

MESTRADO
EVIDÊNCIA E DECISÃO EM SAÚDE

Prevalence estimation from drug consumption data: application to diabetes

Rita Cristina Sanches Oliveira

M

09/2023

FACULDADE DE **MEDICINA**



MESTRADO
EVIDÊNCIA E DECISÃO EM SAÚDE

Prevalence estimation from drug consumption data: application to diabetes

Rita Cristina Sanches Oliveira

M

09/2023

SUPERVISOR: Prof. Doutor António Duarte Teixeira Afonso
Rodrigues
Faculdade de Medicina da Universidade do Minho

COSUPERVISOR: Prof. Doutor Matilde Filipa Monteiro Soares
Faculdade de Medicina da Universidade do Porto



Agradecimentos

Para a elaboração deste trabalho contei com muitas contribuições, as quais agradeço reconhecidamente:

Aos orientadores do trabalho, Professor Doutor António Teixeira Rodrigues e Professora Doutora Matilde Monteiro-Soares, agradeço a partilha do seu conhecimento científico, e das suas opiniões, sempre com simpatia. A sua total disponibilidade foi fundamental para a conclusão de todo o trabalho.

À Associação Nacional de Farmácias (ANF) pela cedência da base de dados que foi utilizada.

Aos colaboradores da ANF, Doutor José Pedro Guerreiro e Dr. Rúben Pereira, pela contribuição e colaboração necessárias à realização da investigação.

Às minhas colegas do Mestrado, pela partilha, estímulo e convívio.

Ao Pedro e à Carla pelo apoio constante e amizade.

Ao Daniel, à minha mãe e ao meu pai, a quem dedico este trabalho, agradeço a motivação e o conforto incondicional.

A todos os meus amigos, porque acreditam em mim.

Sumário

Enquadramento: O conhecimento da prevalência de um evento ou de uma doença é relevante em contexto clínico, quer para o processo de diagnóstico, quer para a tomada de decisão em várias dimensões da saúde. O desenvolvimento de métodos indiretos robustos de estimativa da prevalência que permitam a obtenção de resultados em tempo útil, são uma vantagem para as inúmeras aplicações em saúde. São disso exemplo, o contexto da avaliação de tecnologias da saúde, o processo de introdução no mercado de medicamentos ou até mesmo a pertinência e impacto do desenvolvimento e implementação de políticas de saúde. Os estudos de prevalência são estudos observacionais, habitualmente transversais. No entanto, dependendo da dimensão do contexto (local, regional, nacional ou internacional), estes estudos poderão ser dispendiosos e morosos, o que dificulta um conhecimento atualizado do valor da prevalência.

Este trabalho teve como objetivo estimar a prevalência da Diabetes mellitus tipo 2 na população Portuguesa tendo por base os dados da dispensa de medicamentos das farmácias comunitárias.

Métodos: Foi desenvolvido um estudo observacional, transversal, utilizando uma base de dados de dispensa de medicamentos com indicação para a Diabetes mellitus (códigos ATC: A10A e A10B) nos anos de 2018 e 2021, estratificada por região geográfica. A metodologia baseou-se no desenvolvimento de um modelo sequencial da estimativa de prevalência, obtida através da exposição ao medicamento, utilizando doses diárias definidas por mil habitantes por dia, ajustado à adesão à terapêutica, aos padrões de prescrição e utilização concomitante de medicamentos em estudo.

Resultados: A prevalência global estimada para a Diabetes mellitus tipo 2 no ano de 2018 foi de 13.9% e de 14.2% para o ano de 2021. Todas as regiões de Portugal aumentaram o consumo de medicamentos antidiabéticos de 2018 para 2021, mantendo-se constante a sua distribuição nas diferentes zonas geográficas. Os resultados obtidos revelam um aumento do consumo de medicamentos antidiabéticos, com particular expressão, no ano de 2021, dos antidiabéticos de combinação de dose fixa e dos novos antidiabéticos.

Conclusão: Este trabalho permitiu desenvolver um modelo para obter a prevalência estimada da Diabetes mellitus tipo 2 com base no consumo de medicamentos, através de um método simples, rápido e robusto e que vai de encontro às estimativas encontradas na literatura disponível.

Palavras-chave: Diabetes mellitus; Uso de dados de medicamentos;
Antidiabéticos; Prevalência

Abstract

Background: The knowledge of the prevalence of an event or disease is relevant in clinical settings for diagnosis and decision-making in many healthcare aspects. Prevalence is an important parameter in the assessment of health technologies for the authorization market process or establishing health policies. Prevalence studies are observational studies, usually cross-sectional. However, depending on the size of the context (local, regional, national, or international) these studies can be costly and time-consuming, which makes it difficult to obtain up-to-date knowledge of the prevalence. The development of indirect methods estimating prevalence to obtain faster, less expensive, and more robust results would be an advantage for several healthcare applications.

This study aimed to estimate the prevalence of Type 2 Diabetes mellitus in the Portuguese population based on drug dispensing data from community pharmacies.

Methods: An observational, cross-sectional study was carried out using a database of dispensed medicines with an indication for Diabetes mellitus (Anatomical Therapeutic Chemical codes: A10A and A10B) in the years 2018 and 2021, stratified by geographic region. The methodology was based on a sequential method for the prevalence estimate obtained through exposure to medicines, using daily doses defined per thousand inhabitants per day, and adjusted to adherence to therapy, prescription patterns, and concomitance of antidiabetic drugs.

Results: The estimated overall prevalence of Diabetes mellitus in 2018 was 13.9% and 14.2% for 2021. All regions of Portugal increased their consumption of antidiabetic drugs from 2018 to 2021, and their distribution in the different geographical areas remained constant. The results show an increase in the consumption of antidiabetic drugs, with fixed-dose combination antidiabetics and new antidiabetics being particularly important in 2021.

Conclusion: This work allowed the development of a model to obtain the estimated prevalence of Type 2 Diabetes mellitus based on drug consumption, using a simple, fast, and robust method that was in line with the available evidence.

Keywords: Diabetes mellitus; Drug utilization data; Antidiabetics; Prevalence

Table of contents

Agradecimentos.....	i
Sumário	ii
Abstract	iv
Table of contents.....	v
Acronyms and abbreviations	vi
Figure index	viii
Table index.....	ix
Thesis structure.....	x
Scientific and financial results	xii
1. Introduction.....	1
2. Objectives	3
3. State of the art.....	4
Drug utilization data for prevalence estimations	4
Diabetes mellitus as a chronic disease model.....	7
Medication adherence	12
Off-label use	13
4. Material and Methods	15
5. Results	20
6. Discussion	25
7. Conclusions	32
8. Future research.....	33
9. References	34
Annexes	47

Acronyms and abbreviations

AD	Antidiabetic drugs
ADA	American Diabetes Association
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
DGS	Direção Geral da Saúde (General Direction of Health)
DID	Defined Daily Dose <i>per</i> 1,000 inhabitants <i>per</i> day
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
GDM	Gestational Diabetes mellitus
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin A1c
EHR	Electronic Health Records
HTA	Health Technology Assessment
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
INE	Instituto Nacional de Estatística (National Institute of Statistics)
MPR	Medication possession ratio
NAD	Non-insulin antidiabetic drugs
NHS	National Health Service
PDC	Proportion of days covered
PDD	Prescribed daily dose
RW	Real-world
SGLT2	Sodium-glucose co-transporter 2
SPD	Sociedade Portuguesa de Diabetologia (Portuguese Society of Diabetology)

SU	Sulfonylureas
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
WHO	World Health Organization

Figure index

Figure 1 - Consumption of antidiabetic drugs expressed by Defined Daily Dose <i>per</i> 1000 inhabitants <i>per</i> day by region in 2018 and 2021	19
--	----

Table index

Table 1 - Diabetes mellitus diagnosis criteria	8
Table 2 - Literature data	10
Table 3 - Portugal population, per district	16
Table 4 - Antidiabetic consumption in DID in 2018 and 2021	21
Table 5 - Estimated prevalence of Type 2 Diabetes mellitus from antidiabetic consumption data	23
Table 6 - Sensibility analysis of estimated prevalence of Type 2 Diabetes mellitus	24

Thesis structure

This Thesis is divided into six chapters organized to provide a coherent reading. The focus of each chapter is described below:

1. Introduction

In this chapter, the thesis subject is briefly described and the main motivations for the development of this work are explained.

2. Objectives

The main objective and secondary objectives to be achieved are described.

3. State-of-the-art

This chapter refers to concepts, background, and bibliographic references for the understanding of the topics addressed. It mainly describes prevalence studies applications, examples of drug utilization research studies, the understanding of adherence and polymedication concepts, and the epidemiology and management of Diabetes mellitus.

4. Material and Methods

This chapter explains the methodology, parameter assumptions and sensitivity analysis performed.

5. Results

This chapter describes the results obtained. Tables and figures are presented to improve the understanding of the results.

6. Discussion

The discussion chapter attempts to interpret the results obtained, the comparison with the literature, as well as to expose the limitations of the study.

7. Conclusions

This chapter provides a summary of the research and establishes its connection to the initially proposed objectives.

8. Future research

The proposal for future research to be conducted in this research field is detailed.

Annexes. The annexes contain information that may be relevant and is intended to simplify the reading and understanding of the Thesis. It includes the classification of Diabetes mellitus (Annex I), Anatomical Therapeutic Chemical classification of antidiabetics (Annex II), and American Diabetes Association guidelines for pharmacological management (Annex III).

Scientific and financial results

The authors aim to publish this study in a peer-reviewed and indexed in Web of Science scientific journal.

This study had no financial support.

1. Introduction

The knowledge of an accurate estimate of the prevalence of a disease or clinical condition has a considerable clinical relevance as it defines the *a priori* probability of a diagnosis and supports clinical decision-making, enables the understanding of the burden of diseases and guides future research.

An adequate prevalence estimate is also required for health technology assessment (HTA) processes like medicines, medical devices, therapeutic procedures or health-related interventions, and to provide information to improve clinical practice or health policy making [1]. This approach aims to maximize the value and benefits of health strategies, taking into account the costs and consequences (namely efficacy and effectiveness) through systematic methods of synthesis and modeling of the best available scientific evidence [2].

The knowledge of the prevalence of a condition in the HTA context is a central parameter as its magnitude defines the importance of the medicine/technology to be evaluated in societal, political, economic and clinical terms. The regulatory dynamics associated with these processes would benefit greatly from a regular and dynamic update of the prevalence value.

This continuous updating of the prevalence estimation through classical observational studies is not feasible as they become costly, difficult to implement, and time-consuming. The development of accurate, rapid and validated methods would represent an added value for clinical and regulatory purposes.

The use of drug consumption data has the advantage of being readily accessible information. However, as this surrogate information may not directly relate to diagnosis, it becomes a methodological challenge. Research on drug utilization data is essential to improve the method's robustness.

For the execution and validation of these methods, it is important to find a clinical condition with particular features, namely, high prevalence in the population, chronic in nature, a strong pharmacological relationship with the diagnosis and treated population, a good clinical and epidemiological knowledge

to test the model. We have selected Diabetes mellitus, as this disease complies with all of these criteria.

The development of this type of model for estimating prevalence can be applied to other diseases and the robustness of the estimation can be improved as the inputs of the model are updated.

2. Objectives

The primary objective of the study was to estimate the prevalence of Type 2 Diabetes mellitus (T2DM) in the Portuguese population.

