Universidade de Lisboa

Faculdade de Farmácia

SGLT-2 inhibitors users profile recruited through a Pharmacy-based Intensive Monitoring Study

Analysis of the pharmacotherapeutic profile, drug-drug interactions, and comparison with the population of the randomized controlled trials.

Bernardo Manuel Ribeiro Pereira Simões Crispim

Mestrado Integrado em Ciências Farmacêuticas

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Resumo

Diabetes *Mellitus* (DM) é uma doença crónica que afeta mais de 400 milhões de pessoas globalmente. É caracterizada por hiperglicemia constante devido à incapacidade do organismo produzir insulina, DM tipo 1, ou de utilizar a insulina de forma efetiva, DM tipo 2. Em Portugal, em 2015, a prevalência de DM atingiu 13.3% da população, sendo grande parte dela não diagnosticada. Estima-se que ao DM tipo 2 seja responsável por cerca de 90% do total dos casos, em Portugal e mundialmente, e que atinja maioritariamente os grupos etários mais avançados. Devido à elevada prevalência desta doença na população portuguesa, os seus custos para o Sistema Nacional de Saúde são bastante elevados, representando mais de 10% de todos os custos em saúde anualmente.

Atualmente, existem diversas opções terapêuticas que permitem controlar os níveis séricos de glucose no sangue e, consequentemente, controlar os sintomas da doença e a sua progressão. Fazem parte deste arsenal terapêutico antidiabéticos orais, como a metformina e, que são considerados de primeira linha, após intervenções no estilo de vida, no tratamento da DM tipo 2. Os inibidores do co-transportador de sódio-glucose, da qual faz parte a dapagliflozina, são uma nova classe de fármacos que atuam no sistema de reabsorção de glucose no túbulo proximal renal. Através da inibição deste transportador em específico, a quantidade de glucose excretada na urina aumenta e assim reduz a quantidade sérica de glucose. As mais recentes recomendações terapêuticas aconselham a utilização desta nova classe em monoterapia ou em conjunto com outros fármacos, incluindo insulina. Para além dos benefícios no controlo sérico da glucose, os inibidores de SGLT-2 têm ainda um efeito benéfico na redução do peso corporal, na pressão sanguínea e no colesterol, diminuindo assim os fatores de risco para a doença cardiovascular.

Na população diabética o risco de interações fármaco-fármaco é bastante elevado. Isto acontece por várias razões: com a progressão da doença o controlo da glicémia torna-se mais difícil e na maioria dos casos os regimes farmacoterapêuticos tornam-se mais complexos, com maior número de fármacos necessários para atingir os resultados expectáveis; a diabetes está associada ao aparecimento e à coexistência de diversas patologias, nomeadamente retinopatia, dano neural, hipertensão e dislipidemia, por isso recorre-se a terapias farmacológicas concomitantes para tratamento destas comorbilidades. Uma interação fármaco-fármaco resulta de uma interferência na farmacocinética ou farmacodinamia de um fármaco, provocada pela presença de um outro. Atualmente, as interações entre fármacos são responsáveis por grande parte das reações adversas ao medicamento e por um aumento considerável da incidência de hospitalizações. Relativamente aos fármacos utilizados na diabetes, a sua

toxicidade está associada ao uso concomitante de fármacos como propranolol, AINEs, inibidores da MAO, entre outros. De forma a tornar as terapias eficazes e a promover uma melhor saúde dos doentes, têm sido desenvolvidas diversas tecnologias que permitem aos profissionais de saúde obter rapidamente informação acerca de potenciais interações fármaco-fármaco dentro de um perfil farmacoterapêutico.

O desenvolvimento deste estudo surge da necessidade constante de gerar evidência da utilização dos fármacos na rotina da prática clínica, especialmente quando os fármacos são recentes ou em doenças tão importantes, como é o caso da Diabetes. No momento em que um fármaco passa a estar disponível no mercado, apenas se tem acesso a informação gerada durante os ensaios clínicos relativamente à qualidade, eficácia e a parte do perfil de segurança do fármaco. Esta eficácia apenas se encontra demonstrada para uma determinada população e indicação específica, devido ao ambiente altamente controlado dos ensaios clínicos. No entanto, em contexto real, como as condições clínicas não são tão controladas, os resultados obtidos com a utilização dos fármacos são muitas vezes diferentes daqueles obtidos em ensaios clínicos. Assim, no momento de introdução do medicamento no mercado, existe um vazio no conhecimento na forma de como um fármaco se comporta na realidade, que apenas pode ser reduzido com o desenvolvimento de estudos em contexto real de utilização e com a geração de evidência decorrente da prática clínica.

Este estudo de monitorização intensiva tem como objetivos principais a caracterização da população que utiliza dapagliflozina no tratamento da diabetes e a investigação de potenciais interações fármaco-fármaco entre a dapagliflozina e outra medicação que esteja a ser utilizada pelos participantes do estudo, quer para controlo da diabetes quer para outras patologias.

Este estudo é definido como uma coorte prospetiva que recolhe informação desde o primeiro dia de utilização do fármaco em estudo (dapagliflozina) é tomado. Todas as farmácias comunitárias pertencentes à Associação Nacional das Farmácias que cumpriam os critérios de inclusão (n=1979) foram convidadas a participar, sendo que aceitaram participar 670 farmácias. O recrutamento de participantes decorreu entre os meses de novembro de 2014 e abril de 2015. Os dados foram recolhidos através de um questionário que permitia obter informação sociodemográfica, antropométrica e clínica de auto-reporte dos participantes. As características dos participantes foram descritas através de frequências relativas e absolutas, medidas de dispersão e de tendência central. Procedeu-se à comparação da população do estudo com os dados recolhidos dos ensaios clínicos da dapagliflozina. A obtenção destes ensaios e respetivos artigos científicos foi realizada através da plataforma clinicaltrials.gov e PubMed. Foram ainda analisadas as potenciais interações fármaco-fármaco entre a dapagliflozina e outra

medicação que os participantes estivessem a utilizar, tanto para a diabetes como para outras patologias presente. Esta análise foi feita recorrendo à ferramenta Micromedex®.

Um total de 329 doentes que utilizaram a dapaglifozina pela primeira vez e que preencheram os critérios de elegibilidade foram incluídos no presente estudo. Quanto às características demográficas, ambos os géneros estavam igualmente representados na população; grande parte dos indivíduos encontrava-se no grupo etário dos 56-74 anos de idade; mais de metade da população possuía um índice de massa corporal igual ou superior a 30kg/m^2. Relativamente aos dados clínicos autoreportados: cerca de metade tinha um tempo de duração de diabetes igual ou superior a 10 anos; a grande maioria utilizava mais do que um medicamente para controlo da diabetes (com exceção da dapagliflozina); cerca de 20% utilizava insulina; aproximadamente 85% da população reportaram a coexistência de outras patologias para além de diabetes, algumas delas relacionadas com a progressão desta doença; mais de 90% estavam a tomar medicação para outras patologias para além daquela utilizada no controlo de diabetes.

Em relação à comparação com os ensaios clínicos, na globalidade, as características populacionais dos participantes deste estudo aparentam ser similares com as características dos participantes dos ensaios clínicos da dapagliflozina, no que respeita aos dados sócio-demográficos. No entanto, foram encontradas algumas diferenças, nomeadamente no que diz respeito ao tempo médio de duração de DM dos participantes de alguns dos ensaios. Nem todos os ensaios clínicos apresentavam dados relativamente à prevalência de patologias concomitantes, fatores que bastante prevalentes na população do nosso estudo.

No que diz respeito às interações fármaco-fármaco, foram identificadas interações com vários tipos de insulina, agentes que atuam no eixo renina-angiotensina e bloqueadores-beta. Todas as interações identificadas possuíam a classificação de gravidade moderada, sem necessidade de retirar qualquer um dos fármacos em questão. Recomendava-se, no entanto, uma monitorização mais acentuada, uma vez que as possíveis interações pudessem provocar uma maior incidência de episódios de hipoglicémia.

. Adicionalmente, o estudo contribuiu para o conhecimento do perfil de segurança da dapagliflozina em contexto-real, não existindo interações clinicamente relevantes que pudessem colocar em risco a saúde dos doentes. Como perspetiva de estudos futuros, será importante avaliar a efetividade e o custo-efetividade da dapagliflozina e outros SLGT-2 na rotina da prática clínica, em Portugal.

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Finally, but most important, my family and friends. For being my companions along the five years of course, for being there in the bad and good moments. Word cannot describe I appreciate and blessed I am for having you.

