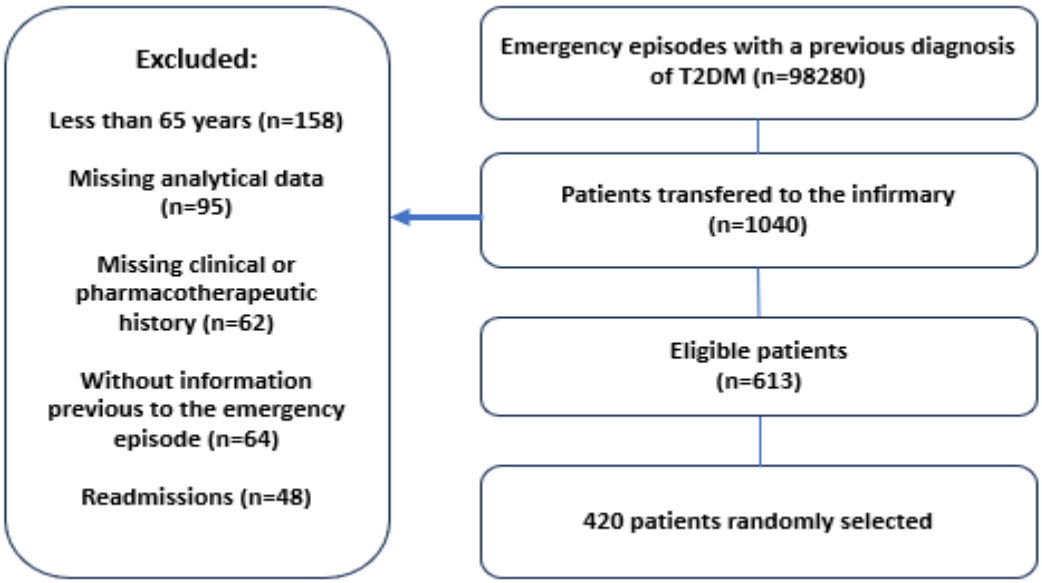

Figure 4.1. Sample Selection

Table 4.1 provides a detailed summary of the patients' characteristics, including their clinical and pharmacological profiles.

Table 4.1. Patients' characteristics at admission.

Age					
Mean	80.59	**Standard deviation**	7.92	**Min-Max**	65-99
			Gender		
			Male (n=204)		**Female (n=216)**
Autonomous			94 (22.4%)		61 (14.5%)
Family support			49 (11.7%)		42 (10.0%)
Institutionalized			61 (14.5%)		113 (26.9%)
Pathological history previous to admission					
Type 2 Diabetes Mellitus			204 (48.6%)		216 (51.4%)
High blood pressure			173 (41.2%)		181 (43.1%)
Heart failure			77 (18.3%)		98 (23.3%)
Atrial fibrillation			38 (9.0%)		45 (10.7%)
Acute myocardial infarction			14 (3.3%)		17 (4.0%)
Dyslipidemia			82 (19.5%)		98 (23.3%)
Chronic kidney disease			65 (15.5%)		91 (21.7%)
Hyperuricemia			30 (7.1%)		42 (10.0%)
Stroke			35 (8.3%)		39 (9.3%)
Obesity			27 (6.4%)		44 (10.5%)
Chronic liver disease			17 (4.0%)		6 (1.4%)
Oncological disease			25 (6.0%)		11 (2.6%)
Chronic obstructive pulmonary disease			19 (4.5%)		17 (4.0%)

Diagnosis at admission			
Decompensated heart failure		43 (10.2%)	66 (15.7%)
Acute chronic kidney disease		46 (11.0%)	67 (16.0%)
Acute kidney injury		66 (15.7%)	51 (12.1%)
Urinary tract infection		14 (3.3%)	28 (6.7%)
Pulmonary embolism		12 (2.9%)	9 (2.1%)
Stroke		18 (4.3%)	19 (4.5%)
Acute myocardial infarction		9 (2.1%)	8 (1.9%)
Respiratory tract infection		56 (12.9%)	65 (15.5%)
Hydroelectrolytic disorders		94 (22.4%)	92 (21.9%)
Bleeding		3 (0.7%)	0 (0.0%)
Gastroenteritis		4 (1.0%)	2 (0.5%)
Acute chronic liver disease		12 (2.9%)	5 (1.2%)
Pancreatitis		3 (0.7%)	3 (0.7%)
Hypoglycemia		2 (0.5%)	2 (0.5%)
Respiratory failure		59 (14.0%)	74 (17.6%)
Sepsis		5 (1.2%)	11 (2.6%)
Antidiabetic drugs included in the therapeutic plan before admission			
Insulin		100 (23.8%)	127 (30.2%)
Sodium-glucose cotransporter inhibitors		54 (12.9%)	54 (12.9%)
Dipeptidyl peptidase inhibitors		111 (26.4%)	107 (25.5%)
Glucagon-like peptide-1 receptor agonists		10 (2.4%)	17 (4.0%)
Metformin		107 (25.5%)	96 (22.9%)
Sulfonylureas		36 (8.6%)	22 (5.2%)
Laboratory parameters at admission			
Glycemia		**Blood creatinine**	
<180 mg/dl	**≥180 mg/dl**	**<1.2 mg/dL**	**≥1.2 mg/dL**
183 (43.6%)	237 (56.4%)	170 (40.5%)	250 (59.5%)

The American Diabetes Association classifies glycemia above 180 mg/dL as hyperglycemia; therefore, patients were classified according to this reference value [4].

A cut-off value of 1.2 mg/dL was considered for blood creatinine levels (the normal range for men is approximately 0.6 to 1.2 mg/dL, and for women, it is between 0.5 and 1.1 mg/dL) [5].

4.3.2. Relationship between Patient Condition prior to Admission, Age, and Gender, and Glycemia Levels

Patients with family support were less likely to be present with hyperglycemia (≥180 mg/dL) at admission (9.5%) compared to autonomous (23.1%) or institutionalized patients (23.8%; p=0.016). No significant associations were observed between gender or age and glycemia levels (p>0.05).

Table 4.2 summarizes association between glycemia levels and these variables.

Table 4.2. Relationship between patient condition, gender, age, and glycemia levels.

	Condition				
Glycemia	**Autonomous**	**Family support**	**Institutionalized**	**Total**	**p-value**
<180 mg/dl	58 (13.8%)	51 (12.1%)	74 (7.6%)	183 (43.6%)	
≥180 mg/dl	97 (23.1%)	40 (9.5%)	100 (23.8%)	237 (56.4%)	0.016[1]
Total	155 (36.9%)	91 (21.7%)	174 (41.4%)	420 (100%)	

[1]Pearson's Chi-Square

4.3.3. Hyperuricemia, Hemoglobin, and AST/ALT Ratio

Higher blood creatinine levels (≥1.2 mg/dL) were significantly associated with hyperuricemia (p=0.001) and glycemia levels ≥180 mg/dL (p=0.005). A linear regression model showed hemoglobin levels declined with age and were lower in females and those with creatinine ≥1.2 mg/dL.

Through a linear regression model, the AST/ALT ratio was inversely correlated with glycemia levels at admission (p<0.0001).

4.3.4. Obesity, Dyslipidemia, and Acute Cardiovascular Disorders

Obese patients with or without dyslipidemia were at higher risk for acute CV disorders, such as HF and stroke (p<0.05).