Secondary objectives are:

- Characterize the evolution of antidiabetic drugs (AD) consumption in the years 2018 and 2021, and its stratification by region;
- Characterize the consumption of AD (insulins and non-insulin antidiabetic drugs – NAD) according to their Anatomical Therapeutic Chemical (ATC) classification in 2018 and 2021;
- Assess the impact of therapeutic adherence and concomitant use of AD in the prevalence estimation.

3. State of the art

Drug utilization data for prevalence estimations

The prevalence of an event is defined as an epidemiological measure of frequency that quantifies the number of existing cases in a population at a given moment in time [3]. Classically, cross-sectional studies aiming to estimate disease prevalence may use primary data collected through questionnaires or interviews (in-person, online, or via phone call) designed to gather the data of interest and to answer the research question.

Electronic Health Records (EHR), archives, reimbursement data, sales and dispensing databases, as well as patient records, constitute secondary data since they are obtained in a context other than that of the study. Often gathered in an administrative and/or clinical context, this information comprises Real-world (RW) data. RW secondary databases have the advantage of usually comprising information from a much larger sample size compared with primary data collection studies. The robustness of using RW data results increases the external validity of the studies, but, due to the nature of the data and inherent biases, decreases the internal validity. The RW-based studies are clinically driven which allows to explore the effectiveness and safety of the medication, but the risk of bias is higher mainly due to the lack of randomization and blinding [4].

Primary data collection may be time-consuming and expensive. On the other hand, secondary databases are more easily accessible data sources if standardized and informatically compatible between healthcare institutions. Laranjo, L. *et al.* performed a cross-sectional study supported by EHR from 514 primary healthcare centers of Lisbon and Tagus Valley region and geographic information systems, for surveillance of chronic diseases, namely DM. Individual-level data from EHRs were considered useful for the purpose, once the quality and comprehensiveness of data is ensured [5].

Obtaining secondary data can be constrained by limitations such as its potential inadequacy or incompleteness, different formats, distribution or inaccessible location, technological challenges in data extraction and analysis, and data quality, among others. However, the integration of databases from different sources (record linkage), such as EHR medical prescriptions and pharmacy systems, leads to an easier and more readily connection between data, namely drug utilization data [6, 7].

Drug utilization data can be collected along the drug-chain cycle (acquisition, storage, distribution, prescribing, treatment compliance, and outcome of treatment), out of databases from regional to international level. Manufacturers, suppliers, regulatory agencies, inpatient and outpatient health institutions (for prescribing data) and pharmacies (for dispensing data) are all data sources commonly used for drug utilization research.

Aggregated data reflects the amount of drugs dispensed or used by the population and does not add any information about how these drugs are individually consumed by patients – thus, these databases are used to perform ecological studies.

A universal system for drug classification and metrics is fundamental for validating and comparing drug utilization data between geographical areas, population subgroups, and others. The World Health Organization (WHO) recommends the internationally widely used system Anatomical Therapeutic Chemical (ATC) classification and the unit of drug measurement Defined Daily Dose (DDD), for drug utilization monitoring and research [8]. This system allows to access standard, stable and valid information on drug consumption available on the market for clinical intervention and monitoring and enables comparable statistics at national and international levels.

The structure of the code of the ATC system comprises:

- 1st level – anatomical/pharmacological main group
- 2nd level – therapeutic/pharmacological subgroup
- 3rd level – therapeutic/pharmacological subgroup
- 4th level - chemical subgroup
- 5th level - chemical substance

The ATC codes are included in the pharmaceutical product information (e.g. Summary of Product Characteristics) approved by the European Medicines Agency (EMA) regulatory supervisor in the European Union [9].

According to the WHO definition, the DDD is the *assumed average daily dose of a drug when used in its main therapeutic indication in adults* [9]. It is defined from the existing experience with the drug, recommendations in the literature and from its manufacturers. Drug consumption, as measured by DDD, is usually expressed as DDD *per* 1000 inhabitants *per* day (DID). The DID calculation allows to roughly determine the proportion of the population that is receiving, per day, the standard treatment of a given drug. Concerning medications utilized on a continuous or chronic basis, such as antidiabetics and antihypertensives, DID is a rough estimation of the number of patients in chronic treatment. The use of DID calculation for the estimation of prevalence is not considered a robust method. Some limitations are associated to the prevalence estimation using indirect methods based on DID, namely [10, 11]: the pharmacological treatment of the disease under study must be almost exclusive for an easy association with its prevalence, which is often not the case; adherence, which reflects the compliance to prescription, is reflected in prescription dispense, implementation of the correct treatment and persistence of the same treatment that impacts in prevalence estimation, and high-quality studies of adherence should be taken into consideration [12, 13]; the complexity of therapeutic regimens may also impact the estimation, particularly when using aggregate drug consumption data, since it will be necessary to predict dosing patterns as well as the concomitant use of drugs [14, 15]; data about the off-label use of medicines are scarce, as it is often associated with a practice that has no legal framework [16]; DID based prevalence estimation can only be used to predict diagnosed and pharmacologically treated diseases.

The indirect method of estimating prevalence based on drug utilization has been tested in several chronic diseases [17-20], such as ocular hypertension [21], inflammatory bowel disease [22], thyroid disorders [23], and DM [24-26].

Although DDD is an estimate of the actual use of the drugs, it does not necessarily reflect the prescribed daily dose (which depends on the posology) or the daily dose consumed (which is related to treatment compliance). It is a technical unit of measurement of the exposure of a given population to a certain drug to perform aggregation of drug subgroups and geographical comparisons. The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions, reflecting the average daily amount of a drug that is prescribed. DDD and PDD are not always identical,

which affects the conclusions to be drawn from the data analysis [9, 27]. Only a concordant DDD and PDD can originate an accurate estimate of the prevalence of chronic diseases.

Drug utilization research applies qualitative and quantitative methods to assess a wide range of subjects such as drug prescription patterns, treatment compliance, geographical comparisons and rational medicine use [11].

Diabetes mellitus as a chronic disease model

DM is characterized by hyperglycemia resulting from an insufficient amount of circulating insulin that prevents glucose from being used by the cells. The causes may be of autoimmune origin with the destruction of the pancreatic β -cells leading to an almost total absence of insulin production (Type 1 diabetes – T1DM); or there may be a decrease in the amount of insulin produced and/or resistance to its action (Type 2 diabetes – T2DM). Due to its chronic nature, complications such as neuropathy, nephropathy, cardiovascular disease and retinopathy can occur [28].

The diagnosis criteria are defined by the General Direction of Health (DGS – Direção Geral da Saúde) [29] and an intermediate hyperglycemia condition (Impaired Fasting Glucose - IFG and Impaired Glucose Tolerance - IGT) is defined, also known as pre-diabetes (Table 1). It is estimated that 26% and 50% of IGT and IFG, respectively, evolve to T2DM in five years [30].

DM may be asymptomatic or decompensation symptoms may be present, which are also taken into account in the diagnosis (such as polyuria, polydipsia, fatigue, and weight loss, among others).

Table 2 - Diabetes mellitus diagnosis criteria [29]

	Diabetes mellitus	Impaired fasting glucose	Impaired glucose tolerance
Fasting glycemia	≥ 126 mg/dl	≥ 110 mg/dl and < 126 mg/dl	
Occasional glycemia	≥ 200 mg/dl		
Oral glucose tolerance test (75g glucose)	> 200 mg/dl at 2h		≥ 140 mg/dl and < 200 mg/dl at 2h
Glycated hemoglobin A1c	$\geq 6,5\%$		

Hyperglycaemia first recognized during pregnancy is generally classified as Gestational Diabetes mellitus (GDM) and has a world prevalence of 14% and 7.8% in Europe [31]. According to the American Diabetes Association (ADA) guidelines, pharmacologic management of GDM should be restricted to insulin since there is evidence of some substances crossing the placenta barrier (e.g. metformin and sulfonylureas) or lack of studies in pregnant women [32].

In 2019, WHO presented an updated classification of DM, excluding subtypes of T1DM and T2DM and adding new types of DM (hybrid forms and unclassified DM) (Annex I) [33]. However, T2DM is the most common form, accounting for 90% to 95% of total diabetes disease [33, 34]. As the onset of T2DM is difficult to identify due to its asymptomatic characteristics, it is estimated that one-third to one-half of the patients are undiagnosed [34].

Diabetes mellitus prevalence

The prevalence of DM is increasing worldwide due to sedentary and obesogenic lifestyles, but the early diagnosis and prolonged life expectancy also contribute to the numbers.

DM has been well monitored by the health authorities and medical associations, namely the Portuguese Diabetes Society (SPD), which conducted a prevalence study in 2009 (PREVDIAB), based on medical diagnoses in primary healthcare, and has been performing updates based on NHS data – reporting an estimated

prevalence of 13.6% in 2018 [28]. However, its main limitation is the voluntary participation of NHS patients and the fact that private healthcare entities are not taken into account.

Pereira, M. *et al.* performed a systematic review to assess the evolution, between 1987 and 2009, of the prevalence of DM and mean blood glucose in Portuguese adults, stratified by sex [35]. The results showed that, while the DM prevalence remained stable in young adults, the disease increased 2 and 3 folds (women and men, respectively) in middle-aged and old adults, between this time-lapse. In 2009, the self-reported DM prevalence was 8.6% and 9.4% among women and men. The limitations of this study were the heterogeneity of DM diagnosis criteria and the use of one single motor search.

Between 2006 and 2007, the Epidemiological Study on the Prevalence of Metabolic Syndrome in the Portuguese Population (VALSIM) was carried out [36]. This cross-sectional study used a representative sample of adults living in mainland Portugal and the islands, followed in primary healthcare, and 16,856 individuals were evaluated, with registration of previous diagnosis and control of fasting glycemia and HbA1c, out of several other parameters. Among the characterization of cardiovascular risks, the prevalence, treatment and control of DM were evaluated. The prevalence of DM in the population using primary healthcare services, adjusted for sex and age, was 14.9%, increased progressively with age and was higher in men (men:16.8%; women:13.2%). The limitations of this study are related to the sampling method, which was conducted by convenience in primary health care, not including individuals who do not seek public health care and who may have undiagnosed DM.

Data from the General Practice Sentinel Network between 1992 and 2015 were used to describe the evolution of DM incidence and to estimate through Poisson regression models the future incidence of DM until 2024. The average increase in DM incidence rate was 4.29% (CI95%: 3.80–4.80) and the study revealed an increase in incidence projections similar to the observed data. Reasons were attributable to the population aging and the higher number of risk groups [37]. The results from the First National Health Examination Survey (INSEF 2015) showed an overall prevalence of diabetes of 9.9% (CI95%: 8.4; 11.5), higher in males than in females (12.1% vs 7.8%). This cross-sectional study was performed on a sample of 4911 adults from the Portuguese primary healthcare centers at a national level, through interviews, physical examination, and blood analysis (for HbA1c, among others) [38].

The WHO published in 2021 some Key Facts about DM [39]:

“

- *The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.*
- *Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.*
- *Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes.*
- *In 2019, diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly caused by diabetes.*
- *A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes.*
- *Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications.”*

The literature data considered most relevant and chosen for comparing the results are compiled in Table 2 along with the bibliographical references.