"Do or do not. There is no try."

- Master Yoda

Data presented in this thesis were collected during a pharmacy-based intensive monitoring study, which is part of an on-going PhD project of the Faculty of Pharmacy from the University of Lisbon (FFUL) / Research Institute for Medicines (iMed.ULisboa) of Carla Torre, supervised by Prof. Dr. Ana Paula Martins and Prof. Dr. Hubert Leufkens.

This pharmacy-based intensive monitoring study was implemented in the Centre for Health Evaluation & Research (CEFAR) that belongs to the National Association of Pharmacies (ANF) and was fully funded by ANF.

Index

Introduction **1**

1. Epidemiology of Diabetes. 1
2. Therapeutic Options. 2
   2.1. SGLT-2 Inhibitors. 6
3. Bridging the GAP between RCT and Routine Clinical Practice. 6
4. Drug-drug Interactions. 8

Objectives **10**

Study Design & Methods **11**

1. Study design, setting and population. 11
2. Data collection 11
3. Analysis. 12
   3.1. Baseline and demographic characteristics. 12
   3.2. Drug-Drug Interaction Analysis. 12

Results **13**

1. Baseline and demographic characteristics 13
2. Drug-Drug Interaction Analysis. 19

Discussion **22**

1. Baseline and demographic characteristics. 22
2. Drug-drug interaction. 25
3. Limitations 26

Conclusions **28**

References **29**

Introduction

1. Epidemiology of Diabetes.

Diabetes is a common chronic disease, spread worldwide, characterized by the inability of the pancreas to produce insulin (type 1 diabetes), or the body to use insulin effectively (type 2 diabetes). While Type 2 Diabetes Mellitus (T2DM) can be prevented with healthy lifestyle, Type 1 Diabetes Mellitus (T1DM) etiology discovery is a challenge for medical community. No matter the type, the major symptom of diabetes is the raise of blood glucose, above the optimal threshold (> 126 mg/dL) (1), with glycated haemoglobin (HbA1c) being the most important biomarker for hyperglycaemia.

If not properly controlled, over time, the high concentrations of blood glucose will lead to serious complications in various organ systems and consequently a higher risk of dying prematurely (2). Cardiovascular system is the most affected by the increased blood glucose concentration, with cardiovascular disease the major cause of death and disability in people with diabetes, approximately 50% of all deaths in these patients (3–5). Although the cardiovascular system is the most harmed, kidney disease, neuropathy, blindness, as well as limbs amputations are other common complications of diabetes (3–6). Beside the health issues mentioned above, the economic cost for the patients and society itself is also a great burden associated with this pathology (5,6).

According to the World Health Organization (WHO) Global Report on Diabetes, in 2014, it was estimated that, globally, 422 million adults were living with Diabetes Mellitus (7). T2DM is the most common form of the disease, representing almost 90% of the cases (7,8). The WHO Global Report also acknowledged that the prevalence of diabetes has been risen over the years, doubling its percentage between 1980 and 2014 (7). In Portugal, the reality has been similar to the rest of the world, although the prevalence is slightly higher, reaching 13,3% of population by 2015, being almost 45% of the cases undiagnosed (6). In Portugal, over 1 million citizens between the age of 20 and 79 years (6) are affected by Diabetes Mellitus, being Portugal one of the European countries with the highest prevalence rate (9). The national annual report issued in 2016, regarding the year of 2015, drawn up by the National Diabetes Observatory, concluded that older age groups have a higher prevalence of diabetes in contrast with younger groups, which is in agreement with the global trend (6). The increasing of diabetes prevalence has also been accompanied by an increase of medicines consumption, either in volume and in value (6). In the year of 2015 alone, the sales of insulin and other glucose lowering drugs (GLD) reached 260 million euros, with 91,6% (238,8M €) reimbursed by the National Health System (NHS) (6). This amount represented a total growth of 269% when

compared to the year of 2006 (6). In 2015 the costs of diabetes represented 1% of the Portuguese GDP and 12% of the government health expenditures (6).

2. Therapeutic Options.

Diabetes has turned up to be a major public health problem all around world with a huge economic impact for the society. Therefore, there has been a great need to invest on the research of diabetes and how it can be treated and controlled, which has resulted in the development of a wide range of treatment options. However, beside the effort and the investment, no cure has been developed, therefore all therapies currently available act as glucose lowering agents and only control of the glycaemic.

Insulin, since its discovery, has been the gold standard treatment for T1DM and further stages of T2DM, when therapy using GLD is not effective (10). According to Portuguese guidelines, insulin use is recommended in advanced stages of the disease (11).

GLDs embrace a wide variety of medicines that have distinct targets in the body with the common goal to reduce the blood glucose levels. Biguanides (metformin), sulfonylureas (e.g. gliclazide), thiazolidine (e.g. pioglitazone), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g sitaglitine), glucagon-like peptide-1 (GLP-1) receptor agonists (e.g.liraglutide) and sodium/glucose cotransporter 2 (SGLT-2) inhibitors (e.g. dapaglifozin) are the GLD available classes (10). These drugs can act by: stimulating the insulin production; improving insulin sensitivity; inhibiting glucose absorption; or increasing glucose excretion (12).

The first approach to control or prevent evolution from prediabetes to T2DM is lifestyle changes, concerning dietary habits and exercise (1,10,12). Randomized Clinical trials (RCT) have shown that individuals with high risk of developing T2DM, have been able to reduce diabetes onset with specific lifestyle interventions (1). Evidence supports the importance of maintaining a healthy and balanced diet with predominance of fruits, vegetables, fibres and protein with low fat content (1,12). According to the American Diabetes Association (ADA) guideline, it is more important to control the type and quality of fat consumed, than lowering the amount of total fat consumption (1). Mediterranean diet is a good option since is relatively rich in monosaturated vegetables fats (1,12). Physical activity and exercise are important interventions that should be adopted as well, in order to prevent T2DM onset. Moderate exercise, focused on aerobic and resistance training combined (1, 12), has an important impact managing HbA1c (12) and improving insulin sensitivity (1). For adults with T2DM, who are overweight, it is beneficial and important the initial loss of 5-10% of body weight (10).

When lifestyle changes are not enough to achieve or maintain glycaemic goals and further T2DM progress, pharmacological interventions must be implemented (1, 10). For this type of the disease, the initial drug treatment is metformin used in monotherapy, which has been the gold standard for a long time (1,10–13). When metformin is contraindicated or not well tolerated, another GLD must be considered, being DPP-4 inhibitor, pioglitazone and sulfonylurea second-line drugs, which can replace metformin (1,10–13).

If glycaemic control is not achieved with initial monotherapy after three months, it should be made a first intensification adding a second GLD to the therapy (1,10–13). American Diabetes Association treatment guideline, states that the second drug choice should be based on patient preference as well as various patient, disease, and drug characteristics. Second drug options can be any of the following: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor antagonists or basal insulin (1) (Figure 1). Insulin injectable therapy should be considered only when blood glucose is ≥ 300-350 mg/dL and/or HbA1c is ≥ 10-12% (1). On the other hand, NICE (10), International Diabetes Federation (IDF)(13) and national (11) guidelines, consider as well patient preference and characteristics, but give preference to DPP-4 inhibitors, pioglitazone or sulfonylurea (Figure 3 and Figure 4). In further T2DM stages, when glycaemic control is not achieved, a second intensification must be made which consists by adding another GLD to therapy, or by the initiation of injectable insulin combined with a GLD, if needed (1,10,11,13). In Portugal, the beginning of insulin therapy is advised when: after 3 months using metformin without glycaemic control and HbA1c > 9%; or, after 3-6 months using 2 GLD without glycaemic control it is intended to reduce Hba1c by 1% (11).

T2DM has a very complex therapeutic regimen which is hampered by its chronic character. These characteristics combined increase the risk of decreased treatment effectiveness due to patient adherence. Ultimately, patients make the final decisions regarding their lifestyle choices and pharmaceutical interventions, thus conditioning the medical outcomes (14).

Patient-centered care should be the core principle when implement a healthcare strategy for individuals with a chronic disease, being particularly appropriate in T2DM. This approach is defined as “providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions” (15). In this process of shared decision-making, health professionals and patient act as partners, exchanging information and discussing options, in order to reach consensus on the therapeutic process (14). With this method

adoption, by engaging patients in their healthcare decisions, may enhance adherence to therapy as well improved medical outcomes (14).