4.3.5. Antidiabetic Therapy and Heart Failure

Patients on insulin (p=0.003), GLP1RA (p=0.023), or a combination of both drugs (p=0.007) were at higher risk of decompensated HF. Conversely, patients on sulfonylureas or metformin-DPP4i combinations had a reduced risk (p<0.05).

Table 4.3 provides details.

Table 4.3. Relationship between Decompensated Heart Failure and Antidiabetic Therapy.

Previously diagnosed heart failure			**Decompensated heart failure at admission**		
Yes	No		Yes	No	
175 (41.7%)	245 (58.3%)		109 (26.0%)	311 (74.0%)	
Antidiabetic drugs	**Decompensated HF (No/Yes)**		**p-value**	**OR**	**Confidence interval 95%**
Insulin	155 (49.8%)	72 (66.1%)	p=0.003[1]	1.959	1.243-3.085
GLP1RA	15 (4.8%)	12 (11.0%)	p=0.023[1]	2.441	1.105-5.395
Sulfonylureas	51 (16.4%)	7 (6.4%)	p=0.009[1]	0.350	0.154-0.796
Insulin + GLP1RA	9 (2.9%)	10 (9.2%)	p=0.007[1]	3.389	1.339-8.579
Metformin + DPP4i	100 (32.2%)	23 (21.1%)	p=0.029[1]	0.564	0.336-0.947
Metformin + Sulfonylurea	38 (12.2%)	3 (2.8%)	p=0.003[2]	0.203	0.061-0.673

[1] Pearson's Chi-Square

[2] Fisher's exact test

4.3.6. Antidiabetic Therapy and Kidney Function

Patients undergoing treatment with metformin (p=0.017) or metformin and DPP4i association (p=0.014) were exposed to a lower risk of AKI or ACKD (Table 4.7). Patients using SGLT2i (p=0.0003), insulin and sulfonylurea association (p=0.026), metformin and SGLT2i association (p=0.026), and DPP4i and SGLT2i association (p=0.007) were exposed to a higher risk of HED. On the other hand, patients using GLP1RA (p= 0.017), insulin and DPP4i association (p=0.034), or DPP4i and GLP1RA association (p=0.003) had a lower risk of HED (Table 4.4).

Table 4.4. Relationship between antidiabetic therapy and acute kidney injury, acute chronic kidney injury, and hydroelectrolytic disorders

Antidiabetic drugs	AKI or ACKD (n=230)	p-value	OR	Confidence interval 95%
Metformin	99(43.0%)	0.017[1]	0.625	0.424-0.920
Metformin + DPP4i	56 (24.3%)	0.014[1]	0.521	0.387-0.902
	Hydroelectrolytic disorders			
SGLT2i	64(34.4%)	0.0003[1]	2.265	1.450-3.539
GLP1RA	6(3.2%)	0.017[1]	0.338	0.134-0.856
Insulin + DPP4i	38(20.4%)	0.034[1]	0.614	0.390-0.967
Insulin + Sulfonylurea	8(4.3%)	0.026[2]	5.213	1.094-24.853
Metformin + SGLT2i	34(18.3%)	0.026[1]	1.870	1.071-3.264
DPP4i + SGLT2i	29(15.6%)	0.007[1]	2.358	1.252-4.440
DPP4i + GLP1RA	0(0.0%)	0.003[2]	0.957	0.932-0.984

[1] Pearson's Chi-Square

[2] Fisher's exact test

4.3.7. Antidiabetic Therapy and Glycemia Levels

Insulin was mainly used by autonomous and institutionalized patients (p=0.0008), while metformin (p=0.003) and GLP1RA (p<0.0001) were mainly used by autonomous patients. Sulfonylureas were mostly used by male patients (p=0.027), while SGLT2i (p=0.0004) and GLP1RA (p<0.0001) by patients within the age group 65–85 years. Patients treated with sulfonylureas (p=0.008), insulin and metformin association (p=0.040), insulin and sulfonylurea association (p=0.048), and DPP4i and sulfonylurea association (p=0.031) were exposed to a higher risk of hyperglycemia (≥180 mg/dL) at admission (Table 4.5).

Table 4.5. Relationship between antidiabetic drugs and glycemia levels at admission

Antidiabetic drugs	Glycemia ≥180 mg/dL (No/Yes)		p-value	OR	Confidence interval 95%
Sulfonylureas	16 (8.7%)	42 (17.7%)	p=0.008[1]	2.248	1.219-4.145
Insulin + Metformin	20 (10.9%)	43 (18.1%)	p=0.040[1]	1.806	1.022-3.194
DPP4i + Sulfonylurea	11 (6.0%)	29 (12.2%)	p=0.031[1]	4.644	1.058-4.492

[1] Pearson's Chi-Square

4.4. Discussion

4.4.1. Glycemia Levels and Patients' Characteristics

Social and family support significantly influence glycemic control in T2DM patients [6,7]. Those with strong support systems exhibit better glycemic outcomes upon admission compared to autonomous or institutionalized individuals. Integrating family involvement into diabetes management can yield improved outcomes, emphasizing the value of educational interventions [8,9].

4.4.2. Impact of Hyperuricemia on Kidney Function and Cardiovascular System

HU is a notable risk factor for CKD and CV disease in T2DM patients. Elevated uric acid levels are linked to increased insulin resistance and kidney dysfunction [10–14]. This study highlighted that HU patients exhibited higher rates of acute CV events and kidney function deterioration, aligning with existing literature [15–18].

4.4.3. Relationship between Hemoglobin Levels, Gender, Age, and Kidney Function

Patients with T2DM are more susceptible to the development of chronic anemia, which may be due to inadequate glycemic control, CKD (that leads to erythropoietin production decrease), presence of T2DM complications, or age >60 years [19–21]. Previous studies have shown that diabetic women and older diabetic individuals are the most vulnerable groups to anemia; furthermore, elevated blood creatinine levels are a significant factor influencing this condition [22,23].

According to this study, female gender, older age, and serum creatinine values above 1.2 mg/dL, are related to lower hemoglobin levels.

4.4.4. Liver Function and Glycemia Levels

Abnormal liver enzyme levels are prevalent in T2DM patients. A decreasing ratio of AST to ALT is associated with declining glucose regulation, metabolic impairment, and organ dysfunction, including NAFDL and CV disease [24,25]. This study observed an inverse relationship between glycemia levels and the AST/ALT ratio, underscoring the intricate interplay between liver function, glycemic control, and metabolic health [26,27].

4.4.5. Patients' Pharmacotherapeutic Profile and Acute Cardiovascular Disease

T2DM is strongly linked to CV diseases, necessitating optimized pharmacotherapy [28,29].

This study revealed that patients treated with sulfonylureas or metformin combinations demonstrated lower risks of HF. However, findings on SGLT2i and HF require further investigation to clarify their cardioprotective roles.

4.4.6. Patients' Pharmacotherapeutic Profile and Kidney Disease

This study demonstrated that metformin and DPP4i combinations reduced the risks of AKI in T2DM patients. SGLT2i, while offering renoprotective benefits, were associated with electrolyte imbalances, necessitating close monitoring of renal parameters during treatment. Although a natriuretic effect and osmotic diuresis are expected, these compounds may also modulate the urinary excretion of potassium, magnesium, phosphate, and calcium. Some of the disturbances of homeostasis are transient, while others may persist, suggesting that the administration of these compounds may induce new electrolyte homeostasis [30].