Table 2 - Literature data

		2018	2021	Reference
Adult diabetes prevalence estimates (20-79 years old)	Global	9.3%	10.5%	Diabetes Atlas 2021, IDF [34]
	Europe	8.9%	9.2%	Diabetes Atlas 2021, IDF [34]
	Portugal	14.2%	13%	Diabetes Atlas 2021, IDF [34]
	Portugal	13.6%		Relatório Anual do Observatório Nacional da Diabetes. 2019 [28]
Non-diagnosed DM	Global	50.1%	44.7%	Diabetes Atlas 2021, IDF [34]
	Europe	40.7%	35.7%	Diabetes Atlas 2021, IDF [34]
	Portugal/T1D	475.2	433.3	Diabetes Atlas 2021, IDF [34]
	Portugal	44%		Relatório Anual do Observatório Nacional da Diabetes. 2019 [28]

T2DM treatment adherence	60%	60%	Sabaté E, Adherence to long-term therapies: evidence for action: WHO; 2003 [40]; Fernandez-Lazaro CI <i>et al.</i> Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study. BMC Family Practice. 2019;20(1):132 [41]
T2DM concomitance factor	0.608	0.608	Duarte-Ramos F, Cabrita J. Using a pharmaco-epidemiological approach to estimate diabetes type 2 prevalence in Portugal. Pharmacoepidemiol Drug Saf. 2006;15(4):269-74 [24]
T2DM insulin users	7.5%	7.5%	Basu S, <i>et al.</i> Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol. 2019;7(1):25-33 [42]

DM: Diabetes mellitus; T2DM: Type 2 Diabetes mellitus; TID: Thousand inhabitants per day; WHO: World Health Organization; IDF: International Diabetes Federation

Diabetes mellitus treatment

Although lifestyle can be a cause of T2DM and its control may have a therapeutic effect [43, 44], the pharmacological approach is required in most patients.

Pharmacological therapy comprises the administration of non-insulin antidiabetic drugs (NAD) - therapeutic subgroups: biguanides, sulfonylureas, alpha glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose co-transporter 2 (SGLT2) - and insulins, for outpatient administration [45]. The ATC for AD drugs is enclosed in Annex II [9].

Clinical guidelines for T2DM management are established and frequently updated by several expert medical associations such as the International Diabetes Federation (IDF), the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the DGS and the Portuguese Society of Diabetology (SPD) [46-48]. A clinical orientation scheme is presented in Annex III. The pharmacological approach usually starts with metformin and evolves to other NAD in monotherapy or combination therapy. When indicated, insulin can be added to optimize glycemic control and to prevent micro and macrovascular complications in the long term, avoiding hypoglycemic episodes [45, 49-51].

The prevalence of insulin monotherapy in T2DM in Europe is unknown, but a study from 2018 estimated that T2DM insulin users in the United Kingdom, Sweden, and Denmark were 12.5%, 11.7%, and 15.8%, respectively. An overall estimate of 7.5% of T2DM insulin users in Europe was reported [42]. In a study from the United States of America conducted in 2014, 12% of patients with T2DM used insulin monotherapy and 14% used insulin combined with NAD [52]. Based on a study from the United Kingdom [53], in 2010, 37% of T2DM patients were treated with insulin. From the VALSIM study, of a total of 3215 people with diabetes, 90.2% were on targeted treatment, meaning 9.8% of the subjects were untreated. Among treated patients, 89% were on oral antidiabetics alone, 6% were on insulin therapy, and 5% were on simultaneous oral antidiabetic and insulin therapy [36]. The scenario has changed with the market authorization of new hypoglycemic agents [54].

Polytherapy is frequent in the treatment of DM resulting in concomitance, which is defined as the administration of two or more drugs simultaneously for the same condition. ADA and EASD treatment guidelines advise up to three NAD plus insulin until HbA1c control but there are some recent studies mainly from Asia aiming for quadruple NAD therapy [15, 55, 56]. Ultimately, the decision is clinical and patient-centered, based on the best available clinical evidence.

Medication adherence

The success of drug therapy for a disease is directly related to treatment accomplishment, increase in survival, and quality of life of the patients.

Cramer *et al.* in 2008 [57] proposed definitions of adherence and persistence that are still used currently. Adherence or medication compliance may be defined as

“the extent to which a medication is taken at the prescribed doses, intervals, and frequency” and persistence as *“the continuation of treatment for the prescribed duration”*.

One of the major problems in analyzing studies on adherence is the variability of terms and metrics. Interesting proposals for updating and standardizing definitions terms and estimations have emerged [58-60].

Non-adherence can be defined as a failure to follow the medical prescription. There are several categorizations of non-adherence such as intentional (active decision, by choice) versus unintentional (passive behavior of forgetfulness or misunderstanding), or primary (failure to fill a new prescription) versus secondary non-adherence (failure on medication use upon filling a prescription) [58, 61]. Several reasons are mentioned for non-adherence to therapy and are related to the difficulty in establishing a long-term commitment to a therapeutic regimen from a clinical (lack of knowledge about the disease, prevalence of adverse effects), a behavioral (misunderstanding or neglect) and a financial perspective. [62, 63]. While secondary non-adherence is the aim of several studies, primary non-adherence is more challenging to study. Although not very suitable for identifying direct non-adherence cases, drug dispensing records are more accessible than prescription and clinical records for indirect calculation of adherence and its indicators.

The main metrics used to measure adherence in chronic diseases are medication possession ratio (MPR) and proportion of days covered (PDC). MPR is the number of days for which the medication is supplied concerning the dispensing period and usually assesses persistence; PDC is the number of days of medication available related to the follow-up period. Adherence is often set as a categorical variable (adherent versus non-adherent) in several studies and defined as a MPR or PDC equal to or greater than 0.80 [62]. This measurement approach does not allow the distinction between primary and secondary adherence and makes it difficult to apply in studies with consumption data [13, 64].

Off-label use

The off-label use of medicines distorts drug consumption data (and related prevalence estimations) from their approved indications, and in most cases their alternative application is unknown.

Off-label use of a drug is defined as the prescription of a drug outside the scope of the therapeutic indications approved in the respective marketing authorization: for a different therapeutic indication than those approved, or for

an authorized indication, but with different specifications than those approved, meaning a different dosage or patient group [16]. It implies that it has not been assessed, or at least validated, by the health authorities, and therefore lacks the same level of scientific evidence as treatments approved for specific indications. The off-label use of AD is not well-documented but some studies suggested the use of NAD in T1DM [65-70], obesity [65, 71], polycystic ovarian syndrome [72-74], dermatological diseases [75, 76] and as a senolytic [77-79]. Recently, EMA approved the SGLT inhibitors dapagliflozin and sotagliflozin as adjuvant treatments to insulin for T1DM in adults [80], and insulins were already recommended in T2DM in previous guidelines. No data metrics of off-label AD use were found.

Pharmacological therapy for DM is mainly exclusive to the disease treatment thus becoming associated with the diagnosis or treatment of patients, being the starting point for the development of a model for prevalence estimation based on the consumption of this group of drugs.

4. Material and Methods

It was conducted a nationwide study of drug dispensing database to support the estimation of the prevalence of T2DM in the Portuguese population. To assess the robustness of the estimation, the model was used to evaluate the prevalence of T2DM in two different time-periods: full-year 2018 and full-year 2021.

Data Source

AD for outpatient use are dispensed in Portugal upon prescription only. Portuguese data were retrieved from the Health Market Research Pharmacy Sales Information System, a national database with representative drug dispensing data at a regional level from ambulatory care. It includes more than 82% of the Portuguese pharmacies.

Data collection was based on the ATC classification system as recommended by the WHO [9].

The data collected covered ATC classes A10A - insulins and analogues and A10B (blood glucose-lowering drugs, excluding insulins), commercialized in Portugal both in 2018 and 2021.

Population

The study population was retrieved from demographic data for 2018 and 2021 (Table 3), including the total national population by the residence district, through the National Official Statistics Agency (INE).

Table 3 - Portugal population, per district.

Region	2018	2021
Aveiro	695702	700957
Beja	141178	144465
Braga	828650	846418
Bragança	124571	122826
Castelo Branco	179038	177995
Coimbra	405267	408609
Évora	152865	152511
Faro	438864	467475
Guarda	144354	142998
Leiria	454592	458672
Lisboa	2271772	2275846
Portalegre	105479	104930
Porto	1778146	1785627
Santarém	429719	425025
Setubal	852328	874926
Viana do Castelo	230954	231293
Vila Real	191894	185705
Viseu	354453	351315
Madeira	253945	250769
Açores	242846	236440
Total	10276617	10344802

Source: National Institute of Statistics (INE) [81]

Population exposure to AD was assumed to correspond to the population consumption, and was expressed as DDD/1000 inhabitants/day (DID, or DDD/TID – thousand inhabitants per day), according to the current WHO Collaborating Centre for Drugs Statistics Methodology criteria [9].

Two indicators were obtained:

1. Total DDD consumed per year was calculated as follows:

$$\text{Total DDD consumed} = \text{No. of units consumed in one year} \times \text{dosage} / \text{DDD}$$

DDD for each drug were based on the ATC Index 2022, regardless of the year to which the consumption refers. The drugs were classified according to the ATC Index 2022 classification, level 5 – active substance.

2. DID: indicates the number of people per 1000 who receive antidiabetic drugs daily and was calculated by

$$DID = \text{Total DDDs consumed} \times 1000 / (\text{No. inhabitants} \times 365 \text{ days})$$

Prevalence estimation model

The estimation of the prevalence of T2DM was performed by applying the formula proposed by Sartor and Walckiers [82]:

$$\hat{p} = \frac{\sum_{i=1}^k \left(\frac{v_i}{c_i} \right)}{N}$$

where:

$\hat{p}$ – estimated prevalence;

k - classes of drugs;

v_i - total amount of NAD sold in Portugal, for the years 2018 and 2021;

c_i - technical unit of drug consumption (DID);

N - estimated resident population in Portugal, for the years of 2018 and 2021.

For the application of this methodology, the authors assumed the following assumptions:

- The treatment of the pathology is mainly pharmacological;
- The drugs used are specific for the pathology considered;
- The administration of the drugs is not seasonal.

The prevalence estimation model was developed in 5 steps, as follows:

Step 1) Number of patients under treatment for DM, based on DID estimation

Exposure to AD was expressed in DID, which reflects the number of DDD dispensed to 1000 inhabitants *per day*. As DDD is the assumed average daily dose of a drug when used in its main therapeutic indication in adults, it is a rough estimation of patients under treatment with AD.

Calculations considered the ATC classification - level 4 - chemical subgroup.

Step 2) Adjustment to treatment adherence

Treatment adherence was assumed to be 60% for all NAD (crude value) [41, 83].

It was considered 100% for insulin AD.

Different adherence estimations were explored in the sensitivity analysis (detailed below).

Step 3) Adjustment to NAD in monotherapy and polytherapy

The concomitance of different antidiabetic pharmacological regimens will impact the prevalence estimation, i.e., two packages in a month may be used to treat one patient or two patients, according to the therapeutic regimen.

It was assumed a concomitance in NAD therapy estimated according to Sartor and Walckiers, 1995 [82], by using the weighting factor (w) achieved as follows:

$$w = \frac{1}{[1 + \pi_2 + (2\pi_3) + (3\pi_4)]}$$

where π_2 , π_3 and π_4 represents the probability of patients taking two, three or four drugs simultaneously.

It was applied a w value of 0.608 that corrects for the proportion of patients taking an association of two, three or four classes of NAD following the Oral Hypoglycaemic Drug Use Study [24].

Step 4) Exclusion of insulin AD users

Insulin users were excluded but it was considered that 7.5% of T2DM patients are insulin AD users [42].