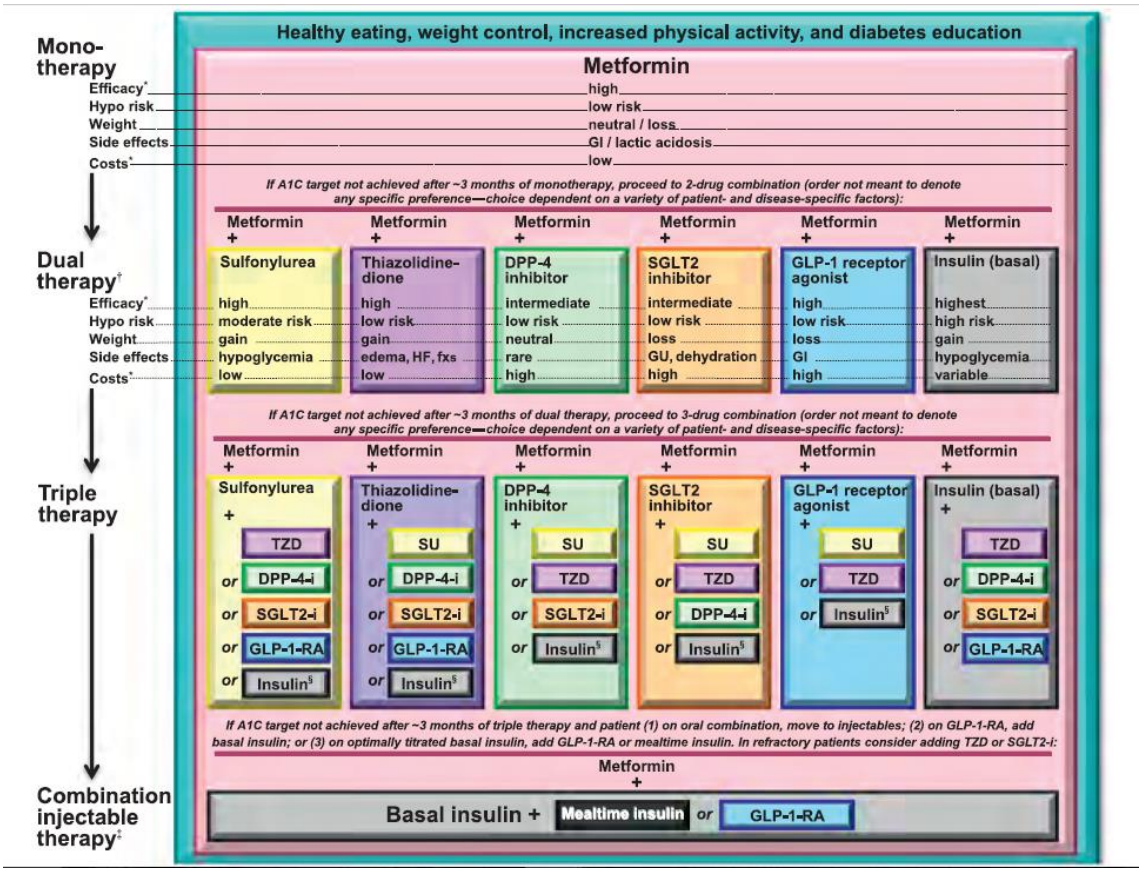

Figure 1 – American Diabetes Association algorithm for T2DM therapy. (1)

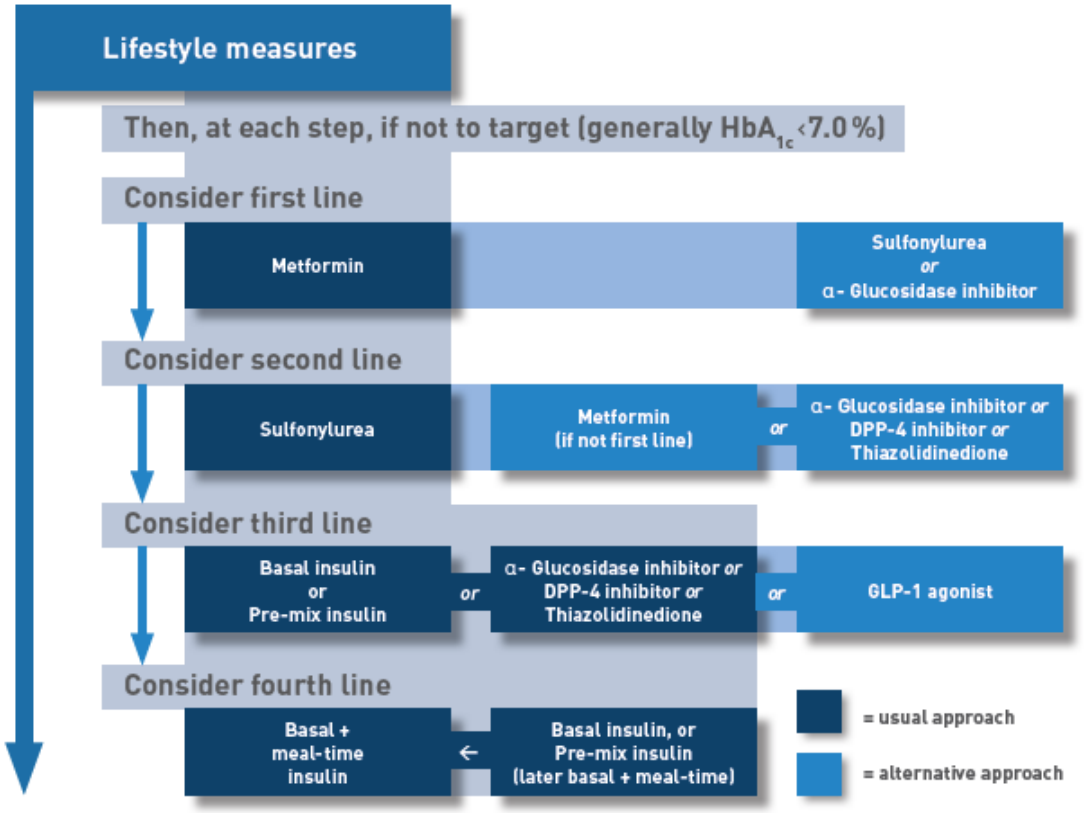

Figure 2 – The National Institute for Health and Care Excellence algorithm for T2DM therapy. (10)

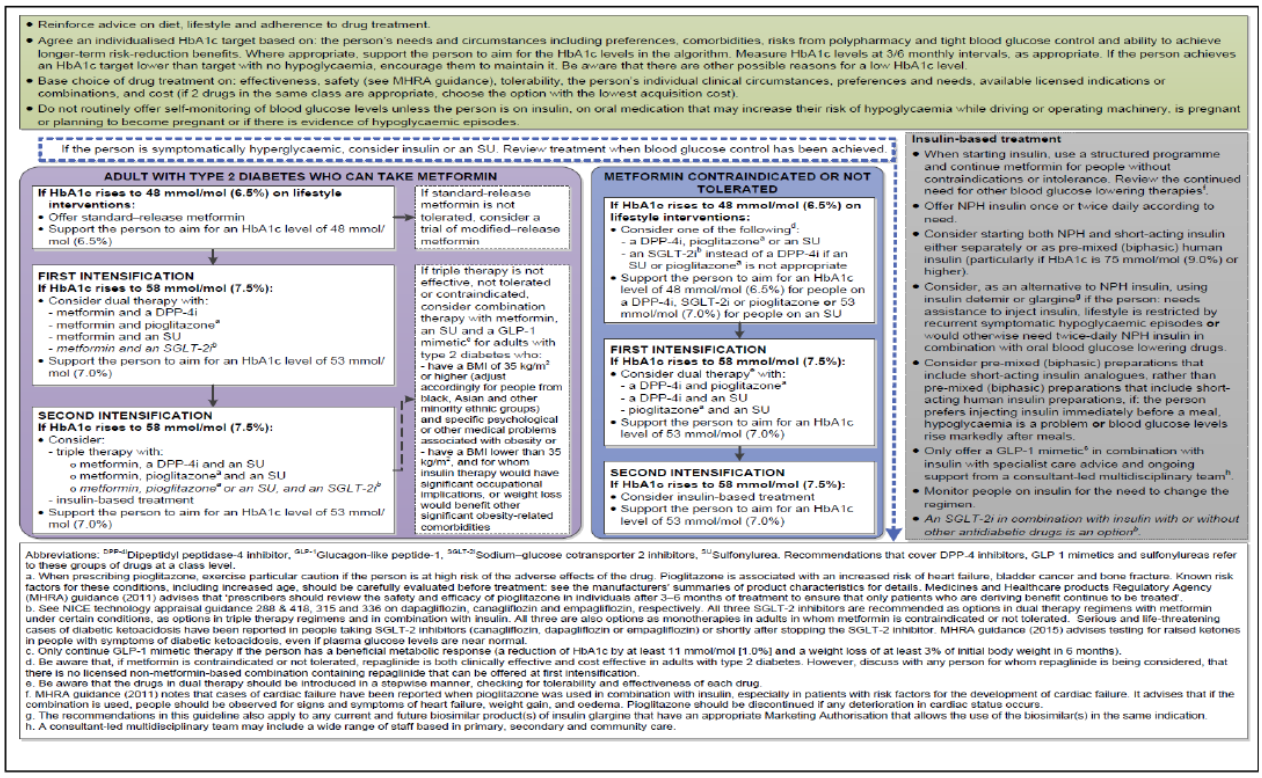

Figure 3 – International Diabetes Federation algorithm for T2DM therapy. (13)