4.4.7. Patterns of Antidiabetic Drug Use

Drug utilization patterns varied across demographics [31]. Metformin was predominantly prescribed to autonomous patients, while insulin was more common among institutionalized individuals. Gender and age also influenced drug choice, highlighting the need for personalized treatment strategies in T2DM management [32].

4.4.8. Relationship between Glycemic Levels at Admission and Antidiabetic Drugs

The effect of antidiabetic drugs on glycemic control in real-world settings often differs from the outcomes seen in clinical trials. Furthermore, factors related to the patient and the therapy itself may contribute to treatment non-adherence [33,34]. Previous studies have shown that the pattern of antidiabetic drug use varies across different age groups and genders [35,36]. On the other hand, therapy-related factors, such as route of administration, treatment duration, complexity (for example, a fixed-dose combination can significantly improve adherence to pharmacological therapy compared to a loose-dose combination), medication type, and side effects, also influence the patterns of antidiabetic drug use [37,38]. In addition, new-generation antidiabetic drugs are less studied than more traditional therapeutic options, so their effects, both in terms of effectiveness and safety, may be less predictable, particularly in more vulnerable populations, such as the elderly [39].

Several comparative studies were carried out to assess the effectiveness of different antidiabetic drugs in glycemic control. In general, inadequately-controlled T2DM patients can benefit from using a combination of two or more different antidiabetic drugs [40,41]. If

the HbA1C level exceeds 7.5% during treatment or if the baseline HbA1C is ≥9%, combination therapy with two oral antidiabetic drugs or insulin may be considered [42,43]. In recent years, significant advancements have been made in the pharmacological treatment of T2DM, making it challenging to stay updated on the latest innovative therapies. Different insulin analogs have varying pharmacokinetics: rapid-acting insulins are used for prandial insulin, while longer-acting insulins provide basal insulin over an extended period. However, insulin is rarely used as a first-line treatment due to the risk of severe hypoglycemia and CV complications, especially with increasing doses and insulin tolerance [44,45]. Metformin remains the recommended first-line treatment for T2DM, effectively lowering fasting plasma glucose and HbA1C [46,47]. Sulfonylureas, widely prescribed for T2DM, are affordable and can be used alone or with metformin, but they carry risks such as hypoglycemia and CV disorders, despite evidence supporting their CV safety [48–51]. DPP4i, which are well-tolerated with minimal side effects, are effective in improving glycemic control, especially when used in combination with metformin or other antidiabetic drugs. Its oral administration and fixed doses, which do not require titration, are additional features that facilitate adherence to this therapy [52,53]. GLP1RA help with glycemic control by promoting insulin secretion and inhibiting glucagon release, while also limiting weight gain and reducing the risk of CV events like heart attacks or strokes. This class is recommended for patients with ASCVD [54,55]. SGLT2i decrease renal glucose reabsorption promoting urinary excretion, and controlling effectively blood glycemia regardless of insulin levels [56,57].

This study suggests that patients treated with insulin (when associated with metformin or sulfonylurea) and sulfonylureas (with or without DPP4i associated) were exposed to a higher risk of hyperglycemia at admission. Some studies demonstrated that patients on insulin were more likely to have poorly controlled glycemia than those on metformin alone [58,59]. Sulfonylureas are generally associated with an increased risk of hypoglycemia, especially in the elderly, which contrasts with this study [60]. Although, most of these patients presented with clinical illnesses causing considerable stress. Stress-induced hyperglycemia is a common response in such situations. This condition develops due to increased peripheral insulin resistance, reduced insulin secretion, and enhanced glucose production [61]. Sulfonylureas stimulate insulin secretion, metformin decreases glucose synthesis, and endogenous insulin acts on its specific receptors. All these mechanisms are affected by stress-induced hyperglycemia, and a more robust approach to glycemic control and stabilization may be necessary. The treatment consists of intravenous insulin infusion [62].

4.5. Main Conclusions

- ✓ Patients with T2DM exhibit substantial clinical heterogeneity and frequently present with multiple comorbidities, necessitating a comprehensive and individualized pharmacotherapeutic approach.
- ✓ Effective disease management requires consideration of all clinical factors that may influence disease progression, including comorbidity burden, therapeutic complexity, and patient-specific risks.
- ✓ Health professionals play a critical role in enhancing patients' health literacy, which directly affects self-management capacity, glycemic control, treatment adherence, and overall quality of life, ultimately contributing to improved clinical outcomes.
- ✓ The findings of this study support previously established clinical and pharmacological associations and indicate that adequate social and family support is linked to better glycemic control and more effective disease self-management.
- ✓ Several factors may have influenced the results, including the monocentric design of the study, which may limit generalizability.

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Chapter 5

Acute Kidney Injury and Electrolyte Imbalances Caused by Dapagliflozin Short-Term Use

5.1. Introduction

Beyond its benefits in glycemic control, dapagliflozin has demonstrated substantial CV and renal benefits, including reductions in HF hospitalizations, MACE, and progression of CKD across diabetic and non-diabetic populations. Despite these therapeutic advantages, uncertainties remain regarding the short-term impact of SGLT2i on urinary sodium handling and electrolyte homeostasis, particularly in patients with CKD, who are inherently predisposed to hydroelectrolytic disturbances such as hyponatremia and hyperkalemia. Concomitant therapies, including ACEi, ARBs, and diuretics may further increase the risk of electrolyte imbalance or AKI. Given these concerns, real-world evidence on the early renal and electrolyte effects of dapagliflozin in hospitalized patients is still limited [1-3].

This study evaluates the short-term influence of dapagliflozin on renal function and electrolyte balance in inpatients receiving the drug for the first time, and compares these findings with adverse drug reaction patterns reported in the EV database. The aim is to generate clinically relevant insights to inform therapeutic decision-making and optimize patient outcomes.

5.2. Materials and Methods

5.2.1. Study Design and Sampling

A retrospective study was conducted involving adult patients, with or without T2DM, who received their first prescription of dapagliflozin during hospitalization. Patients who had not previously taken any SGLT2i, who had taken dapagliflozin for a minimum of 5 consecutive days, and for whom the bioanalytical parameters under study were available, were included.

The study period encompassed 23 months, from 1 September 2021 to 31 July 2023, at the LHUG and 30 months, from 1 January 2021 to 30 June 2023, at the LHUCB. Ethics approval was obtained from the Ethics Committee of the LHUG (SFTSS-REQ-22021; approval date: 3 April 2023) and the LHUCB (35/2023; approval date: 29 May 2023), as well as formal authorization by the Institution's Board of Directors. Patient consent was waived, as the Ethics Committees of the LHUG and LHUCB deemed it unnecessary for this retrospective study.

Therefore, the inclusion criteria were as follows:

- ✓ age ≥ 18 years;
- ✓ patients (with or withoutT2DM) who had never taken an SGLT2i;
- ✓ patients who took dapagliflozin for the first time for at least 5 consecutive days during the period of hospitalization;
- ✓ patients for whom the bioanalytical parameters under study (blood glucose, creatinine, sodium, and potassium levels) were available both before dapagliflozin prescription (baseline) and 5 to 8 days after prescription (endpoint).

To estimate the prevalence of short-term renal dysfunction and electrolyte imbalance among the patients receiving dapagliflozin, with a 95% confidence level and 5% precision, and assuming an expected prevalence of 20% (derived from a pilot study conducted by the researchers and which included 124 patients), a sample size of 246 patients was determined to be necessary.