Step 5) Prevalence estimation of T2DM patients under pharmacological treatment

Prevalence was obtained as a ratio of the number of patients in treatment for T2DM estimated in the previous steps *per* Portuguese population.

Step 6) Prevalence estimation of T2DM

To obtain an overall estimation of the prevalence of T2DM in Portugal, a percentage of non-diagnosed T2DM was considered: 44% for 2018 [28] and 35.7% for 2021 [34] of non-diagnosed patients.

Sensitivity analysis

A sensitivity analysis was performed by varying key parameters used in the base-case analysis. Each of these assumptions was changed while all other variables were held constant.

It was assessed the effect on T2DM estimated prevalence of changing the following parameters for the extreme values found in literature:

- Medication adherence: 50% and 92% [83-85];
- T2DM insulin users: 6% and 15.8% [36, 42];
- The concomitant factor: $w=0.596$ [86];
- non-diagnosed T2DM patients: 9.8% and 50% [34].

The data were processed using Microsoft Office Excel 2007 software.

5. Results

Characterization of AD consumption in Portugal

Figure 1 shows the AD consumption, measured in DID, in Portugal and its regions in 2018 and 2021.

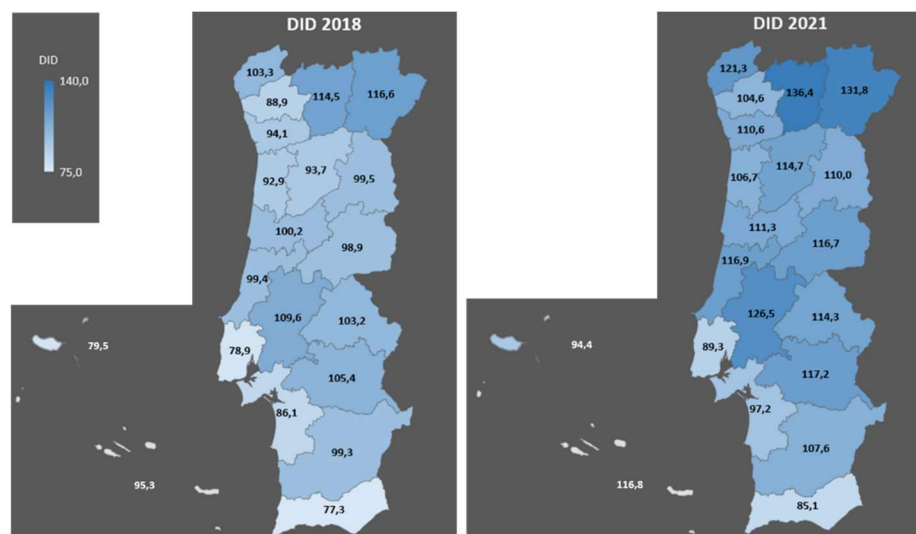


Figure 1 – Consumption of antidiabetic drugs expressed by Defined Daily Dose *per* 1000 inhabitants *per* day by region in 2018 and 2021.

The consumption of AD in Portugal in 2018 and 2021 increased from 91 DID to 104.9 DID. The region of lowest consumption in 2018 was Lisbon and in 2021 was Faro, while the highest occurred in Bragança in both periods. All regions in Portugal increased AD consumption from 2018 to 2021.

The insulin consumption increased in 2018 and 2021 from 15.5 DID to 16.0 DID (% change of +3.2%) while NAD consumption experienced an increase from 75.4 DID to 88.9 DID (% change of +17.9%), respectively.

The regions with the highest NAD consumption in 2018 were Vila Real and Bragança, and similar ranked positions were found in 2021. Lisbon and Faro were the regions with the lowest NAD consumption in 2018 and 2021.

Table 4 presents the AD consumption by ATC subgroups level four.

Table 4 – Antidiabetic consumption in DID in 2018 and 2021

ATC code	Description of the ATC code	DID (% ¹)		Variation ² (2018-2021, %)
		2018	2021	
A10AB	Fast-acting insulins	2.8 (3.1%)	3.3 (3.1%)	16.8
A10AC	Intermediate-acting insulins	1.8 (2.0%)	1.3 (1.2%)	-26.8
A10AD	Combined-acting insulins	4.0 (4.4%)	3.3 (3.1%)	-16.8
A10AE	Long-acting insulins	7.0 (7.7%)	8.1 (7.7%)	15.3
A10A	Insulins	15.5 (17.0%)	16.0 (15.2%)	3.2
A10BA	Biguanides	24.2 (26.6%)	24.5 (3.4%)	1.4
A10BB	Sulphonylureas	14.5 (15.9%)	11.5 (11.0%)	-20.5
A10BD	Oral fixed-dose combinations	22.4 (24.6%)	28.3 (27.0%)	26.5
A10BF	α -glucosidase inhibitors	0.7 (0.8%)	0.4 (0.4%)	-45.7
A10BG	Glitazones	0.4 (0.4%)	0.4 (0.4%)	-11.7
A10BH	DPP-4 inhibitors	7.0 (7.7%)	7.6 (7.2%)	8.9
A10BJ	GLP-1 analogues	1.6 (1.8%)	4.9 (4.7%)	196.8
A10BK	SGLT2 inhibitors	4.4 (4.8%)	11.2 (10.7%)	153.0
A10BX	Other non-insulin antidiabetics	0.2 (0.2%)	0.1 (0.1%)	-40.1
A10 B	Non-insulin antidiabetics	75.4 (82.9%)	88.9 (84.7%)	17.9
Total A10	Antidiabetics	91.0	104.9	15.3

¹. Share of DID of each drug in overall AD consumption;

². Absolute variation of DID from 2018 to 2021.

In 2018, insulins represented 17.0% of total AD consumed and in 2021 decreased to 15.3%. NAD increased from 82.9% to 84.7% from 2018 to 2021. Among NAD, sulphonylureas showed the larger decrease in consumption, and oral fixed-dose combinations, DPP-4 inhibitors, GLP-1 analogues and SGLT2 inhibitors presented a growth in their consumption. While in 2018 the most consumed NAD subgroup was biguanides (24.2 DID), in 2021 oral fixed-dose combinations reached the highest value (28.3 DID).

From Table 4 it can be observed that there has been a change in the pattern of NAD consumption between 2018 and 2021. Biguanides and oral fixed-dose combinations are the most consumed subgroups in the two years analysed. However, the consumption of sulphonylureas is clearly decreasing and the trend is increasing of the newest NAD: DPP-4 inhibitors, GLP-1 analogues and SGLT2 inhibitors. By the analysis of absolute variation represented in Table 4, it can be seen that GLP-1 analogues and SGLT2 inhibitors increased 3 and 2.5 times in absolute value, while sulphonylureas, α -glucosidase inhibitors, and other non-insulin antidiabetics represented the largest decline in an absolute basis consumption.

Prevalence of Diabetes in Portugal

The number of patients in treatment as well as the AD consumption for T2DM increased for every region and at the national level between 2018 and 2021. Prevalence of treated T2DM has also increased but not in the case of overall prevalence, by taking into account the non-diagnosed patients. The regions of Coimbra, Lisboa, and Setúbal experienced no variation in the overall prevalence, and for the regions of Beja, Évora, Faro, Guarda e Portalegre this value has even reduced, despite the growth at the national level (Table 5).

Table 5 – Estimated prevalence of Type 2 Diabetes mellitus from antidiabetic consumption data

Region	N. patients in treatment for DM ¹		N. patients under treatment for DM ²		Prevalence of treated T2DM patients (%) ³		Overall prevalence of T2DM (%) ⁴	
	2018	2021	2018	2021	2018	2021	2018	2021
Aveiro	65315	75645	54322	64443	7.8	9.2	13.9	14.3
Beja	14173	15723	12159	13542	8.6	9.4	15.4	14.6
Braga	74463	89563	63971	78413	7.7	9.3	13.8	14.4
Bragança	14678	16368	12379	14070	9.9	11.5	17.7	17.8
Castelo Branco	17882	20991	14429	17555	8.1	9.9	14.4	15.3
Coimbra	41017	45944	32594	37924	8.0	9.3	14.4	14.4
Évora	16286	18073	14000	15766	9.2	10.3	16.4	16.1
Faro	34275	40214	28303	34120	6.4	7.3	11.5	11.4
Guarda	14510	15904	12101	13615	8.4	9.5	15.0	14.8
Leiria	45654	54204	38138	46200	8.4	10.1	15.0	15.7
Lisboa	181282	205529	153755	177216	6.8	7.8	12.1	12.1
Portalegre	11007	12126	9340	10482	8.9	10.0	15.8	15.5
Porto	169066	199690	143733	173001	8.1	9.7	14.4	15.1
Santarém	47601	54357	40418	46830	9.4	11.0	16.8	17.1
Setúbal	74195	85955	62095	73303	7.3	8.4	13.0	13.0
Viana do Castelo	24114	28366	20824	24827	9.0	10.7	16.1	16.7
Vila Real	22214	25621	19369	22760	10.1	12.3	18.0	19.1
Viseu	33572	40745	28179	35033	7.9	10.0	14.2	15.5
Madeira	20411	23940	17904	21493	7.1	8.6	12.6	13.3
Açores	23377	27908	19295	23595	7.9	10.0	14.2	15.5
Total	945090	1096864	797307	944187	7.8	9.1	13.9	14.2

DM – Diabetes mellitus; T2DM – Type 2 Diabetes mellitus

¹. Based on DID estimation, and adjustment to adherence and therapeutic concomitance

². Exclusion of T2DM are insulin users

³. Estimated prevalence of T2DM treated patients based on AD consumption

⁴. Overall estimated prevalence of T2DM considering non-diagnosed patients.

By using an indirect method to estimate the prevalence based on AD consumption, the prevalence of T2DM was 7.8% in 2018 and 9.1% in 2021 for patients under pharmacological treatment.

The overall estimated prevalence considering non-diagnosed patient assumption was 13.9% and 14.2%, in 2018 and 2021, respectively.

Sensitivity analysis

Table 6 shows the prevalence estimates obtained by changing some of the parameters using a sensitivity analysis.

Table 6 – Sensibility analysis of estimated prevalence of Type 2 Diabetes mellitus

Parameters	Scenario	Prevalence of treated T2DM patients (%)		Overall prevalence of T2DM (%)	
		2018	2021	2018	2021
Base estimated prevalence¹		7.8	9.1	13.9	14.2
Medication adherence	50%	9.3	10.9		
	92%	5.1	6.0		
T2DM insulin users	6.0%	7.9	9.3		
	15.8%	7.7	9.1		
Concomitance factor (w)	0.596	7.6	9.0		
Non-diagnosed T2DM patients	9.8%			8.6	10.1
	50%			15.5	18.3

T2DM – Type 2 Diabetes mellitus

¹. Base-case scenario parameters: Medication adherence 60%, T2DM insulin users 7.5%; w factor 0.608; Non-diagnosed patients 44% (2018) and 35.7% (2021).

6. Discussion

This study was able to obtain an estimated prevalence of T2DM of 13.9% and 14.2% for 2018 and 2021, respectively. Therefore, we believe we have developed an easy-to-implement and updated method to estimate the prevalence of clinical conditions without resorting to primary data obtained through questionnaires that may be time-consuming, or databases that are difficult to obtain and complex to compute.