2.1. SGLT-2 Inhibitors.

The most recent class of drugs marketed for diabetes treatment are the SGLT-2 inhibitors. These new drugs work by inhibiting SGLT-2 receptors of the proximal renal tube responsible for reabsorbing about 90% of the filtered glucose in the kidney (4,16). They inhibit 30-50% of the reabsorption of filtered glucose (17), which results in an increased amount of urinary glucose excretion, hence leading to a reduction on blood glucose concentration (16,17). However, the risk of hypoglycaemia is minimal (18). Because the mechanism of action is dependent on blood glucose levels and independent of insulin action, the risk of hypoglycaemia is minimal and may be used in any stage of T2DM treatment course (16,17,19). All three SGLT-2 inhibitors, canagliflozin, dapagliflozin, and empagliflozin, have been approved by FDA and EMA for use as a diet adjunct to improve glycaemic control in adults (16) In Portugal, in 2017, dapaglifozin alone or in fixed-dose with metformin and empagliflozin were reimbursed (20).

Current guidelines suggest that SGLT-2 inhibitors could be used as monotherapy, in patients that cannot tolerate or have a contraindication to metformin, or as an add-on therapy to metformin as a second or third intensification of the therapy (1,14,16). Furthermore, SGLT-2 inhibitors can be used for dual and triple combination therapy with any GLD, including insulin (16,21). Beside the effect on managing glycaemia and T2DM progression, SGLT-2 inhibitors have other beneficial non-glycaemic effects, including a reduction on body weight and blood pressure, increase in plasma concentrations of HDL and a decrease of protein C-reactive (16,18,22).

By promoting the excretion of glucose via urinary tract, due to its unique mechanism of action, the therapy with SGLT-2 inhibitors is related to an increase, 3 to 4 times, in the number of cases of uro-genital tract infections (16–18), as well as several adverse reactions related to volume depletion (e.g. orthostatic hypotension) and osmotic diuresis (e.g. polyuria) (16). Since these drugs can cause changes on blood volume and osmotic pressure, it is expected to alter cardiovascular function. However, a study conducted by Bernard Zinman and colleagues, concluded that, comparing with a placebo, patients with T2DM with high risk of cardiovascular events who were being treated with empagliflozin once daily, had a lower rate of dying from cardiovascular causes (23).

3. Bridging the GAP between RCT and Routine Clinical Practice.

Medicines must demonstrate additional value for patients, health and payers, and therefore the marketing authorization approval requires an extensive, well-documented and controlled clinical investigations (24). Randomized Controlled Trials (RCTs) are the gold-standard studies to prove efficacy, safety, and quality of drugs and, for such reason,

the support for marketing authorization requests. This facts rests on high internal validity of RCTs, due to the randomization process and the use of strict inclusion and exclusion criteria that minimize bias and allow a great control of variables (25). However, at the time of marketing approval, the evidence based on RCTs only demonstrate efficacy and safety for a specific label and a specific population (26), due to the strict conditions on which they were performed. This fact represents a problem to trials external validity since the clinical conditions where medicines are used are very often different from those under RCT environment.

The difference on clinical outcomes between RCTs and the routine clinical practice comes up mainly because the characteristics of the population that use the medicine are different from the population of the RCTs (27,28); and because the clinical practise does not follow the label strictly, since the decision of any clinical intervention is based on how it will improve patient health in a certain moment (27–29).

This difference in the outcomes has been addressed as the knowledge gap commonly known as efficacy-effectiveness gap (27,28). Efficacy, assessed by RCTs, is defined as "whether an intervention produces the expected result under ideal circumstances" (30), whereas effectiveness "measure the degree of beneficial effect under real world clinical settings" (30). Eichler *et al.* (27) argued that the reason for this gap is the variability in drug response and described two types of variability sources: biological and behavioural factors. Biological variability arises from the genetic differences between individuals that influences the drug effect on the organisms, and other non-genetic intrinsic (e.g. sex, age, body weight, comorbidities, etc) and extrinsic (e.g. environmental influences such as pollution) factors (27). The second source of variability, behavioural, is related with the prescribing and drug handling (e.g. the inappropriate use of drugs off-label and medication errors); and patient adherence (e.g. fluctuations in dose-timing regimens to non-adherence), which is a cause of avoidable morbidity, mortality, and lost productivity (27).

On every treatment, there is an inherent risk that may or may not supplant the benefit of taking that drug, depending on the conditions of use. Of course, regulators only give marketing authorization to drugs that clearly show and prove that the benefit supplants the risk of usage, but sometimes the public health interest demands a rapid access to a drug that lack information regarding its safety profile, making the balance between risk and benefit unclear. However, regulators had the capacity to respond to this challenge by introducing flexible pathways (e.g. conditional marketing authorization in the EU) when benefits, arising from the immediate availability, overweight the risks of introducing a drug that requires additional studies to prove a positive benefit-risk balance (31). This concept was entitled as "adaptive pathways", which is a prospective and

integrated process that includes the cooperation of all stakeholders and addresses drug lifecycle as a continuum (31). Because of the constant real-world data extraction, this process allows to bridge the gap between efficacy and effectiveness gradually, with the participation of all stakeholders throughout this process.

4. Drug-drug Interactions.

Patients with T2DM are subject to a complex therapy due to a higher prevalence of comorbidities, such as cardiovascular disease (32,33), that need to be treated, and, as the disease progresses, the use of combination therapies since single drug therapies becomes ineffective (33). As the pharmacokinetics and pharmacodynamics characteristics of each drug are different, they can interact among them and alter their properties, therefore, changing the response to a drug or even cause a an adverse drug reaction (33,34). The relation between two drugs used concomitantly is named Drug-Drug Interaction (DDI) (34–36). As a result of polypharmacy, patients with T2DM, have an increased risk of developing adverse drug reactions, due to DDIs (37) such as hypoglycaemia in patients receiving sulphonylureas and other drugs that interact with CYP2C9 (38). Such interactions may lead to an increased risk of hospitalization and higher healthcare costs (35,39), not to mention the health problem to the patient itself.

DDI may be classified, according to its mechanism, as Pharmacokinetics, when involves absorption, distribution, metabolism, and excretion (ADME); and Pharmacodynamics when the receptor function is affected, there is an interference with a biological/physiological process or when is produced an additive/opposed pharmacological effect (34,36). DDIs are associated with approximately 10-17% of every adverse drug events (ADE) (36,39) and are the cause of up to 2.8% of the hospital admissions (39). The frequency of DDIs is associated with increasing age, female gender, the use of a higher number of drugs and the presence of specific health conditions such as renal failure (36,40), among other factors. In the literature, the most frequently reported DDIs are related to use of anticoagulants, potassium sparing-diuretics, potassium supplements, ACE inhibitors, and carbamazepine (40). Regarding diabetes therapy, increased GLD toxicity is associated with the concomitant use of chloramphenicol, cimetidine, propranolol, non-steroidal anti-inflammatory drugs and MAO inhibitors (40). The long-term use of metformin is associated with the inhibition of vitamin B12 absorption, thus increasing the risk of anaemia or peripheral neuropathy (32,40). Kasichayanula and colleagues also studied the existence of potential interactions between dapagliflozin and several common used drugs, but no clinical evidence was found (32,41).

To improve therapies effectiveness, patient wellbeing, and to reduce healthcare costs, it is of extreme importance that healthcare professionals have knowledge and awareness of DDIs existence (36,37). Healthcare technologies, such as electronic medical record and databases like Micromedex®, are advancing rapidly and can help healthcare professionals (36,42) to improve patient treatment and medical outcomes (37,42).