5.2.2. Data Collection

The patients' data were retrieved from the GHAF®, SClinico®, and Modulab® hospital platforms (accessed between 24 March 2023 and 4 August 2023) for the Local Health Unit of Guarda. Similarly, data were gathered from the Glintt®—Integrated Management System of the Medicine Circuit and SClinico® hospital platforms (accessed from 24 June 2023 to 30 June 2023) for the Local Unit Health of Cova da Beira.

The following variables were analyzed:

- ✓ Age and gender;
- ✓ Medical history: T2DM, HBP, HF, and CKD;
- ✓ Blood glycemia, creatinine, sodium, and potassium levels [both before dapagliflozin prescription (baseline) and 5 to 8 days after prescription (endpoint)]. The exact endpoint day (between day 5 and day 8 after dapagliflozin prescription) was determined following the KDIGO guidelines, which define AKI as an abrupt decrease in kidney function occurring within 7 days [4]. Due to limitations in data availability, most of the hospitalized patients did not have analytical parameters available daily or on weekends.
- ✓ Concomitant medication: furosemide, spironolactone, ACEis, ARBs, and potassium supplementation.

Additionally, ICSRs data were obtained from the EV database, accessed at www.adrreports.eu (accessed on 7 February 2024):

I. Qualitative and quantitative analyses of the main outcomes of the ICSRs were conducted from 1 January to 31 December, 2023;

II. The information collected included sex, age group, outcomes, number of AKIs, hyponatremia, and hypokalemia events per ICSR, as well as reported concomitant medications (furosemide, ACEi, ARBs, or spironolactone)

5.2.3. Statistical Analysis

The statistical analysis was performed using IBM SPSS statistics 28 (IBM, Armonk, NY, USA). The categorical variables were described using absolute and relative frequencies (percentages). A Wilcoxon signed-rank test, Pearson's chi-square test, and Fisher's exact test were used, with a statistical significance level set at 5% ($p < 0.05$).

5.3. Results

5.3.1. Sample Characterization

A cohort of 246 patients was analyzed for short-term effects of dapagliflozin (Figure 5.1).

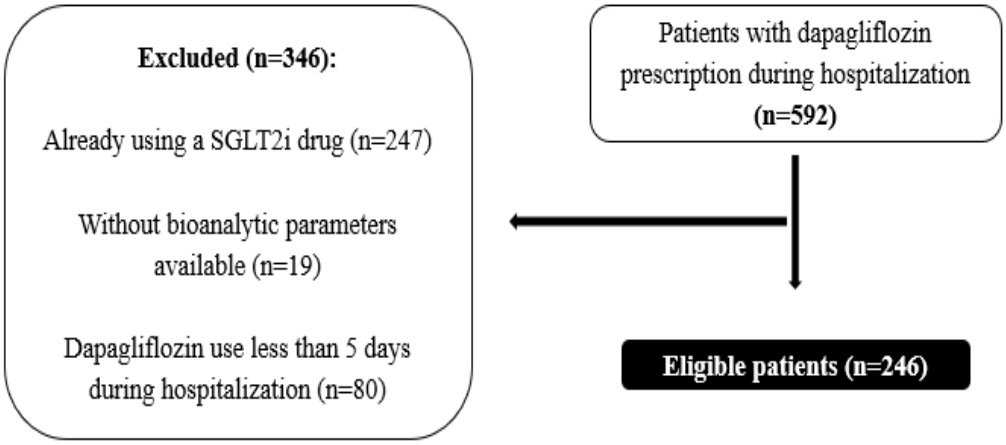

Figure 5.1. Sample selection

Comorbidities included a previous diagnosis of T2DM in 149 patients (60.6%), HBP in 185 (75.2%), HF in 114 (46.3%), and CKD in 64 (26.0%) (Table 5.1). Notably, 174 patients (70.7%) were concomitantly using furosemide, 94 (39.2%) spironolactone, 88 (35.8%) an ACEi, 86 (35.0%) an ARB, and 77 (31.7%) received potassium supplementation (Table 5.1).

Table 5.1. Sample characterization

Age (Mean ± Std)	**78.70 ± 10.72**
Comorbidities	
Type 2 diabetes mellitus	149 (60.6%)
High blood pressure	185 (75.2%)
Heart failure	114 (46.3%)
Chronic kidney disease	64 (26.0%)
Concomitant medication	
Furosemide	174 (70.7%)
Spironolactone	94 (38.2%)
Angiotensin-converting enzyme inhibitors	88 (35.8%)
Angiotensin receptor blockers	86 (35.0%)
Potassium supplementation	77 (31.7%)

5.3.2. Effects of Dapagliflozin on Renal Function

AKI occurred in 22.4% of cases, with higher blood creatinine levels at the endpoint compared to baseline (p=0.0001). Electrolyte imbalances included increased hyperkalemia and hyponatremia prevalence. Table 5.2 presents these findings.

Table 5.2. Blood creatinine levels and acute kidney injury (n= 246)

Blood creatinine (mg/dL)	Mean ± std	Min-Max	*p*-value
baseline	1.26 ± 0.59	0.49-4.18	0.0001[3]
endpoint	1.39 ± 0.77	0.39-6.55	
Creatinine increase ≥ 0.3 mg/dL (n=55)			
Gender	**Male**	28 (50.9%)	0.878[1]
	Female	27 (49.1%)	
Age (years)	**< 65**	4 (7.3%)	0.232[1]
	65-75	8 (14.5%)	
	76-85	22 (40.0%)	
	> 85	21 (38.2%)	

[1]Pearson's chi-square test
[3]Wilcoxon signed-rank test

5.3.3. Effects of Dapagliflozin on Electrolyte Balance

Blood sodium levels were significantly higher before dapagliflozin administration (mean rank = 117.36) than at the endpoint (mean rank = 107.55), (p=0.0009) as well as the percentage of patients with hyponatremia at the endpoint (p=0.0146) (Table 5.3). Conversely, blood potassium levels were significantly lower before dapagliflozin administration (mean rank = 98.64) than at the endpoint (mean rank = 127.82) (p<0.0001) as well as the percentage of patients with hyperkalemia at the endpoint (p=0.0002) (Table 5.4).

The use of furosemide did not show a statistically significant association with the occurrence of hyponatremia at the endpoint (p=0.089). Regarding hyperkalemia occurrence at the endpoint, there was no statistically significant association found with potassium supplementation (p=0.243), ACEis (p=0.096), or spironolactone administration (p=0.149). However, a statistically significant association was observed with the administration of ARBs and hyperkalemia occurrence (p=0.017) (Table 5.4).