Characterization of AD consumption

AD consumption increased between 2018 and 2021, with overall values of 91 DID and 104.9 DID, respectively. ADs showed more pronounced growth than insulins, rising from 75.4 DID in 2018 to 88.9 DID in 2021, and insulins maintained their value at 15.5-16.0 DID.

To our knowledge, at the moment, there are no published analyses of AD consumption data for 2021 for Portugal. However, a study by Moura *et al.* [87] analysing AD consumption data from 2005 to 2017 found overall AD consumption rates of 49.3 DID in 2005 and 88.2 DID in 2017. The same study stated that the consumption of insulins was 15.4 DID and NADs was 72.9 DID. The insulin consumption results are in agreement in both studies for the adjacent years, demonstrating stability in insulin consumption. In fact, the study by Moura *et al.* showed an increase in insulin consumption between 2005 and 2017. However, rates of insulin consumption are now stable. The main reason underlying these results is that this type of treatment is mostly prescribed to T1DM, which represents a small proportion of the overall DM. The results of NAD consumption described in the present study, for 2018, are similar to those, but slightly higher. This fact may be justified by the increasing trend of NADs over the years and that Moura *et al.* study shows data of prescribed AD in NHS only, hence excluding other health subsystems and the regions of Madeira and Azores.

The pattern of AD consumption changed between 2018 and 2021 with a decrease in SU and growth in combination ADs and DPP-4 inhibitors, GLP-1 analogues and SGLT2 inhibitors. In 2018 the NADs that showed the highest consumption were biguanides (24.2 DID) followed by dose-fixed combinations (22.4 DID). In the study by Moura *et al.* similar but slightly lower values were reached (biguanides - 23.1 DID; dose-fixed combinations - 21.4 DID). The so-called new ADs (GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) in both studies showed very similar values, taking into account the analysed years.

The 2019 National Diabetes Observatory Annual Report, reported an overall AD consumption of 68.1 DID for 2017. OECD data for pharmaceutical consumption published DID rates of 70.2 (2018), 74.0 (2019) and 76.6 (2020) [88]. Differences may be explained by the evaluation of different metrics (e.g. calculation of DIDs of fixed-dose combinations) and databases (population covered).

Regarding and growth in consumption of most recent AD agents, the trend is also increasing across Europe, as shown by a study of 11 European countries [89].

Some reasons can be pointed for the increase in AD consumption, such as increased prevalence of DM, increased longevity, increased early diagnosis and consequent increase in treated patients, possible treatment of situations classified as pre-diabetes, more aggressive clinical approach with higher doses, change in prescribing patterns in line with new guidelines, and the emergence of fixed-dose NAD combinations following the growing scientific evidence.

The geographical distribution of AD consumption remains constant across regions comparing the year 2018 with 2021. Comparing 2018 data published by Moura *et al.* [87], it shows that the regions with the highest consumption are Bragança (109.9 DID) and Vila Real (107.8 DID) and the regions with the lowest consumption are Lisbon (76.4 DID) and Faro (69.1 DID). Similar trend results were obtained in the present study for 2018 (Bragança: 116.6 DID; Vila Real: 114.5 DID; Lisbon: 78.9 DID; Faro: 77.3 DID). The increasing trend was seen across regions and with similar distribution.

Prevalence estimation

This study found an overall and treated estimated prevalence of T2DM of 13.9% and 7.8%, for 2018, and 9.1% and 14.2% for 2021, respectively. These results

reveal the global growth trend justified by population aging, early diagnosis, and the consequent increase in the treated population.

The increased prevalence of obesity in childhood and adolescence also changes the epidemiological picture of T2DM, with its onset at increasingly earlier ages [90].

The National Diabetes Observatory publishes an annual report to generate and disseminate reliable and scientifically credible information on Diabetes in Portugal, using as a data source essentially registered and collected information on Diabetes in the Portuguese NHS. It is based on the first large epidemiological study on DM carried out in the country, the PREVDIAB, with in-person data collection in 2008 on a sample of 5167 individuals, and which has been updated with population data from the national censuses [91]. The latest annual report of the national diabetes observatory published in 2019, estimated a DM prevalence of 13.6%.

The IDF performs frequent estimates of diabetes prevalence for several countries based on the best quality data available at the time of analysis. These estimates depend on the type of data sources, ranging from peer-reviewed publications, national survey data, or data from regulatory bodies. The quality of the data is highly dependent on the diagnostic method chosen for DM, sample size and representativeness, date the study was conducted, type of study, and type of publication. Predicted future estimates are based only on projected changes in age, sex, and rural-urban place of residence, as defined by the United Nations [92]. The IDF prevalence estimates for Portugal for the years 2018 and 2021 were 14.2% and 13%, respectively.

This study reached a result that falls within the estimates considered for comparison, although not exactly with the same trend since the IDF predicts a decrease in prevalence in Portugal in 2021, contrary to the results obtained, which probably reflect more complex prescription patterns.

Prevalence estimation model: adherence to medication in DM

It is important to contextualize the assumed parameters for the application of the proposed prevalence estimation model from aggregate drug consumption data, and how they may influence the results, whereas the methodologies used for comparison use individual data.

Adherence to therapy is an important parameter that is reflected in drug consumption and the consequent effectiveness of the prescribed therapy. Studies on adherence to AD are scarce and none applied to the Portuguese population were found.

It is very difficult to assess adherence in DM and several studies diverge in terms and metrics to achieve a consensus. Pasina *et al.* obtained a non-adherence rate reported (n=100) in 55.1% of the patients at the first follow-up and 69.6% 3 months from hospital discharge, in elderly patients receiving polypharmacy, confirming that age is a predictor of higher non-adherence [63, 93]. A survey performed in 2016 in Slovakia (n=117) found adherence to pharmacological treatment up to 83% in females and 79% in males, and over 70% of all age categories up to 75 years old. [85]. In Italy, a study conducted in 2017, obtained rates of non-adherence, ranging from 8% to 13% for AD [84]. According to the WHO report of 2003, the average adherence to long-term therapy for chronic diseases in developed countries is approximately 50%, and in developing countries, lower adherence rates are encountered [40, 83]. Some systematic reviews approached the adherence of NAD and performed interesting comparisons between them, but none provided a crude adherence estimate as a reference [13, 94, 95]. A recent cross-sectional study on adherence in chronic diseases performed in Spain found a proportion of adherent patients to treatment of 55.5% [41].

Regarding the study of primary adhesion, Raebel *et al.* in 2012 performed a retrospective observational cohort study to identify primary non-adherence for hypertension, diabetes, and hyperlipidemia. The proportion of primary non-adherent patients varied by therapeutic class, and a value of 13% was found to primary non-adherence rate for antidiabetic drugs [96].

In this study, the knowledge of the primary adherence that is reflected in the dispensing of the prescribed drugs is of main interest. Considering the range of estimations published in the literature, a treatment adherence of 60% was considered as a base-case scenario.

Prevalence estimation model: concomitant use of AD drugs

For the application of the model, it was also necessary to adjust for the concomitant use of AD, according to the most recent guidelines for DM treatment management which sometimes may reach two, three, or four medications.

Some studies about prescribing patterns have been performed in recent years, but only a few reflect the usage of new NAD. Heintjes *et al.* conducted an

observational study by analyzing the EHR of antidiabetic drug prescription/dispensing in four European countries (Netherlands, Spain, Italy and the United Kingdom) from 2007 to 2012 ($n=295923$). Prescription patterns were categorized as first-line: oral monotherapy (metformin, a SU, a TZD, a DPP4 inhibitors, other oral antidiabetic drug, a GLP1, or insulin); second-line: dual oral therapy (combined metformin + SU, any oral combination treatment including a TZD, and any oral combination treatment including a DPP4 inhibitor); third-line: triple oral therapy (or oral/insulin or oral/GLP-1 combination therapy); fourth-line: insulin only, a GLP-1 only, and a combination of insulin + GLP-1. Combining all countries, 47% initiated first-line treatment, 28% intensified second-line treatment, 19% intensified to third-line treatment, and 7% evolved to fourth-line treatment [86].

In Italy, a regional observational study was performed in 2016 ($n=14679$) of new users of AD, considering only first-line treatment (monotherapy, fixed-dose combination and dual therapy). The results showed a dispensing rate of 86.9% for monotherapy, 9.7% for fixed-dose combination therapy, and 3.4% for dual therapy. However, this study did not account for therapy intensification, that is, 2nd, 3rd or 4th line treatments [97]. Another study conducted in Spain in 2013-2014 ($n=65167$) obtained similar results [98]. Other researchers are dedicated to assessing the same subject though not achieving a general prescription pattern for concomitance [98, 99].

In the present study, it was used the weight factor (w) for medicines associations calculation methodology developed by Sartor *et al.*, 1995 [82] based on a study by Duarte-Ramos *et al* [24]. The same methodology was used by other authors [22]. The weight factor used ($w= 0.608$) was obtained in a national cross-sectional survey, conducted from December 2003 until March 2004. Taking into account the study period, it is easy to notice that the prescribing patterns will not correspond to the current ones, namely polytherapy. The mentioned study by Heintjes *et al* [86] obtained updated prescribing patterns and their results were used to recalculate the weight factor for associations. The factor obtained ($w=0.596$), yielded estimated prevalence values for treated T2DM of 7.6% for 2018 and 9.0% for 2021, proving to have little influence on the final estimation. It was then considered the weight factor of Duarte-Ramos [24] obtained for the Portuguese population. For longitudinal monitoring, it is important to consider the periodic collection of primary data on prescription patterns, which will allow the acquisition of information to calculate the correction factor w and adjust the estimates.

A proportion of non-treated DM (44%) was considered based on the National Diabetes Observatory Annual Report for the Portuguese population in 2018 [28]. A value of 35.7% was considered for 2021, based on the International Diabetes Federation for Europe [34]. It is possible that this estimate is not accurate considering that it can only be known from in-person surveys.

Strengths and limitations

This study has some limitations that are discussed below.

Firstly, the model can only estimate the prevalence of diagnosed and treated DM, due to data origin.

Access to aggregate data requires parameter adjustments with assumptions that are not always precise and appropriate to the study population, influencing their validity. For the same reason, the outcome cannot be stratified by sex or age, as clinically valuable information. It can only inform geographical distribution.

The database used does not include inpatient consumption. However, it includes other health subsystems not identified in the NHS databases.

Therapeutic adherence is a parameter that influences AD consumption and for which there are no updated estimations for the Portuguese population. The existing information shows a very large variation between studies. The adherence considered to be 60% for all NAD and 100% for insulins certainly does not correspond to real-world, since there will be some non-adherence in insulins, although not significant, and adherence among NAD will not be homogeneous, since it is directly linked to adverse effects and costs, which are very different among ATC subclasses.

The dispensing data do not reflect exactly the prescription clinical practice. The prescribing patterns have been changing over the years and the concomitance factor used will not be updated for the emergence of new NAD and combinations, with the increase of polytherapy and the trend towards the introduction of increasingly earlier insulin use for the control of hyperglycemia and prevention of future complications. The estimates used for several parameters were based on the available literature, which is not always updated, is related to other populations or does not use robust methods, biasing the final estimated result.

This study did not consider the off-label use of NAD, outside the main and authorized indication due to lack of information. However, its impact on the prevalence estimation was considered residual.

Compared with other studies using prescription data or data not covering the entire population, the use of dispensing obtained from a sample representing 82% of the pharmacies in Portugal, with a homogeneous geographical distribution, is a strength of the study consolidating the results presented.