Objectives

Through an intensive monitoring study conducted under a PhD umbrella in the Faculty of Pharmacy of Lisbon, the present study has two main objectives:

1) to define and characterize the population under dapagliflozin treatment in Portugal and to compare with RCT population in order to contribute to assess RCT external validity.

2) To investigate potential drug-drug interactions between dapagliflozin and other concomitant medication, either for diabetes or other diseases.

Study Design & Methods

1. Study design, setting and population.

Data presented in this article were collected during a pharmacy-based intensive monitoring study, which is part of an on-going PhD project of the Faculty of Pharmacy from the University of Lisbon (FFUL) / Research Institute for Medicines (iMed.ULisboa). This project was implemented in the Centre for Health Evaluation & Research (CEFAR) that belongs to the National Association of Pharmacies.

Intensive monitoring is methodologically defined as an observational, prospective inception cohort study of subjects exposed to the drug of interest and in this study, was focused on gathering longitudinal information since the first day of drug use of the recently launched GLD. The data presented in this study refers only to baseline data of dapagliflozin participants.

Invitation letters and the study brochure were sent to all pharmacy owners of community pharmacies from the National Association of Pharmacies (ANF) that fulfilled the inclusion criteria (i.e. required software, participation in at least one research study in the previous 4 years and had an average daily sale of ≥ 1 inhibitor of dipeptidyl peptidase 4 (DPP-4)/ glucagon-like peptide-1 (GLP-1) package) (n=1979; 67.80% of all Portuguese pharmacies). Pharmacists who agreed to participate were invited to attend a half-day training session in which study objectives and methodology were explained.

Eligible study population consisted of type 2 diabetic patients, first users (defined as who did not take the monitored drug during the 6 months prior to recruitment, as self-reported by the patients) of dapagliflozin.

Pharmacists were instructed to systematically recruit all eligible patients between 15 November 2014 and 15 April 2015. For the eligible subjects who did not wish to participate, information regarding the age group, gender, the monitored antidiabetic drug acquired and the medical specialty responsible for subject's prescription were collected through a refusal log form.

2. Data collection

At baseline, patients had a structured face-to-face interview with a trained pharmacist to collect socio-demographic (birth date, gender, highest educational level completed, co-residence status and number of people living in subject's household, employment status) and anthropometrics data (weight and height were measured at recruitment by pharmacy staff in order to calculate the body mass index (BMI)). Patients were divided according to BMI categories developed by WHO [underweight <18.50, normal range 18.50 - 24.99, overweight ≥ 25.00 (pre-obese 25.00-29.99 and obese

≥30.00)]. Self-reported clinical data included age at time of type 2 diabetes diagnosis, usual diabetes outpatient clinical care (e.g. primary care; hospital specialized diabetes care appointments; private practice), co-morbidities and diabetes related conditions/complications (e.g. retinopathy, nephropathy, diabetic foot) and concomitant therapy). Information about type 2 diabetes treatment (monitored drug and other current antidiabetic treatment) included dose and prescribed posology. Concurrent diseases were classified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). All co-medication therapy and type 2 diabetes treatment were coded according to the Anatomic Therapeutic Classification (ATC). Past type 2 diabetes treatment experience (drugs used and reported motives for discontinuation) prior to enrolment was collected.

3. Analysis.

3.1. Baseline and demographic characteristics.

Baseline characteristics were described for all participants. Discrete variables were summarized by absolute and relative counts and missing values were stated in the corresponding summary table. Continuous variables were summarized using central tendency measures and dispersion, i.e., mean, and standard deviation (SD), median and inter-quartile range (IQR).

Population characteristics will be compared between monitored drugs clinical trials subjects' data and the Portuguese intensive monitoring recruited subjects. The selection of the RCTs was based on the fact that they were used to support the application for marketing authorization. RCTs results and respective scientific papers, were retrieved from clinicaltrials.gov plataform and PubMed.

3.2. Drug-Drug Interaction Analysis.

Two main analysis of drug-drug interaction (DDI) were performed: (1) potential interactions between DAPA and other medicines used in diabetes; (2) potential interactions between DAPA and other medicines used for other comorbidities.

To assess the DDIs, Micromedex® electronic database system was used to identify and analyse the pattern of DDIs. Micromedex® contains a separate tool that screens and identifies any potential DDI within the same pharmacotherapeutic profile. On entering the drugs one by one, the software lists the possible DDIs and categorizes them according to: effect, severity (contra-indicated, serious, moderate, mild, and unknown), onset (rapid, delayed, and unspecified), management, documentation status (excellent, good, fair, poor, unlikely, and unknown), and literature reports.

Results

1. Baseline and demographic characteristics

A total of 670 (33.86%) pharmacies accepted to participate in the study and 385 (19.45%) recruited at least one patient. Regional (p=0.0974) and urban/sub-urban/rural setting (p=0.3716) distribution of pharmacies with recruited patients was similar to the universe of overall community pharmacies but had significantly more pharmacists in their staff (p<0.0001).

A total of 1569 patients were invited to participate, of whom 231 refused to participate. A total of 1328 eligible patients were considered in the main study, of which 329, were using dapagliflozin as a drug for T2DM management.

Gender was practically equally represented within the population, being female proportion slightly higher (50.46%). The population mean age was 61.5 years old (SD 10.40 years), and 218 (66.26%) individuals were between 56 and 74 years of age. More than half of the population (52.89%) had its body mass index above or equal to 30 kg/m^2, being the mean value of 30.98 kg/m^2 (SD 5.28 kg/m^2).

T2DM duration within the population ranged between less than 1 year of duration [22 (6.69%)] and over 10 years of duration [166 (50.46%)]. 79 individuals (24.01%) presented a diabetes duration between 1 and 5 years, while 44 (13.37%) had diabetes between 6 and 9 years of duration. A large number of individuals [290 (88.15%)] were taking 1 or more drugs for T2DM besides dapagliflozin, 122 (37.08%) were taking 3 or more drugs and 65 (19.76%) individuals were currently using insulin. The average number of drugs taken for T2DM, including dapagliflozin, within the population was 3.07 (SD 1.16) per individual. More than a half of the population [189 (57.45%)] reported that had discontinued medication for T2DM in the past.

93.01% of the population, which represents a total 279 individuals, reported the use other medicines for other concomitant pathologies. Renin-Angiotensin System (ATC code C09) drugs and Lipid Modifying Agents (ATC code C10) were the most common drugs taken by the population with 201 (61.09%) and 195 (59.72%) users, respectively.

Regarding other present comorbidities, 73 individuals (22.19%) reported the existence diabetes complications, being retinopathy [58 (17.63%)] the most frequent, followed by diabetic foot [26 (7.90%)]. Likewise, 279 (85.11%) individuals reported the coexistence of other chronic diseases, being the average number of other pathologies per patient 1.66 (SD 1.07). Hypertension [218 (66.26%)] and Dyslipidaemia [181 (55.02%)] were the most common conditions presented within the population.

Relatively to results from the RCTs, the data regarding demographic characteristics are presented in Table 2 and eligibility criteria in Table 3. The mean ages

across the different populations are very similar, ranging from 47.6 years in one of Ferrannini study cohort (43)(43) to 59.3 years in Wilding (44) study. Gender distribution was closely equally represented on every study, being the greater difference in Bailey study, with 42.96% of female and 57.04% of males. All individuals from the different studies had BMI ≥25 kg/m^2, except in the Bailey study. In comparison, our study results can be related to the ones shown by RCTs, except the population mean age that is slightly higher in our study. T2DM mean duration presented varied largely across the different studies. For example, Ferrannini *et al.* reported results of 0.45, 0.4, and 1.4 years on the three cohorts, while Wilding *et al.* reported a mean duration of 14.2 years, being the highest value. In parallel, our study revealed a higher T2DM mean duration than the ones found by Ferrannini (43), Bailey (45,46), Strojeck (47), and Rosentock (48). Bailey *et al.*, Strojek *et al.*, and Wilding *et al.* were the only studies that reported data regarding other comorbidities, such as hypertension and history of cardiovascular disease. Although, Bailey study was the only that reported data relative to diabetes-related condition, such as neuropathy (1), retinopathy (0), and microalbuminuria (1). Bailey (46) and Wilding (44) studies were the only ones that retrieve data regarding other concomitant medication, such as antihypertensive agents, lipid-lowering agents, and acetylsalicylic acid, being the last two only reported by Wilding (44). Like these studies, we found as well in our study the existence of several pathologies related or not-related to diabetes, but in a higher prevalence. Consequently, we also found, a higher prevalence of other concomitant drugs.