Table 5.3. Blood sodium levels at baseline and at the endpoint (n=246)

Blood sodium (mEq/L)	Mean ± std				Min-Max	*p*-value
Baseline	139.05 ± 4.52				119-158	0.0009[3]
Endpoint	138.48 ± 5.36				115-161	
	Baseline (n; %)	T2DM (n; %)	HBP (n; %)	HF (n; %)	CKD (n; %)	
<135	25 (10.2%)	12 (4.9%)	20 (8.1%)	9 (3.7%)	11 (4.5%)	0.0146[1]
135-145	213 (86.6%)	133 (54.1%)	161 (65.4%)	102 (41.5%)	51 (20.7)	
>145	8 (3.3%)	4 (1.6%)	4 (1.6%)	3 (1.2%)	2 (0.8%)	
	Endpoint (n; %)					
<135	43 (17.5%)	26 (10.6%)	32 (13.0%)	26 (10.6%)	14 (5.7%)	
135-145	188 (76.4%)	112 (45.5%)	140 (56.9%)	83 (37.3%)	47 (19.1%)	
>145	15 (6.1%)	11 (4.5%)	13 (5.3%)	5 (2.0%)	3 (1.2%)	

[1]Pearson's chi-square test
[3]Wilcoxon signed-rank test

Table 5.4. Blood potassium levels at baseline and at the endpoint (n=246)

Blood potassium (mmol/L)	Mean ± std	Min-Max	*p*-value
baseline	4.19 ± 0.60	2.5-6.2	
endpoint	4.44 ± 0.62	2.8-6.4	<0.0001[3]

	Baseline (n; %)	T2DM (n; %)	HBP (n; %)	HF (n; %)	CKD (n; %)	
<3.5	28 (11.4%)	13 (5.3%)	24 (9.8%)	14 (5.7%)	4 (1.6%)	
3.5-5.0	196 (79.7%)	125 (50.8%)	144 (58.5%)	92 (37.4%)	55 (22.4%)	
>5.0	22 (8.9%)	11 (4.5%)	17 (6.9%)	8 (3.3%)	5 (2.0%)	
	Endpoint (n; %)					0.0002[1]
<3.5	8 (3.3%)	4 (1.6%)	5 (2.0%)	3 (1.2%)	1 (0.4%)	
3.5-5.0	197 (80.1%)	16 (51.2%)	149 (60.6%)	96 (39.0%)	50 (20.3%)	
>5.0	41 (16.7%)	19 (7.7%)	31 (12.6%)	15 (6.1%)	13 (5.3%)	
Blood potassium at the endpoint	**≤5 mmol/L (n; %)**	**>5 mmol/L (n; %)**				
Potassium supplementation	61 (79.2%)	16 (20.8%)				0.243[1]
ACEi	78 (88.6%)	10 (11.4%)				0.096[1]
ARB	65 (75.6%)	21 (24.4%)				0.017[1]
Spironolactone	74 (78.7%)	20 (21.3%)				0.149[1]

[1]Pearson's chi-square test
[3]Wilcoxon signed-rank test

5.3.4. Comparisons with Adverse Drug Reaction Profiles Reported in the EudraVigilance Database

From January 1, 2023, to December 31, 2023, a total of 2666 ICSRs have been reported based on suspicion of dapagliflozin use. Of these, 1517 (56.9%) were reported for male patients, 1033 (38.7%) for female patients, and 116 (4.4%) did not specify sex. The age distribution indicated that 1017 cases (38.1%) were in the age group 65–85 years, 612 (23.0%) were in the age group 18-64 years, 199 (6.5%) in the age group >85 years, and 833 (31.2%) had no specified age group. Among the reported cases, 1425 (53.5%) were for the treatment of Diabetes Mellitus, 237 (8.9%) for CKD, and 502 (18.9%) for HF (Table 5.5).

Regarding the most reported by system organ classes, 394 cases (14.8%) were related to Renal and Urinary disorders, 126 (4.7%) to Cardiac disorders, 314 (11.8%) to Gastrointestinal disorders, and 595 (22.3%) to Infections (Table 5.5).

Statistical analysis revealed no statistically significant difference between concomitant use of furosemide and AKI (p=0.770) or hyponatremia (p=0.066), nor between concomitant use of ACEis (p=0.335) or ARBs (p=1.000) and hyperkaliemia. However, there was a statistically significant difference between concomitant use of spironolactone and hyperkaliemia (p=0.002) (Table 5.5).

Table 5.5. Individual Cases Safety Reports Analysis from 1 January 2023 to 31 December 2023

Individual Case Safety Reports	**2666 (100%)**
Sex	
Male	1517 (56.9%)
Female	1033 (38.7%)
Not Specified	116 (4.4%)
Age group	
16-64	612 (23.0%)
65-85	1017 (38.1%)
>85	199 (7.5%)
Not specified	838 (31.4%)

		Use		
Individual cases reported by system organ classes	**Total**	**Chronic Kidney Disease** 237 (8.9%)	**Diabetes Mellitus** 1425 (53.5%)	**Heart Failure** 502 (18.9%)
Renal and urinary disorders	394 (14.8%)	53 (13.5%)	226 (57.4%)	113 (28.7%)
Cardiac disorders	126 (4.7%)	6 (4.8%)	41 (32.5%)	46 (36.5%)
Gastrointestinal disorders	314 (11.8%)	25 (8.0%)	137 (43.6%)	56 (17.8%)
Infections	595 (22.3%)	33 (5.5%)	303 (50.9%)	122 (20.5%)

Concomitant Drug/Adverse Drug Reaction				
	Acute Kidney Injury (n=98)	***p*-value**	**Hyponatremia (n=21)**	***p*-value**
Furosemide (n=120)	5 (4.2%)	0.770[1]	3 (2.5%)	0.066[2]
	Hyperkaliemia (n=17)		***p*-value**	
Spironolactone (n=89)	4 (4.5%)		0.002[2]	
ACEi (n=186)	2 (1.1%)		0.335[2]	
ARA (n=364)	2 (0.5%)		1.000[2]	

[1] Pearson's Chi-Square

[2] Fisher's exact test

5.4. Discussion

Studies have consistently shown that dapagliflozin improves glycemic control in T2DM patients. This study supports these findings, demonstrating a significant reduction in blood glucose levels within the first 5 to 8 days of dapagliflozin administration. While the glucose-lowering effect can start after a single dose, its clinical significance may take up to a week to become apparent [5].

Observational studies have reinforced the findings from placebo-controlled clinical trials, showing a decrease in AKI episodes among T2DM patients treated with SGLT2i compared to alternative glucose-lowering therapies [6,7]. SGLT2i are increasingly prescribed to non-diabetic patients with CKD due to their ability to slow renal function decline by reducing glomerular hypertension, regardless of their effect on blood glucose levels [8,9].

Dapagliflozin demonstrated rapid glycemic control in T2DM patients. However, its use was associated with transient declines in eGFR and increased risks of AKI and electrolyte imbalances, particularly hyperkalemia and hyponatremia. These findings emphasize the need for careful renal function monitoring, especially in vulnerable populations.

SGLT2i initiation typically leads to an initial decline in eGFR, followed by partial recovery over time [10,11]. These initial dips in eGFR are usually seen 2-4 weeks after starting SGLT2i, with partial recovery by week 12 [12–14]. Some researchers suggest that modest reductions in eGFR should not lead to SGLT2i treatment discontinuation [15].

SGLT2i exert significant effects on sodium and glucose reabsorption in the proximal tubules, increasing renal glucose and sodium excretion [16]. It showed a decrease in blood sodium levels following dapagliflozin administration, likely due to enhanced renal sodium excretion, highlighting the importance of monitoring natremia to prevent neurological complications. Previous studies have suggested that SGLT2i use may cause transient reductions in extracellular fluid volume [16–19]. Interestingly, concomitant use of furosemide did not appear to exacerbate hyponatremia.

SGLT2i have also been associated with a lower risk of severe hyperkalemia in high-risk T2DM patients or those with CKD, without increasing the risk of hypokalemia [20–23]. However, a higher incidence of hyperkalemia was observed at the endpoint, highlighting the need for careful potassium monitoring, particularly in patients receiving concurrent ARBs.