This method allowed to estimate DM prevalence simply and will benefit from evolving drug utilization research, especially studies on primary and secondary adherence, prescribing patterns and off-label use of AD, to refine the assumed parameters.

7. Conclusions

An estimate of T2DM prevalence was achieved from aggregate AD drug consumption data, with similar results to those obtained by the standard methodologies. Nevertheless, the developed method can be improved by more and precise estimates for the assumed parameters.

The geographical distribution of AD consumption remained constant in the studied years. The results clearly show growth in AD consumption with particular emphasis on fixed-dose combinations and new NADs.

The developed method, based on information collected in the pharmacy network widely distributed throughout Portugal, has the advantage of accessing a large and representative sample size of the population, can be repeated periodically, and can be regionally stratified, identifying and exploring differences for that purpose.

This study contributes to the development of pharmacoepidemiology and drug utilization data in particular. Less complex methods, even if not as accurate as classical methods, allow the fast updating of health policies, clinical guidelines, or pharmacoeconomic studies.

8. Future research

As it has been discussed so far, there is still a long road until these methods can substitute or complement the traditional methods for the estimation of the prevalence of clinical conditions. So that more accurate results can be achieved, the following research is proposed:

- a) The development of a descriptive observational study with individual NAD prescribing and dispensing data from a study cohort, will allow prevalence estimation based on individual data with more accurate results;
- b) Comparison between the two proposed models could validate the use of easily accessible aggregated data;
- c) For further comprehensive research, the development of studies that contribute to the estimation of the adherence medication, prescribing patterns, and off-label use.

9. References

- [1] Wulsin L, Dougherty A, Bureau CSLCR. A Briefing on Health Technology Assessment: California State Library, California Research Bureau; (2008).
- [2] Lourenço Ó, & Silva, V. Avaliação económica de programas de saúde - Essencial sobre conceitos, metodologia, dificuldades e oportunidades. *Revista Portuguesa de Medicina Geral e Familiar*. (2008);24(6):729-52.
- [3] Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal*. (2003);20(1):54-60.
- [4] Chodankar D. Introduction to real-world evidence studies. *Perspect Clin Res*. (2021);12(3):171-4.
- [5] Laranjo L, Rodrigues D, Pereira AM, Ribeiro RT, Boavida JM. Use of Electronic Health Records and Geographic Information Systems in Public Health Surveillance of Type 2 Diabetes: A Feasibility Study. *JMIR Public Health Surveill*. (2016);2(1):e12.
- [6] Wettermark B, Zoëga H, Furu K, Korhonen M, Hallas J, Nørgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. *Pharmacoepidemiol Drug Saf*. (2013);22(7):691-9.
- [7] Hallas J, Hellfritzsche M, Rix M, Olesen M, Reilev M, Pottegård A. Odense Pharmacoepidemiological Database: A Review of Use and Content. *Basic Clin Pharmacol Toxicol*. (2017);120(5):419-25.

- [8] Bachhav SS, Kshirsagar NA. Systematic review of drug utilization studies & the use of the drug classification system in the WHO-SEARO Region. *Indian J Med Res.* (2015);142(2):120-9.
- [9] WHO. Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2022 Oslo(2021)
[Available from:
https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/].
- [10] Rasmussen L, Wettermark B, Steinke D, Pottegård A. Core concepts in pharmacoepidemiology: Measures of drug utilization based on individual-level drug dispensing data. *Pharmacoepidemiol Drug Saf.* (2022);31(10):1015-26.
- [11] Elseviers M, Wettermark B, Almarsdottir AB, Andersen M, Benko R, Bennie M, et al. *Drug Utilization Research: Methods and Applications* (2016).
- [12] Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. *Clin Ther.* (2006);28(9):1411-24; discussion 1410.
- [13] Evans M, Engberg S, Faurby M, Fernandes J, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: A systematic literature review. *Diabetes Obes Metab.* (2022);24(3):377-90.
- [14] Lin Y-Y, Weng S-F, Hsu C-H, Huang C-L, Lin Y-P, Yeh M-C, et al. Effect of metformin monotherapy and dual or triple concomitant therapy with metformin on glycemic control and lipid profile management of patients with type 2 diabetes mellitus. *Frontiers in Medicine.* (2022);9.
- [15] Moon JS, Suh S, Kim SS, Jin HY, Kim JM, Jang MH, et al. Efficacy and Safety of Treatment with Quadruple Oral Hypoglycemic Agents in Uncontrolled

Type 2 Diabetes Mellitus: A Multi-Center, Retrospective, Observational Study. *Diabetes Metab J.* (2021);45(5):675-83.

[16] Rusz C-M, Ősz B-E, Jítcă G, Miklos A, Bătrînu M-G, Imre S. Off-Label Medication: From a Simple Concept to Complex Practical Aspects. *International Journal of Environmental Research and Public Health.* (2021);18(19):10447.

[17] Chini F, Pezzotti P, Orzella L, Borgia P, Guasticchi G. Can we use the pharmacy data to estimate the prevalence of chronic conditions? a comparison of multiple data sources. *BMC Public Health.* (2011);11:688.

[18] Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A, et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. *J Health Serv Res Policy.* (2005);10(4):232-8.

[19] Purkiss SF, Keegel T, Vally H, Wollersheim D. A comparison of Australian chronic disease prevalence estimates using administrative pharmaceutical dispensing data with international and community survey data. *Int J Popul Data Sci.* (2020);5(1):1347.

[20] Slobbe LCJ, Füssenich K, Wong A, Boshuizen HC, Nielen MMJ, Polder JJ, et al. Estimating disease prevalence from drug utilization data using the Random Forest algorithm. *Eur J Public Health.* (2019);29(4):615-21.

[21] Walckiers D, Sartor F. Results of an epidemiological study on drug-treated intraocular hypertension in Belgium. *J Clin Epidemiol.* (1996);49(4):489-93.

[22] Azevedo LF, Magro F, Portela F, Lago P, Deus J, Cotter J, et al. Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach. *Pharmacoepidemiology and Drug Safety.* (2010);19(5):499-510.

- [23] Vaes B, Ruelens C, Saikali S, Smets A, Henrard S, Renard F, et al. Estimating the prevalence of diabetes mellitus and thyroid disorders using medication data in Flanders, Belgium. *Eur J Public Health*. (2018);28(1):193-8.
- [24] Duarte-Ramos F, Cabrita J. Using a pharmaco-epidemiological approach to estimate diabetes type 2 prevalence in Portugal. *Pharmacoepidemiol Drug Saf*. (2006);15(4):269-74.
- [25] Cohen R, Fontbonne A, Weitzman S, Eschwege E. Estimation of the prevalence of diabetes mellitus in Israel based on hypoglycemic drug supply and consumption. *Diabete Metab*. (1990);16(2):59-63.
- [26] Purkiss S, Keegel T, Vally H, Wollersheim D. Estimates of drug treated diabetes incidence and prevalence using Australian administrative pharmaceutical data. *Int J Popul Data Sci*. (2021);6(1):1398.
- [27] WHO. International Working Group for Drug Statistics Methodology, Collaborating Centre for Drug Statistics Methodology, Collaborating Centre for Drug Utilization Research, Clinical Pharmacological Services. Introduction to drug utilization research. Geneva: World Health Organization; (2003).
- [28] SPD. Sociedade Portuguesa de Diabetologia. Relatório Anual do Observatório Nacional da Diabetes. (2019).
- [29] DGS. Direção Geral da Saúde. Norma nº 002/2011. Diagnóstico e Classificação da Diabetes Mellitus(2011).
- [30] Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. *Cochrane Database Syst Rev*. (2018);10(10):Cd012661.
- [31] Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, et al. IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus

Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. *Diabetes Res Clin Pract.* (2022);183:109050.

[32] Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. 15. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* (2022);45(Suppl 1):S232-s43.

[33] WHO. World Health Organization. Classification of diabetes mellitus. Geneva(2019).

[34] IDF. International Diabetes Federation. Diabetes Atlas 2021. Available from: www.diabetesatlas.org.

[35] Pereira M, Carreira H, Lunet N, Azevedo A. Trends in prevalence of diabetes mellitus and mean fasting glucose in Portugal (1987-2009): a systematic review. *Public Health.* (2014);128(3):214-21.

[36] Cortez-Dias N, Martins S, Belo A, Fiuza M. Prevalence, management and control of diabetes mellitus and associated risk factors in primary health care in Portugal. *Rev Port Cardiol.* (2010);29(4):509-37.

[37] de Sousa-Uva M, Antunes L, Nunes B, Rodrigues AP, Simões JA, Ribeiro RT, et al. Trends in diabetes incidence from 1992 to 2015 and projections for 2024: A Portuguese General Practitioner's Network study. *Prim Care Diabetes.* (2016);10(5):329-33.

[38] Barreto M, Kislaya I, Gaio V, Rodrigues AP, Santos AJ, Namorado S, et al. Prevalence, awareness, treatment and control of diabetes in Portugal: Results from the first National Health examination Survey (INSEF 2015). *Diabetes Res Clin Pract.* (2018);140:271-8.

[39] WHO. World Health Organization. Health topics: Diabetes [Available from: <https://www.who.int/health-topics/diabetes>].

- [40] Sabaté E. Adherence to long-term therapies: evidence for action: World Health Organization; (2003).
- [41] Fernandez-Lazaro CI, García-González JM, Adams DP, Fernandez-Lazaro D, Mielgo-Ayuso J, Caballero-Garcia A, et al. Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study. *BMC Family Practice*. (2019);20(1):132.
- [42] Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. *Lancet Diabetes Endocrinol*. (2019);7(1):25-33.
- [43] Esposito K, Maiorino MI, Petrizzo M, Bellastella G, Giugliano D. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. *Diabetes Care*. (2014);37(7):1824-30.
- [44] Pot GK, Battjes-Fries MC, Patijn ON, Zijl Nvd, Pijl H, Voshol P. Lifestyle medicine for type 2 diabetes: practice-based evidence for long-term efficacy of a multicomponent lifestyle intervention (Reverse Diabetes2 Now). *BMJ Nutrition, Prevention & Health*. (2020):bmjnph-2020-000081.
- [45] DGS. Direção Geral de Saúde. Norma 052/2011 Abordagem terapêutica farmacológica na diabetes mellitus tipo 2(2011).
- [46] Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. (2022);45(Suppl 1):S125-s43.
- [47] Rui Duarte MM, J. Silva Nunes, Pedro C. Melo, João F. Raposo, Davide Carvalho, pelo Grupo de Trabalho para as Recomendações Nacionais da SPD sobre a Terapêutica da Diabetes Tipo 2. SPD National Recommendations for the Treatment of Hyperglycemia in Type 2 Diabetes – Update Based in the

ADA/EASD Joint Position Statement. *Revista Portuguesa de Diabetes*. (2018);4(13):154-80.

[48] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. (2018);41(12):2669-701.

[49] DGS. Direção Geral da Saúde. Norma n° 025/2011. Insulinoterapia na Diabetes Mellitus tipo 2. (2011).

[50] IDF. International Diabetes Federation. Global Guideline for type 2 diabetes(2012).

[51] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. (2012);35(6):1364-79.

[52] Wallia A, Molitch ME. Insulin Therapy for Type 2 Diabetes Mellitus. *JAMA*. (2014);311(22):2315-25.

[53] Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. *Diabetes Obes Metab*. (2014);16(6):553-9.