Table 1 - Baseline and Demographic Characteristics

N	329	
Age (years)		
< 55	79	24,01%
56 - 64	111	33,74%
65 - 74	107	32,52%
≥75	27	8,21%
Mean (deviation)	61,5 (10,40)	
NR*	5	1,52%
Gender		
male	163	49,54%
female	166	50,46%
NR	0	
BMI (kg/m^2)		
< 25	33	10,03%
25,00 - 29,99	114	34,65%
≥ 30,00	174	52,89%
Mean (deviation)	30,98 (5,28)	
NR	8	2,43%
T2DM duration		
< 1	22	6,69%
[1-5]	79	24,01%
[6-9]	44	13,37%
≥ 10	166	50,46%
Mean (deviation)	10,92 (8,61)	
NR	18	5,47%
Usual diabetes outpatient clinical care		
Primary care	124	37,69%
Hosp. specialized DM care	36	10,94%
Private care	21	6,38%
Other	6	1,82%
NR	142	43,16%
Number of other substances for T2DM		
0	39	11,85%
[1-2]	168	51,06%
≥ 3	122	37,08%
NR	0	
Current use of insulin		
Yes	65	19,76%
NR	0	
Patients discontinued Diabetes medication in the past		
Yes	189	57,45%
NR	0	
Diabetes related conditions		
Yes	73	22,19%
Retinopathy	58	17,63%
Nephropathy	16	4,86%
Diabetic foot	26	7,90%
NR	3	0,91%

Chronic Diseases		
0	49	14,89%
[1-2]	227	69,30%
≥ 3	52	15,81%
NR	1	0,30%
Hypertension	218	66,26%
Dyslipidaemia	181	55,02%
Heart failure	30	9,12%
Renal failure	6	1,82%
Others	12	3,65%
Number of different medicines		
0	23	6,99%
[1-2]	106	32,22%
[3-4]	105	31,91%
≥ 5	95	28,88%
C09 - Renin-Angiotensin system	201	61,09%
C10 - Lipid modifying agents	195	59,27%
B01 - Antithrombotic agents	98	29,79%
A02 - Antiacids	65	19,76%
C07 - Beta Blocking agents	62	18,84%
N05 - Psycholeptics	63	19,15%
C03 - Diuretics	42	12,77%
C08 - Calcium Channel Blockers	42	12,77%
N06 - Psychoanaleptics	54	16,41%

*Non-responders

Table 2 - Baseline and Demographic Characteristics of randomized controlled trials used in marketing authorization application

Dapagliflozin in Monotherapy		**Dapagliflozin in Monotherapy**				**Dapagliflozin in combination with Metformin**		**Dapagliflozin in combination with Glimepiride**		**Dapagliflozin in combination with Thiazolidinedione**		**Dapagliflozin added to patients using Insulin**	
Bailey *et al.*		**Ferrannini *et al.***				**Bailey *et al.***		**Strojek *et al*.**		**Rosentock *et al*.**		**Wilding *et al.***	
	DAPA 10mg		DAPA 10mg (Primary Cohort)	DAPA 10mg AM (Explanatory Cohort)	DAPA 10mg PM (Explanatory Cohort)		DAPA 10mg + Metformin		DAPA 10mg + Glimepiride		DAPA 10mg + Pioglitazone		DAPA 10mg
N	76	**N**	70	76	39	**N**	135	**N**	151	**N**	140	**N**	194
Age		**Age**				**Age**		**Age**		**Age**		**Age**	
Mean	50,6	Mean age	50,6	50,7	47,9	Mean age	52,7	Mean age	58,9	Mean age	53,8	Mean age	59,3
Gender		**Gender**				**Gender**		**Gender**		**Gender**		**Gender**	
Male	34	Male	34	39	23	Male	77	Male	66	Male	59	Male	87
Female	36	Female	36	37	16	Female	58	Female	85	Female	81	Female	107
BMI		**BMI**				**BMI**		**BMI**		**BMI**		**BMI**	
< 25	1	Mean	33,6	33,3	31,1	Mean	31,2	≥ 25	120	≥ 25	130	BMI	33,4
≥ 25	69	**T2DM duration**				**T2DM duration**		≥ 30	68	≥ 30	72	**T2DM duration**	
≥ 30	51	Mean duration	0,45	0,4	1,4	Mean	6,1	**Prior history of cardiovascular disease**	46			Mean	14,2
T2DM duration								**Hypertension**	113			**Duration of Insulin treatment**	
Mean duration	2,3							**T2DM duration**				Mean	6,3
Diabetes-related condition								Mean duration	7,2			**History of cardiovascular disease**	
Neuropathy	1											Hypertension only	92
Retinopathy	0											≥ 1 condition other than hypertension	83
Microalbuminuria	1											**Concomitant medications**	
Hypertension	29											Antihypertensive agents	163
Anti-hypertensive agents	29											Lipid-lowering agents	134
												Acetylsalicylic acid	108

Table 3 – Eligibility Criteria of randomized controlled trials used in marketing authorization application

	Bailey *et al.*	Ferrannini *et al.*	Bailey *et al.*	Strojek *et al.*	Rosentock *et al.*	Wilding *et al.*
Inclusion Criteria	• Males and females; • T2DM; • ≥18 and ≤77 years old; • BMI ≤ 45 kg/m^2; • HbA1c ≥7.0 and ≤10.0 % • Must be able to perform self-monitoring of blood glucose; • C-peptide ≥1.0 ng/mL.	• Males and females; • T2DM; • ≥18 and ≤77 years old; • BMI ≤ 45 kg/m^2; • Group 1 HbA1c ≥7.0 and ≤10.0%; Group 2 HbA1c ≥10.1 and ≤12.0%; • Drug naive (defined as never having received prescription medications for diabetes, having received prescription medications for diabetes for <24 weeks since the original diagnosis;	• Males and females; • T2DM; • ≥18 and ≤77 years old; • BMI ≤ 45 kg/m^2; • HbA1c ≥7.0 and ≤10.0 %; • Metformin total daily dose ≥1500 mg/day for at least 8 weeks.	• T2DM; • ≥18 years old; • Treatment with a stable sulphonylurea monotherapy dose that is at least half the maximal recommended dose for a minimum of 8 weeks prior to study; • HbA1c ≥7.0 and ≤10.0 %.	• Males and females; • T2DM; • ≥18 years old; • BMI ≤ 45 kg/m^2; • HbA1c ≥7.0 and ≤10.5 %	• T2DM; • Ongoing treatment with metformin on a stable dose of ≥1500 mg/day for at least 12 weeks prior to enrolment; • HbA1c ≥6.5 and ≤8.5.0 %; • ≥30 years for males ≥ 55 years for females
Exclusion Criteria	• Currently unstable or serious cardiovascular, renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease.	• Positive for hepatitis B and C; • History of diabetes insipidus; • Symptoms of poorly controlled diabetes, • Severe uncontrolled hypertensions (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg); • Any cardiac/vascular impairment within 6 months of enrolment: • History or prevalent hepatic/renal disease; • Malignancy within 5 years of enrolment visit; • Immunocompromised status; • Administration of any antidiabetic therapy for more than 14 days (consecutive or not) during the 12 weeks prior to enrolment • Administration of any antidiabetic therapy, other than any previously specified, at any dose, at any time during the 4 weeks prior to enrolment • Bariatric surgery or lap-band procedure;	• Symptoms of severely uncontrolled diabetes; • Currently unstable or serious cardiovascular, renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease.	• Type 1 Diabetes; • Hepatic and/or renal impairment.	• Symptoms of severely uncontrolled diabetes; • Currently unstable or serious cardiovascular, renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease; • Calculated Cr-Clearance <50 mL/min.	• Type 1 Diabetes; • Body weight change >5% within 3 months prior to enrolment; • Renal and liver impairment.

2. Drug-Drug Interaction Analysis.

Across the study population, a total of 233 DDI with DAPA were identified, using Micromedex® tool. Medication for T2DM was responsible for 75 (32.19 %) of all identified DDIs, whereas, drugs that were used for other pathologies, account a total of 158 (67.81%).

Regarding other concomitant T2DM therapy (Table 5), only were identified DDIs between DAPA and insulin and analogues [75 (32.19%)], being insulin glargin the drug which contributed most for the amount of DDIs [23 (9.87%)], followed by isophane human insulin [13 (5.58%]) and insulin detemir [12 (5.15%)]. No other interactions between DAPA and other medicines for T2DM treatment (e.g. sulphonylureas) were identified.