Despite the limitations of this study, including its retrospective design and limited sample size, the real-world data provide important insights into the clinical implications of dapagliflozin therapy. By capturing data from routine clinical practice, this study aimed to bridge the gap between controlled clinical trials and everyday patient care, thereby supporting evidence-based decision-making and enhancing diabetes management.

5.5. Main Conclusions

- ✓ This retrospective analysis offers important insights into the short-term effects of dapagliflozin on renal function and electrolyte homeostasis in patients with T2DM.
- ✓ Dapagliflozin rapidly lowered blood glucose levels within the first days of treatment, highlighting its effectiveness as a fast-acting antidiabetic agent.
- ✓ A significant post-treatment increase in serum creatinine was observed, indicating the need for vigilant renal function monitoring, particularly during the first weeks of dapagliflozin initiation.
- ✓ Electrolyte disturbances (hyponatremia and hyperkalemia) were common among treated patients, underscoring the necessity of routine electrolyte evaluation and individualized risk-mitigation strategies.

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Chapter 6

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

6.1. Introduction

Beyond glucose regulation, both SGLT2i and GLP1RA have demonstrated beneficial effects on common T2DM-associated complications, including HF, CKD, obesity, and hepatic steatosis. Large-scale trials have confirmed the renal-protective and CV benefits of SGLT2i, particularly in patients with HFrEF, leading to guideline endorsements by major cardiology societies. GLP1RA additionally provide favorable effects on body weight, lipid profiles, and liver steatosis, although their long-term CV and renal outcomes in real-world populations require further study [1-3].

While clinical trials establish efficacy under controlled conditions, real-world studies are critical to evaluate performance in heterogeneous patient populations, often with multiple comorbidities. This study investigates the real-world effectiveness of SGLT2i and GLP1RA in T2DM patients followed in a hospital diabetology consultation, assessing impacts on renal function, CV risk, weight, and glycemic control over one year. Outcomes are compared with adverse event reports from the EV database to provide a comprehensive assessment of safety and therapeutic value in routine clinical practice.

6.2. Materials and Methods

6.2.1. Study Design and Sampling

This was a retrospective observational study conducted at the hospital diabetology consultation service of the LHUG, 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 LHUG (Approval Reference: SFTSS-REQ-22022), as well as formal authorization by the Institution's Board of Directors. Patient consent was waived, as the Ethics Committee of the LHUG deemed it unnecessary for this retrospective study.

6.2.2. 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.

6.2.3. Inclusion criteria

- Diagnosis of T2DM;
- Antidiabetic pharmacotherapeutic regimen unchanged during the analysis period;
- Availability of complete baseline and follow-up data for parameters, including eGFR, glycated hemoglobin (HbA1c), blood sodium and potassium levels, weight, and CV risk scores.

6.2.4. 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.

6.2.5. 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, 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;
- ✓ Renal function: eGFR, calculated using CKD-EPI formula;
- ✓ CV risk: Estimated 10-year CV risk was calculated using the European Society of Cardiology's HeartScore® tool, adapted for the Portuguese population.

6.2.6. 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). 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.

6.2.7. 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 2021 equation. Patients with baseline eGFR values of less than 60 mL/min/1.73 m2 were classified as having CKD [4]. Changes in eGFR over the study period were compared between patients treated with SGLT2i and those not receiving these agents.

6.2.8. Cardiovascular risk calculation

CV risk was assessed using the HeartScore® tool, which estimates the 10-year risk of fatal and non-fatal CV events. The tool is based on the SCORE2 algorithm and was used to

calculate CV risk at baseline and endpoint, with a focus on the effects of SGLT2i and GLP1RA treatments on these outcomes

6.2.9. Individual Case Safety Reports from EV database

In addition to evaluating clinical outcomes, safety data were obtained from the EV database. ICSRs for SGLT2i (e.g. Jardiance®, Forxiga®), GLP1RA (e.g. Ozempic®, Victoza®), DPP4i (e.g. Januvia®), metformin, and long-acting insulins (e.g. Lantus®, Levemir®) were analyzed from 1 January 2021, to 31 December 2023. Reported adverse events of interest included AKI, AMI, and cerebrovascular accidents. Pearson's chi-square test was used to assess differences in adverse event incidence between treatments.

6.3. Results

6.3.1. 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 6.1), 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.

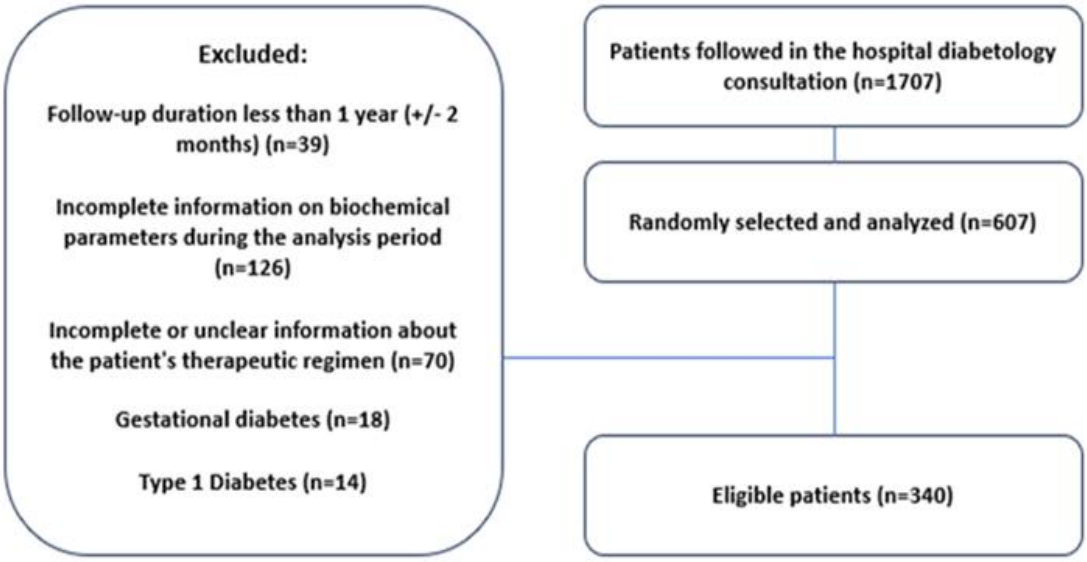


Figure 6.1. Sample selection

6.3.2. Sample characterization

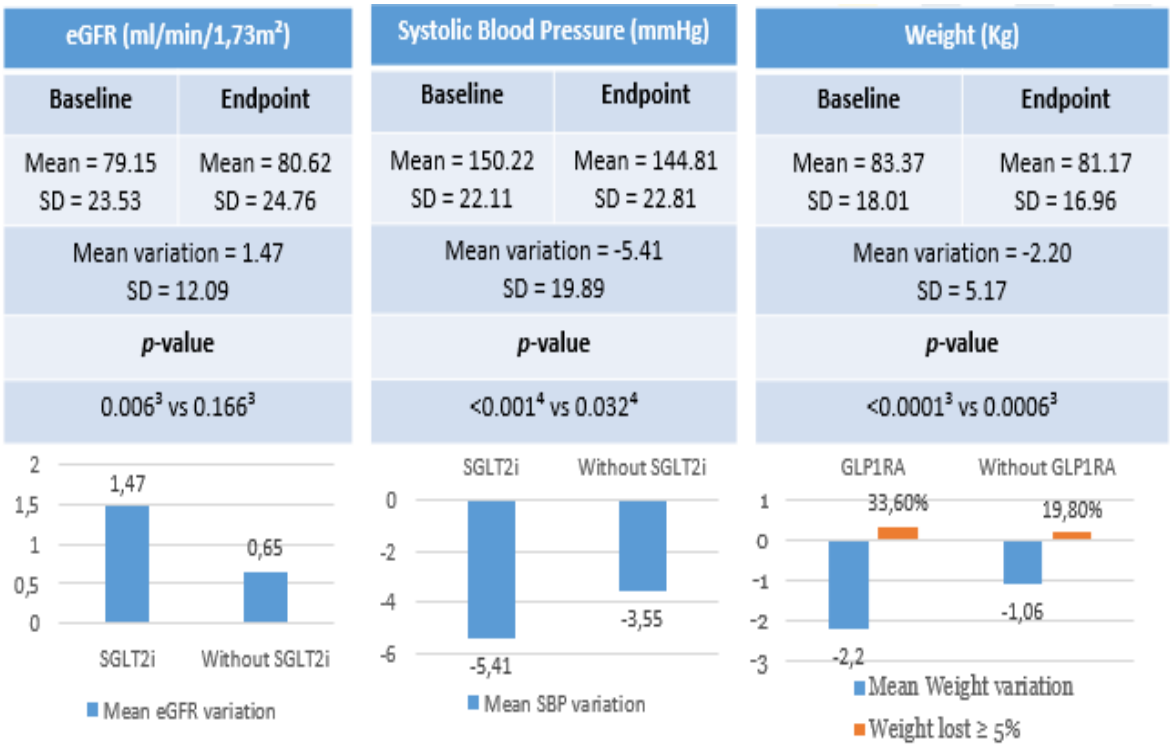
Among 340 patients analyzed, 58.2% were treated with SGLT2i and 42.1% with GLP1RA (Table 6.1).

Table 6.1. 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
SBP (mmHg)		151.26	147.00	96-249	78-229	21.17	22.66
DBP (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%)
GLP1RA			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%)

6.3.3. SGLT2i effects on kidney function and systolic blood pressure and GLP1RA effects on weight

SGLT2i improved renal function (p=0.006) and reduced systolic blood pressure (SBP) (p=0.0002). GLP1RA was associated with significant weight loss (p<0.0001) (Figure 6.2).



³Wilcoxon signed-rank test
⁴Paired samples t- test

Figure 6.2. SGLT2i effects on kidney function and systolic blood pressure and GLP1RA effects on weight.

6.3.4. SGLT2i and GLP1 RA effects on cardiovascular risk and HbA1c

Both treatment groups showed significant reductions in CV risk scores. For patients treated with GLP1RA, CV risk scores decreased from baseline to endpoint (p=0.002). Similarly, patients treated with SGLT2i saw reductions in CV risk scores (p=0.004) (Table 6.2).

Table 6.2. GLP1RA and SGLT2i Effects on Cardiovascular Risk Scores.

	Baseline		Endpoint		*p*-value
	Mean	SD	Mean	SD	
GLP1RA (n=143)	10.59	7.05	10.08	6.94	0.002[3]
SGLT2i (n= 198)	11.36	7.57	10.94	7.39	0.004[3]
GLP1RA and SGLT2i (n=104)	10.96	7.30	10.56	7.19	0.040[3]
Without GLP1 RA and/or SGLT2i (n=103)	13.94	9.36	13.37	9.13	0.010[3]

[3]Wilcoxon signed-rank test

Among patients with baseline HbA1c ≥ 7.0% (n=212), both SGLT2i (p=0.002) and GLP1RA (p=0.010) treatments were associated with significant reductions in HbA1c levels after one year (Table 6.3).

Table 6.3. SGLT2i and GLP1RA Effects on HbA1c after 1 year of treatment

HbA1c at baseline ≥ 7.0%	**Baseline**		**Endpoint**		**mean variation**	***p*-value**
	Mean	SD	Mean	SD		
GLP1RA (n=94)	8.41	0.98	8.13	1.25	-0.28	0.010[4]
SGLT2i (n= 135)	8.21	1.15	7.91	1.20	-0.30	0.002[3]
Total (n=212)	8.36	1.27	8.05	1.31	-0.31	0.0001[3]

[3]Wilcoxon signed-rank test
[4]Paired samples t- test

6.3.5. SGLT2i effects on blood sodium and potassium levels

No significant associations 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.

6.3.6. 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 EV database for SGLT2i and 16,121 for GLP1RA. The adverse events analyzed included AKI, AMI, and cerebrovascular accidents. The incidence of AMI was significantly lower for GLP1RA (0.06%, p<0.0001) compared to other treatments. Both SGLT2i and GLP1RA demonstrated a low incidence of AKI and cerebrovascular accidents (p<0.0001) (Table 6.4).

Table 6.4. 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[1]	p<0.0001[1]	p<0.0001[1]

[1] Pearson's chi-square test

6.4. Discussion

This study confirmed the multifaceted benefits of SGLT2i and GLP1RA in improving renal function, blood pressure, weight, and CV risk scores. SGLT2i significantly reduced SBP and improved eGFR, while GLP1RA demonstrated superior weight reduction. Adverse events were minimal, reinforcing their safety profiles.

6.4.1. Renal function

A significant improvement in eGFR was observed in patients treated with SGLT2i. This finding is consistent with landmark trials such as the DAPA-CKD and EMPA-KIDNEY trials, which demonstrated renoprotective effects of SGLT2i in patients with CKD, independent of diabetes status [5,6]. The improvement in eGFR is particularly significant, as it suggests that SGLT2i can slow the progression of renal function decline impairment in T2DM patients [7]. However, the modest magnitude of improvement in real-world settings compared to clinical trials may reflect the complexities of patient comorbidities and variations in adherence.

6.4.2. Blood pressure reduction

Recent evidence has shown that SGLT2i can significantly improve SBP in patients with T2DM, in addition to their cardioprotective effects in patients with HF [8–11]. A significant reduction in SBP was observed in patients treated with SGLT2i, supporting previous evidence of their antihypertensive effects. SGLT2i promote natriuresis and osmotic diuresis, which contribute to reducing blood pressure [12]. These findings support previous evidence from studies which highlighted antihypertensive effects alongside CV protection. Integrating SGLT2i into treatment regimens for hypertensive patients with T2DM may thus represent a valuable strategy for reducing overall CV risk.

6.4.3. Weight reduction

The weight-reducing effects of GLP1RA were notable, with over one-third of patients achieving clinically significant weight loss (defined as ≥5% reduction). This outcome mirrors results from clinical trials, underscoring GLP1RA's dual role in managing glycemia and obesity [13,14]. GLP1RA has gained approval for the treatment of obesity, and our findings further reinforce its role in weight management in patients with T2DM [15]. Although adherence challenges in real-world settings may impact the extent of weight loss, these agents remain a cornerstone for patients with concomitant obesity and T2DM [16–19].

6.4.4. Cardiovascular risk

Both SGLT2i and GLP1RA demonstrated significant reductions in CV risk scores, reinforcing their roles as essential therapies for high-risk T2DM populations. SGLT2i were particularly effective in reducing HF hospitalizations and MACE, consistent with data from several trials [20–22]. Similarly, GLP1RA showed promise in reducing CV events, as evidenced by LEADER and SUSTAIN-6 [23,24]. These findings emphasize the importance of prioritizing these agents for patients with established CV disease or elevated CV risk factors.