Drugs used in other pathologies (Table 5) were the most prevalent and contributed the most to the amount of interactions. The most frequent DDI was related to the concomitant use of perindopril [29 (12.45%)], followed by bisoprolol and ramipril [27 (11.59%)]. From all the drugs analysed, the only classes of drugs that interact with DAPA, according to Micromedex® DDIs checker, were beta blocking agents [68 (29.18%)] and agents acting on the renin-angiotensin system [90 (38.63%)].

In terms of severity, 100% of the identified DDIs, either in the group of drugs used for diabetes either in the group of drugs used for other pathologies, had the classification of moderate. In respect with onset, not specified interactions onset was the most prevalent category representing 70.82%, whereas delayed onset accounted for 29.12%. Only beta-blocking agents had a specific onset classification (delayed).

Of the study population (329 participants) a total of 162 (49.24%) participants reported at least one DDIs, 55 (16.72%) participants reported the existence of more than 1 DDI and 14 (4.26%) reported more than 3 DDIs (Table 7).

Table 4 - Drug-Drug interactions between dapagliflozin and other medication for diabetes

Substance	N		Severity class	Clinical consequence	Onset
Insulin Aspart	1	0,43%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Glulisin	2	0,86%	Moderate	increased risk of hypoglycaemia	not specified
Human Insulin	2	0,86%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Lispro	5	2,15%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Lispro (Protamine)	7	3,00%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Aspart (Protamine)	10	4,29%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Detemir	12	5,15%	Moderate	increased risk of hypoglycaemia	not specified
Human Insulin Isophane	13	5,58%	Moderate	increased risk of hypoglycaemia	not specified
Insulin Glargin	23	9,87%	Moderate	increased risk of hypoglycaemia	not specified

Table 5 – Drug-Drug interactions between dapagliflozin and medication for other conditions other than diabetes

Substance	N		Severity Class	Clinical Consequence	Onset
Perindopril	29	12,45%	moderate	increased risk of hypoglycaemia	not specified
Bisoprolol	27	11,59%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Ramipril	27	11,59%	moderate	increased risk of hypoglycaemia	not specified
Lisinopril	15	6,44%	moderate	increased risk of hypoglycaemia	not specified
Carvedilol	14	6,01%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Enalapril	14	6,01%	moderate	increased risk of hypoglycaemia	not specified
Nebivolol	11	4,72%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Timolol	6	2,58%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Atenolol	5	2,15%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Propranolol	3	1,29%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Trandolapril	3	1,29%	moderate	increased risk of hypoglycaemia	not specified
Zofenepril	2	0,86%	moderate	increased risk of hypoglycaemia	not specified
Carteolol	1	0,43%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed
Sotalol	1	0,43%	moderate	may result in hypoglycaemia or hyperglycaemia; decreased symptoms of hypoglycaemia.	delayed

Table 6 – Number of interactions regarding ATC code

ATC Code		N
C09A – Angiotensin-Converting-Enzyme Inhibitor	90	38,63%
A10A - Insulins and Analogues	75	32,19%
C07A - Beta Blocking Agents	68	29,18%

Table 7 – Number of interactions per individual

Number		N
0	167	50,76%
1	107	32,52%
2	41	12,46%
≥ 3	14	4,26%

Discussion

To the best of our knowledge this observational study is one of the first studies conducted in Portugal that captures real world data regarding the utilization of dapagliflozin in outpatient care. The study provides a picture of the dapagliflozin real users population, and contributes to assess RCTs external validity within the Portuguese population. In addition, the assessment of DDIs with dapagliflozin contributes to the knowledge of its complete safety profile.

1. Baseline and demographic characteristics.

As expected, since T2DM is more prevalent in elderly individuals (6,7), the vast majority of the studied participants had between 56 and 74 years old [(66.26%)]. These results are, as well, consistent with the data reported by the Portuguese national annual report drawn up by the National Diabetes Observatory in 2016, which stated that most of the population affected by DM has between 60 and 79 years old (6). Nunes *et al.* (49) observational study based on data retrieved from General Practice Sentinel Network, also stated a higher prevalence of T2DM in older age groups, generally, in more advanced ages in women than in men. Nunes, also projected a higher incidence rate in women, in the age group of 65-74 years old, and, in men, in the age group of 55-64 age groups, by the year of 2022 to 2024 (49).

The risk of developing T2DM is strongly linked to an excess of body fat, overweight and obesity, being these characteristics common within the diabetic population (1,14). According to WHO, it's considered overweight in adults, when the BMI is above 25.00 kg/m^2 (50). Analysing our study population BMI, we reported that 87.54% participants were overweight and 52,89% obese, according to WHO guidance. Regarding body mass index, the RCTs revealed that almost the entire study population included in different trials were overweight, and a considerable number of individuals is obese.

We stated that slightly more than a half of our population [166 (50.46%)] had T2DM for more than 10 years, being the mean duration of it 10.92 years. Although, the chosen RCTs placed no restrictions for study recruitment eligibility regarding T2DM duration, it can be seen a clear difference between the studies from Bailey (46), Ferrannini (43), which reported a mean T2DM duration of 2.3, 0.45, 0.4, and 1.4 years, being the last three relative to the different branches in Ferrannini study. In contrast, the population from Bailey (45), Strojek (47), and Wilding (44) studies, had higher means T2DM duration, 6.1, 7.2, and 14.2 years of duration, respectively, values that are more similar to those presented in our population. Duration of diabetes above 10 years is considered a risk factor directly related with poor glycaemic control over time (1). This helps to

explain the fact that 290 (88.15%) individuals of the study population are using more than 1 substance for T2DM treatment, 122 (37.08%) are using more than 3 substances, and 65 (19.76%) are current users of insulin.

Over time, it is common for T2DM patients to develop conditions associated with this pathology, such as retinopathy, nephropathy, diabetic foot, and nerve damage, which are the most common (1,13,14). These conditions arise due to microvascular complications associated with higher blood glucose levels, and are also related to older people and longer duration of diabetes (7). The most common of all diabetes condition related is retinopathy (7) which is also evidenced in our study population, affecting 58 (17.63%) individuals, which is considerably lower than the 35% of prevalence observed within the global diabetic population (7).

Bailey *et al.* (46) (Table 2) also reported data regarding the prevalence of diabetes-related complications within the study population, but only one case of neuropathy and microalbuminuria were identified. Diabetic foot is, as well, a very common situation among the diabetic population that arise in consequence of diabetic neuropathy and peripheral arterial disease, which can be related to the former, and represent a major cause of morbidity and mortality in these individuals. This study revealed that the prevalence of this condition was 7.90%. However, this finding is slightly lower than the study conducted by Tesfamichael *et al.* (51) that found a prevalence of 13.6%. This variation might be due to differences regarding demographic and geographic characteristics, since the study was made in Ethiopia. In Portugal in the year of 2015, there were 1643 case of hospitalization due to diabetic-foot ulcer complications, which represents a decrease of 220 cases compared to the previous year (6). The number of lower limb amputations due to diabetes decreased as well in 2015 (6).

All T2DM patients are at higher risk, more than double when compared to non-diabetic population, to develop cardiovascular disease (CVD) or any cardiovascular events (13,14). T2DM is considered a major risk factor for cardiovascular disease, due to its related microvascular complications, and increased blood glucose levels that can disrupt lipoproteins levels, thus developing dyslipidaemia which is as well as CVD risk factor (14,52,53).

Hypertension is a very common pathology among population with a prevalence above 60% (depending how it is defined and/or the use of antihypertensive medication), according to Colosia *et al.* (54). We found that 66.26% patients reported hypertension, which is consistent with the results pointed out by Colosia (54). Bailey *et al.* (46) clinical trial of dapagliflozin used in monotherapy, showed 36.71% patients were diagnosed to hypertension and were as well medicated (46). Other randomized controlled trials of dapagliflozin showed the existence of individuals as well that had hypertension, or prior

cardiovascular disease (table 2). Wilding *et al.* (44) reported a prevalence of hypertension of 47.42%, and that 42.78% of the population were diagnosed with one or more cardiovascular condition other than hypertension (44). Since hypertension is a major risk for both CVD and the aggravation of microvascular diabetic-related complications (1), it is crucial to implement a good management of hypertension plan, in order to achieve effective blood pressure control (13). Current guidelines predict what pharmacological interventions can be made to reduce blood pressure, being the indicate medicine class of agents acting on the renin-angiotensin system (1,13,55). Collected data regarding the pharmacotherapeutic profile of our individuals showed a high consumption of medicines used for hypertension management as well used for CVD, such as renin-angiotensin system acting agents [201 (61.09%)], antithrombotic agents [98 (29.79%)], beta-blocking agents [62 (19.76%)], diuretics [42 (12.77%)], and calcium channel blockers [42 (12.77%)].These results suggest that a higher proportion of our population is using more than one substance for CVD complications treatment, since there is consumption of 445 substances, which is in accordance with the guidelines, that most patients with diabetes will need often more than one drug to achieve blood pressure control (14, 17, 19). Reed *et al.* (56), studied the effect of SGLT-2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) on blood pressure in patients with T2DM in order to predict the ability to reduce cardiovascular (CV) risk. This study concluded that SGLT-2 inhibitors have a clear effect in reducing blood pressure and lowering body weight, which is indicative of their potential to reduce CV risk within diabetic population. However, the study could not assess the SGLT2 blood pressure lowering effect on CV outcomes. Nevertheless, there are several RCTs, such as the EMPA-REG OUTCOME (23), that reported the beneficial CV effect of SGLT2. EMPA-REG OUTCOME in particularly, reported that patients with T2DM and high CV risk, that took a daily dose of empagliflozin, had a lower rate of death from CV causes (23).

Lipoprotein abnormalities are frequently present in T2DM patients. These abnormalities include hypertriglyceridemia, reduced plasma HDL cholesterol and altered LDL size, resulting in dyslipidaemia (53). The appearance of diagnosed cases of dyslipidaemia within our study population was considerable high, affecting more than half of our sample. These results are slightly higher than the ones found by Tseng *et al.* (57) that show a prevalence of dyslipidaemia of 43.58% in women and 39.45% in men, but lower than those revealed by Dixit and colleagues (58) where a prevalence above 70% was reported. We found as well, that 59.27% of the population were under lipid modifying agents treatment. The clinical trial developed by Wilding *et al.* (44) also reported that 69.07% of its sample was using the same medicine class.

2. Drug-drug interaction.

In the present study, DDIs were assessed with the help of Drug REAX-Micromedex® system, which has been a common resource used by other studies and by clinicians. This tool provides instant access to drug-drug, drug-food, drug-ethanol, drug-lab test reaction, and classifies DDIs according to its severity, clinical outcome, onset, and support documentation. Kheshti *et al.* (59) designed a study to compare five common DDI software programs, in which Micromedex® was included, regarding accuracy and comprehensiveness, and he concluded the following: Micromedex® had a 60.3% of correct answers, being the highest of 69.8%; had the second highest accuracy score (236); Micromedex® showed the highest specificity; and had the second highest total score.

Patients with T2DM, have an elevated risk for cardiovascular disease, in particular those under insulin regimen and with advanced age (41). Therefore, diabetic patients often require the co-administration of several medicines to guarantee an effective control of not only glycaemia, but also blood pressure, lipid composition, hearth rate, etc. (32,41). Polypharmacy is frequently in advanced ages and is directly related to higher prevalence of DDIs, since the number of used drugs increases (60). Polypharmacy, can also explain the fact that 162 (49.24%), almost half of the population, reported the existence of one or more potential DDI (table 7), since a vast proportion of our population was taking more than one drug.

The concomitant administration of dapagliflozin and medicines that act on the renin-angiotensin system, such as angiotensin-converting-enzyme (ACE) inhibitor (e.g. perindopril) were signalled by Micromedex® checker, for establishing a moderate interaction. According to Micromedex®, a moderate severity interaction may result in exacerbation of the patient's condition and/or could require therapy modification. However, when looking for further information regarding the interaction, no specific mechanism was provided by Micromedex® neither any evidence was found on literature. Even though, in patients under insulin regimen, blood glucose levels should be closely monitored, since ACE inhibitors can increase the tissue sensitivity for insulin which may increase the risk of hypoglycaemia (61). Beta-blocking agents, such as bisoprolol and timolol, were also signalled for an interaction with DAPA. These medicines do not induce hypoglycaemia directly, but can mask the early warning symptoms, such as tachycardia, may worsen them, and can interfere with recovery of serum glucose levels (61,62). Beta blockers can also cause deterioration in long-term glycaemic control and some adverse effects on the lipid profile (62). Studies have shown that these effects can be diminished with newer beta-1 selective drugs (61) or with the concomitant use of an alpha blocker (62). Interactions between DAPA and other commonly used drugs have been studied

and no clinically relevant impact was found. Kasichayanula *et al.* (41) studied the potential relation between DAPA and simvastatin, valsartan, warfarin, and digoxin and concluded that no significant changes were observed in the pharmacokinetic parameters of DAPA or in the other drugs. Kasichayanula used the same rational for assessing the potential effect of rifampin and mefenamic acid on the pharmacokinetics and pharmacodynamics of DAPA (63). Since DAPA is primarily metabolized by UGT1A9, modulators of this enzyme could increase or decrease the exposure of DAPA (63). Small changes in pharmacodynamic response were found, but were not considered clinical relevant, and ultimately, the concomitant use of DAPA and rifampin or mefenamic acid was well tolerated (63).

In this study, we found that a vast proportion of our population was using more than one medicine for diabetes management. So, it was important to evaluate the existence of potential DDI between DAPA and other GLD. We identified moderate severity interactions between DAPA and all types of insulin present in our population. According to Micromedex®, the combination of DAPA with insulin can modify glucose metabolism by increasing effects of each other, which can potentiate the risk of hypoglycaemia. For a proper therapy management, dose adjustment and more frequent glucose monitoring might be necessary (62). However, Wilding *et al.* (44) have shown the beneficial effect of the combination between DAPA and insulin, as well the safety of its use. No other interactions were found with other GLD, which is in line with other studies that aimed to evaluate the safety of DAPA within combined therapies in Diabetes. Kasichayanula *et al.* (41) concluded that DAPA can be safely used when co-administered with pioglitazone, metformin, glimepiride, and sitagliptin with no effect on pharmacodynamic or pharmacokinetic of DAPA.

3. Limitations

This study provides relevant information on the characteristics of T2DM patients initiating dapaglifozin in routine clinical practice, however some limitations require discussion. Firstly, pharmacies self-selection could have occurred since participation was not mandatory. Nevertheless, the regional and setting distribution of participating pharmacies were similar to the universe of overall Portuguese pharmacies. Second, clinical data collected at baseline was self-reported by the patient and was not confirmed with physician, thus it could be associated with some degree of inaccuracy. However, baseline questionnaire was fulfilled by the pharmacist and all personal history of T2DM and other co-morbidities were considered present when patients recalled a medical diagnosis of these conditions. This study was limited in demonstrating prescriber compliance to treatment guidelines because it does not provide information about

treatment process steps. Another limitation of our study was that was not possible to evaluate if T2DM was well controlled or not, since no data regarding HbA1c was collected. Since no statistical analysis tests were conducted in order to compare our study population with the population retrieved from RCT studies, it was not possible to determine if the differences found were statistical significant.

Limitations to this DDIs analysis arise from the software itself and quality of the reported information. It is important for DDI screening software, such as Micromedex®, to support their content with valid references. Many drug interactions are related to the dose of drugs in use. Ideally, Micromedex® should be able to ignore interactions if the drugs are given in doses that will not result in interaction (59). Other limitation related to software is patient demographic characteristics and dosing schedule that are not considered, which can affect clinical relevance of DDIs. These results are from empiric nature and clinical trials and observational studies with longer duration are required to support the evidence presented here. Patients treatment behaviours were not assessed, but it is acknowledged that it can influence the incidence and severity of DDI.

Conclusions

Characterizing the real-world population is of great importance, especially in recent available drugs, such as dapagliflozin, since real evidence supporting its use is limited. The existence of observational studies such as ours are indispensable to narrow the gap knowledge between current clinical practice and RCT environment. Overall, we found that our population is similar to the general diabetic population, as well, and in general to the one represented on dapagliflozin clinical trials. In addition, we contributed to the assessment of the dapagliflozin safety profile of, where no clinical relevant DDI were found. However, it is important to point out that only known and documented DDIs were assessed. Therefore, clinicians and pharmacist's awareness as well pharmacovigilance professionals play an extremely important role identifying unknown DDI with dapagliflozin.

Further, studies assessing new GLD cost-effectiveness and cost-beneficial in routine clinical practice are essential, since T2DM treatment represents high costs for both patients and payers in Portugal.

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