6.4.5. Glycemic control (HbA1c)

Both drug classes achieved significant reductions in HbA1c, although the magnitude of improvement was slightly attenuated compared to clinical trials [25,26]. This discrepancy may stem from real-world challenges such as polypharmacy, adherence issues, and the presence of advanced comorbidities. Nevertheless, the observed reductions underscore the effectiveness of these therapies in optimizing glycemic control in routine clinical practice [27,28].

6.4.6. Safety profile and adverse events

Real-world data from the EV database confirmed the favorable safety profiles of SGLT2i and GLP1RA. Gastrointestinal side effects, particularly with GLP1RA, were the most frequently reported ADRs, highlighting the importance of gradual dose escalation and patient education [29-32]. Notably, both drug classes exhibited low incidences of AKI and CV events, further supporting their safety and effectiveness in complex patient populations [29,33]. Future research should focus on mitigating ADRs to enhance treatment adherence and outcomes.

6.4.7. Clinical implications

Integrating SGLT2i and GLP1RA into individualized treatment plans offers significant advantages beyond glycemic control, including CV risk reduction, renal protection, and weight management. However, successful implementation requires tailored approaches that account for patient-specific factors such as comorbidities, adherence, and socioeconomic barriers. These findings underscore the need for multidisciplinary strategies to optimize therapeutic outcomes and improve quality of care for patients with T2DM.

6.5. Main Conclusions

- ✓ This study provides real-world evidence supporting the effectiveness and safety of SGLT2i and GLP1RA in the management of T2DM.
- ✓ Both drug classes provided benefits beyond glycemic control, such as preservation of renal function, weight loss, and reduction of CV risk. These effects, observed in routine clinical practice, align with results from controlled clinical trials, underscoring their essential role in T2DM management.
- ✓ Analysis of adverse events from the EV database further supports the favorable safety profiles of SGLT2i and GLP1RA compared to other antidiabetic agents, particularly with lower incidences of AKI, CV events, and cerebrovascular accidents.
- ✓ Given these benefits, SGLT2i and GLP1RA should be considered for broader use, especially in T2DM patients with increased CV and/or renal risk.
- ✓ While these findings underscore the clinical value of these agents in real-world settings, further prospective studies with larger and more diverse populations are warranted to fully assess their long-term effectiveness and safety, particularly in high-risk patients and those with multiple comorbidities.

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Chapter 7
General Discussion

This doctoral thesis provides an integrated evaluation of the safety and effectiveness profiles of SGLT2i and GLP1RA in diverse real-world clinical settings, including emergency department admissions, hospitalizations, and outpatient diabetology consultations, supplemented by systematic pharmacovigilance data analysis from the EV database. The research addresses key knowledge gaps in the translation of clinical trial evidence to routine patient care, with special emphasis on elderly patients, multiple comorbidities, and polypharmacy scenarios that characterize contemporary diabetic cohorts.

The studies conducted demonstrate that SGLT2i consistently lower blood glucose levels, reduce systolic blood pressure, and confer substantive renoprotection, as evidenced by both clinical outcomes and declines in hospitalization rates for heart failure, in line with pivotal trials such as DAPA-CKD and EMPA-KIDNEY [1-3]. Critically, transient reductions in eGFR and electrolyte disturbances (e.g., hyponatremia, hyperkalemia) are observed during treatment initiation, justifying the need for vigilant laboratory surveillance for high-risk patients. GLP1RA, meanwhile, exhibit pronounced efficacy in weight management and cardiovascular risk reduction. Weight loss and improvement in cardiometabolic parameters, including reduced HbA1c, reinforce GLP1RA as essential agents for T2DM patients, especially those with concomitant obesity and CV disease risk factors. These findings reflect and reinforce results from controlled trials such as LEADER and SUSTAIN-6 [4,5]. The most frequent adverse events reported for GLP1RA were gastrointestinal disturbances, which were generally manageable with personalized titration and patient education strategies.

The thesis highlights the necessity of tailoring therapeutic approaches to patient-specific factors, including age, gender, comorbidity burden, and social support systems. SGLT2i and GLP1RA require strategic deployment, and combinations involving metformin and DPP4i were found to offer safer profiles in regard to acute complications. Conversely, drug utilization patterns varied with demographic variables and patient social circumstances, stressing the importance of personalized diabetes management and integrated care.

The comparative safety analysis against EV pharmacovigilance data underscores the low incidences of acute renal injury and MACE for SGLT2i and GLP1RA in hospital and outpatient settings. However, limitations inherent to spontaneous reporting systems, including underreporting and lack of granular clinical detail, must be considered when interpreting these findings.

This thesis contributes to the growing recognition of SGLT2i and GLP1RA as key pharmacological pillars in managing T2DM, offering substantive benefits that transcend glycemic control, specifically, CV and renal protection alongside weight management. Ongoing evaluation and real-world monitoring will support the continuous refinement of their clinical application, maximizing therapeutic benefits while minimizing risk across patient populations with complex needs.

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Chapter 8

Conclusions and Recommendations for Future Research

8.1. Conclusions and Limitations

The findings of this dissertation underscore the significant contributions of SGLT2i and GLP1RA to the management of T2DM. Both drug classes demonstrated multifaceted benefits extending beyond glycemic control, including renal protection, CV risk reduction, and weight management.

- SGLT2i: These agents were effective in lowering blood glucose levels, reducing SBP, and preserving renal function, consistent with evidence from clinical trials like DAPA-CKD and EMPA-KIDNEY. However, potential risks such as transient declines in eGFR and electrolyte imbalances underscore the need for careful monitoring, especially during treatment initiation.
- GLP1RA: This class of drugs showed pronounced effects on weight reduction and CV risk mitigation, as corroborated by trials like SUSTAIN and LEADER. Gastrointestinal adverse events, although frequently reported, were generally manageable with dose adjustments and patient education.

Real-world data from the EV database provided a comprehensive understanding of the safety profiles of these therapies, highlighting low incidences of AKI and MACE compared to traditional antidiabetic drugs. These findings align with and reinforce the outcomes of controlled clinical trials, emphasizing the relevance of SGLT2i and GLP1RA as integral components of T2DM therapy.

While the study provides valuable insights, several limitations should be noted:

1. **Monocentric Data Collection:** The reliance on data from a single center may limit the generalizability of the findings. A multicenter approach would provide a broader perspective and enhance external validity.
2. **Population Characteristics:** The advanced age and comorbidities of the study population may not fully represent younger or healthier cohorts, potentially limiting the applicability of findings to diverse patient groups.
3. **Missing Data:** The absence of complete data for some patients may have introduced bias, particularly in analyses where exclusions were necessary due to incomplete records.

4. **Real-World Confounding Factors:** The observational nature of the study introduced uncontrolled variables, such as variations in lifestyle, adherence, and concomitant treatments, which may have influenced the outcomes.
5. **Reliance on EV Data:** Safety data derived from spontaneous reports in the EV database may be subject to reporting bias and lack detailed patient-specific information.

8.2. Recommendations for Future Research

1. Conduct multicenter studies to further validate these findings across diverse patient populations and healthcare settings.

2. Explore the long-term outcomes of SGLT2i and GLP1RA therapy, with particular focus on hard endpoints such as mortality and progression of chronic diseases.

3. Investigate strategies to minimize ADRs, particularly the gastrointestinal effects associated with GLP1RA.

4. Develop real-world monitoring tools to optimize therapeutic outcomes and improve medication adherence among patients with T2DM