[54] Ni X, Zhang L, Feng X, Tang L. New Hypoglycemic Drugs: Combination Drugs and Targets Discovery. *Frontiers in Pharmacology*. (2022);13.

- [55] Cho YK, Lee J, Kim HS, Park J-Y, Jung CH, Lee WJ. Clinical Efficacy of Quadruple Oral Therapy for Type 2 Diabetes in Real-World Practice: A Retrospective Observational Study. *Diabetes Therapy*. (2020);11(9):2029-39.
- [56] Ku EJ, Lee DH, Jeon HJ, Oh TK. Long-term effectiveness and safety of quadruple combination therapy with empagliflozin versus dapagliflozin in patients with type 2 diabetes: 3-year prospective observational study. *Diabetes Res Clin Pract*. (2021);182:109123.
- [57] Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. (2008);11(1):44-7.
- [58] Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care*. (2013);51(8 Suppl 3):S11-21.
- [59] Arnet I, Abraham I, Messerli M, Hersberger KE. A method for calculating adherence to polypharmacy from dispensing data records. *International Journal of Clinical Pharmacy*. (2014);36(1):192-201.
- [60] Basu S, Garg S, Sharma N, Singh MM. Improving the assessment of medication adherence: Challenges and considerations with a focus on low-resource settings. *Ci Ji Yi Xue Za Zhi*. (2019);31(2):73-80.
- [61] Oliboni L, de Castro M. Adesão à Farmacoterapia, que universo é esse? Uma revisão narrativa. *Clinical & Biomedical Research*. (2018);38:178-95.
- [62] Swe K, Reddy SSK. Improving Adherence in Type 2 Diabetes. *Clin Geriatr Med*. (2020);36(3):477-89.

- [63] Yap AF, Thirumoorthy T, Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. *Geriatr Gerontol Int.* (2016);16(10):1093-101.
- [64] Sapkota S, Brien JA, Greenfield J, Aslani P. A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 diabetes--impact on adherence. *PLoS One.* (2015);10(2):e0118296.
- [65] Tsushima Y, Zhou K, Bena JF, Kashyap SR. Prevalence and Clinical Determinants of Obesity in Adults With Type 1 Diabetes Mellitus: A Single-Center Retrospective Observational Study. *Endocr Pract.* (2022);28(4):378-83.
- [66] Hughes MS, Bailey R, Calhoun P, Shah VN, Lyons SK, DeSalvo DJ. Off-label use of sodium glucose co-transporter inhibitors among adults in type 1 diabetes exchange registry. *Diabetes Obes Metab.* (2022);24(1):171-3.
- [67] Sjöholm Å. Using adjuvant pharmacotherapy in the treatment of type 1 diabetes. *Expert Opin Pharmacother.* (2021);22(16):2143-8.
- [68] Lane K, Freeby M. Adjunctive therapies in type 1 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes.* (2021);28(1):8-13.
- [69] El Hage L, Kashyap SR, Rao P. Use of SGLT-2 Inhibitors in Patients With Type 1 Diabetes Mellitus. *J Prim Care Community Health.* (2019);10:2150132719895188.
- [70] Bayona Cebada A, Nattero-Chávez L, Alonso Díaz S, Escobar-Morreale HF, Luque-Ramírez M. Efficacy and Safety of SGLT2 Inhibitors in Type 1 Diabetes After the Introduction of an Off-Label Use Protocol for Clinical Practice. *Diabetes Technol Ther.* (2020);22(3):208-15.
- [71] Sari C, Seip RL, Umashanker D. Case Report: Off Label Utilization of Topiramate and Metformin in Patients With BMI ≥ 50 kg/m² Prior to Bariatric Surgery. *Front Endocrinol (Lausanne).* (2021);12:588016.

- [72] Ayub M, Gul S, Zehra F. Report: Metformin potential in predisposing arthralgia, type II cross reactivity secondary to group A streptococcus infection & other comorbidities in treating PCOS. *Pak J Pharm Sci.* (2019);32(3):1107-10.
- [73] Nathan N, Sullivan SD. The utility of metformin therapy in reproductive-aged women with polycystic ovary syndrome (PCOS). *Curr Pharm Biotechnol.* (2014);15(1):70-83.
- [74] Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. *Gynecol Endocrinol.* (2019);35(3):198-206.
- [75] Sung CT, Chao T, Lee A, Foulad DP, Choi F, Juhasz M, et al. Oral Metformin for Treating Dermatological Diseases: A Systematic Review. *J Drugs Dermatol.* (2020);19(8):713-20.
- [76] Stanescu AMA, Simionescu AA, Florea M, Diaconu CC. Is Metformin a Possible Beneficial Treatment for Psoriasis? A Scoping Review. *J Pers Med.* (2021);11(4).
- [77] Piskovatska V, Storey KB, Vaiserman AM, Lushchak O. The Use of Metformin to Increase the Human Healthspan. *Adv Exp Med Biol.* (2020);1260:319-32.
- [78] Mohammed I, Hollenberg MD, Ding H, Triggle CR. A Critical Review of the Evidence That Metformin Is a Putative Anti-Aging Drug That Enhances Healthspan and Extends Lifespan. *Front Endocrinol (Lausanne).* (2021);12:718942.
- [79] Piskovatska V, Stefanyshyn N, Storey KB, Vaiserman AM, Lushchak O. Metformin as a geroprotector: experimental and clinical evidence. *Biogerontology.* (2019);20(1):33-48.

- [80] New add-on treatment to insulin for treatment of certain patients with type 1 diabetes. EMA/141347/2019 [press release]. 2019.
- [81] População residente em Portugal [Internet]. [cited 26/06/2022]. Instituto Nacional de Estatística. [Available from: www.ine.pt].
- [82] Sartor F, Walckiers D. Estimate of disease prevalence using drug consumption data. *Am J Epidemiol.* (1995);141(8):782-7.
- [83] Wabe NT, Angamo MT, Hussein S. Medication adherence in diabetes mellitus and self management practices among type-2 diabetics in Ethiopia. *N Am J Med Sci.* (2011);3(9):418-23.
- [84] Spadea T, Onorati R, Baratta F, Pignata I, Parente M, Pannacci L, et al. Monitoring adherence to pharmacological therapy and follow-up examinations among patients with type 2 diabetes in community pharmacies. Results from an experience in Italy. *PLoS One.* (2021);16(9):e0256478.
- [85] Masaryková L, Tesař T, Lehocká U, Bernáthová K. Evaluation of adherence to treatment in patients suffering from diabetes mellitus. *Ceska Slov Farm.* (2020);69(2):67-74.
- [86] Heintjes EM, Overbeek JA, Hall GC, Prieto-Alhambra D, Lapi F, Hammar N, et al. Factors Associated with Type 2 Diabetes Mellitus Treatment Choice Across Four European Countries. *Clin Ther.* (2017);39(11):2296-310.e14.
- [87] Moura AM, Martins SO, Raposo JF. Consumption of antidiabetic medicines in Portugal: results of a temporal data analysis of a thirteen-year study (2005-2017). *BMC Endocr Disord.* (2021);21(1):30.
- [88] Database of consumption of antidiabetic drugs (ATC A10), in DHD and by year, for several countries [Internet]. [cited 26/06/2022]. Available from: <http://www.oecd.org/health/health-data.htm>.

- [89] Mardetko N, Nabergoj Makovec U, Locatelli I, Janez A, Kos M. Uptake of new antidiabetic medicines in 11 European countries. *BMC Endocr Disord.* (2021);21(1):127.
- [90] Kansra AR, Lakkunarajah S, Jay MS. Childhood and Adolescent Obesity: A Review. *Front Pediatr.* (2020);8:581461.
- [91] Gardete-Correia L, Boavida JM, Raposo JF, Mesquita AC, Fona C, Carvalho R, et al. First diabetes prevalence study in Portugal: PREVADIAB study. *Diabet Med.* (2010);27(8):879-81.
- [92] Aschner P, Karuranga S, James S, Simmons D, Basit A, Shaw JE, et al. The International Diabetes Federation's guide for diabetes epidemiological studies. *Diabetes Res Clin Pract.* (2021);172:108630.
- [93] Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging.* (2014);31(4):283-9.
- [94] McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab.* (2018);20(4):1040-3.
- [95] Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: a review. *Diabetol Metab Syndr.* (2022);14(1):12.
- [96] Raebel MA, Ellis JL, Carroll NM, Bayliss EA, McGinnis B, Schroeder EB, et al. Characteristics of patients with primary non-adherence to medications for hypertension, diabetes, and lipid disorders. *J Gen Intern Med.* (2012);27(1):57-64.
- [97] Moreno Juste A, Menditto E, Orlando V, Monetti VM, Gimeno Miguel A, González Rubio F, et al. Treatment Patterns of Diabetes in Italy: A Population-Based Study. *Front Pharmacol.* (2019);10:870.

- [98] Moreno-Juste A, Poblador-Plou B, Aza-Pascual-Salcedo M, González-Rubio F, Malo S, Librero López J, et al. Initial Therapy, Regimen Change, and Persistence in a Spanish Cohort of Newly Treated Type 2 Diabetes Patients: A Retrospective, Observational Study Using Real-World Data. *Int J Environ Res Public Health*. (2020);17(10).
- [99] Ingrasciotta Y, Bertuccio MP, Crisafulli S, Ientile V, Muscianisi M, L'Abbate L, et al. Real World Use of Antidiabetic Drugs in the Years 2011-2017: A Population-Based Study from Southern Italy. *Int J Environ Res Public Health*. (2020);17(24).

Annexes

Annex I: Diabetes mellitus classification [33]

Form of DM	Description
Type 1	Autoimmune β -cell destruction and absolute insulin deficiency; onset most common in children and young adults
Type 2	Progressive loss of insulin due to various degrees of β -cell dysfunction and insulin resistance; commonly associated with overweight and obesity
Hybrid forms	
- Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving type 1 in adults but more often has features of the metabolic syndrome, a single GAD autoantibody and retains greater β -cell function (ex – LADA)
- Ketosis-prone type 2	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune-mediate
Other specific types	
- Monogenic defects of β -cell function	Caused by specific gene mutations, has several clinical manifestations requiring different treatments, some occurring in the neonatal period, others by early adulthood
- Monogenic defects in insulin action	Caused by specific gene mutations; has features of severe insulin resistance without obesity; diabetes develops when β -cells do not compensate for insulin resistance
- Diseases of the exocrine pancreas	Various conditions that affect the pancreas can result in hyperglycaemia

- Endocrine disorders	Occurs in diseases with excess secretion of hormones that are insulin antagonists
- Drug- or chemical-induced	Some medicines and chemicals impair insulin secretion or action, some can destroy β -cells
- Infection-related diabetes	Some viruses have been associated with direct β -cell destruction
- Uncommon specific forms of immune-mediated diabetes	Associated with rare autoimmune diseases
- Other genetic syndromes sometimes associated with diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes
- Unclassified diabetes	Used to describe diabetes that does not fit into other categories. This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis

Hyperglycaemia first detected during pregnancy

DM in pregnancy	Type 1 or type 2 diabetes first diagnosed during pregnancy
Gestational DM	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy

DM: Diabetes mellitus; GAD: Glutamic Acid Decarboxylase; LADA: Latent autoimmune diabetes in adults

Annex II: Anatomical Therapeutic Chemical classification of antidiabetic drugs [9]

Medicines used in Diabetes treatment have the following ATC classification:

A ALIMENTARY TRACT AND METABOLISM

A10 DRUGS USED IN DIABETES

A10A INSULINS AND ANALOGUES

A10AB Insulins and analogues for injection, fast-acting

A10AC Insulins and analogues for injection, intermediate-acting

A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting

A10AE Insulins and analogues for injection, long-acting

A10AF Insulins and analogues for inhalation

A10B BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS

A10BA Biguanides

A10BB Sulfonylureas

A10BC Sulfonamides (heterocyclic)

A10BD Combinations of oral blood glucose lowering drugs

A10BF Alpha glucosidase inhibitors

A10BG Thiazolidinediones

A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors

A10BJ Glucagon-like peptide-1 (GLP-1) analogues

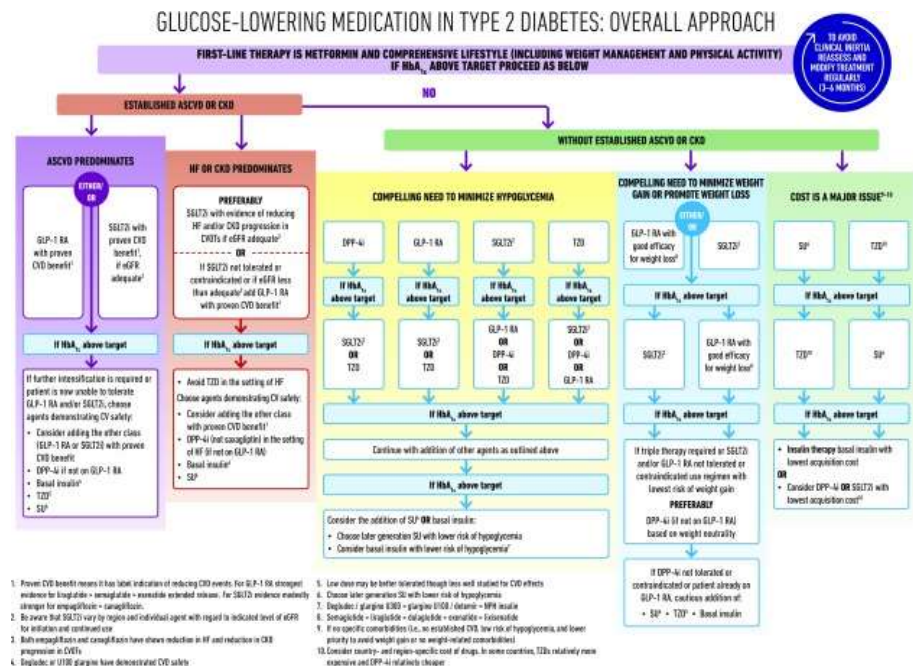
A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors

A10BX Other blood glucose lowering drugs, excl. insulins

A10X OTHER DRUGS USED IN DIABETES

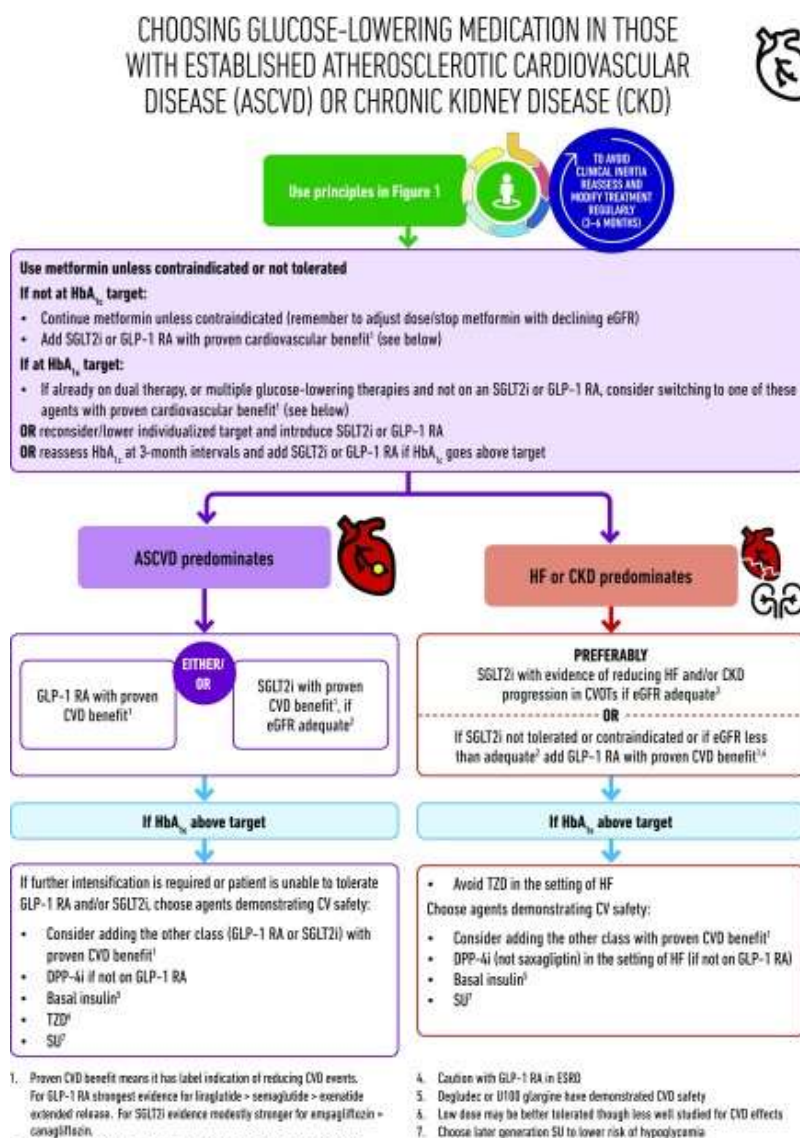
A10XA Aldose reductase inhibitors

Annex III – Pharmacological management of T2DM



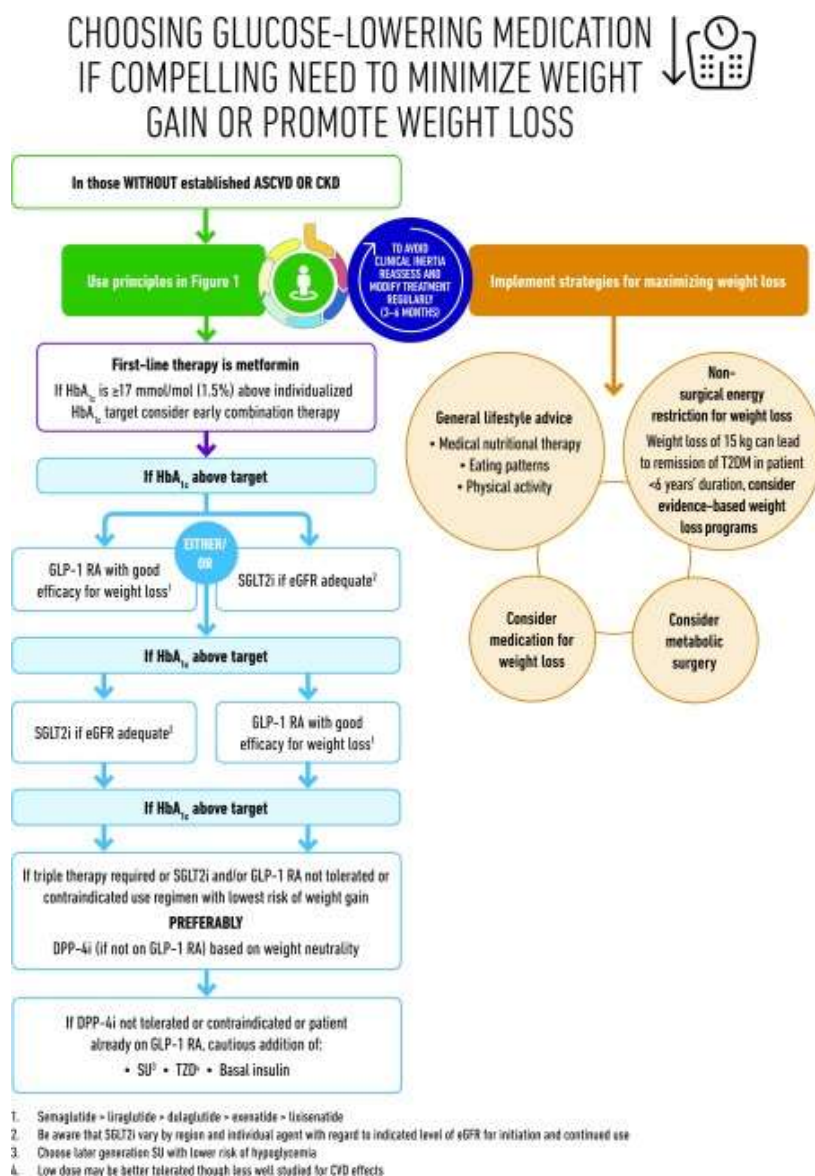
Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Figure A1 – Glucose-lowering medication overall approach scheme for T2 DM according to Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])



CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

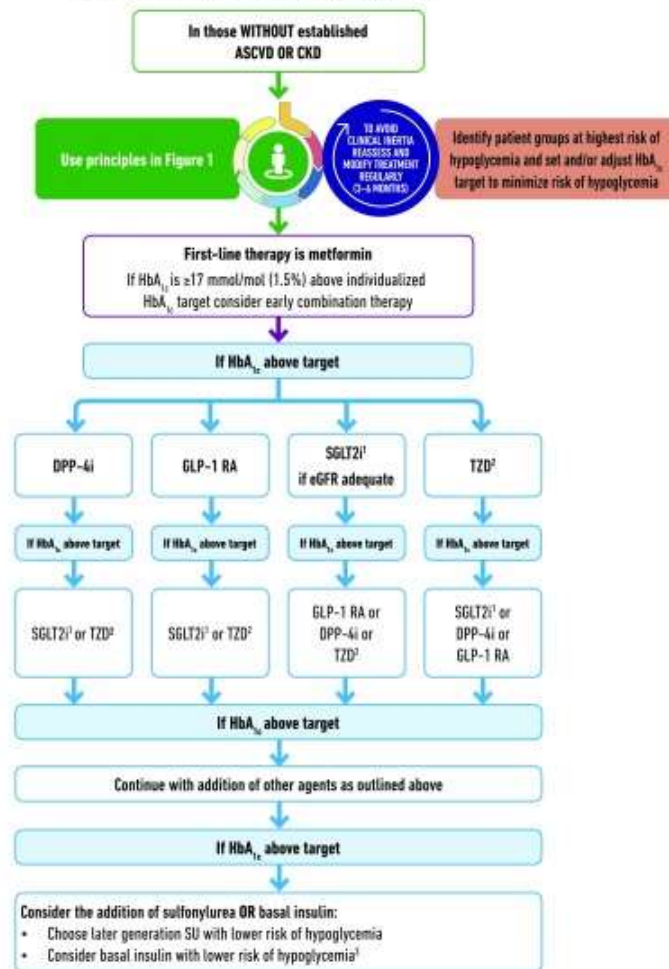
Figure A2 – Choosing glucose-lowering medication in those with established ASCVD, HF, and CKD according to the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])



GLP-1 RA, glucagon-like peptide 1 receptor agonist; T2DM, type 2 diabetes; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Figure A3 – Choosing glucose-lowering medication if compelling need to minimize weight gain or promote weight loss according to Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



1. Be aware that SGLT2i vary by region and individual agent, with regard to indicated level of eGFR for initiation and continued use

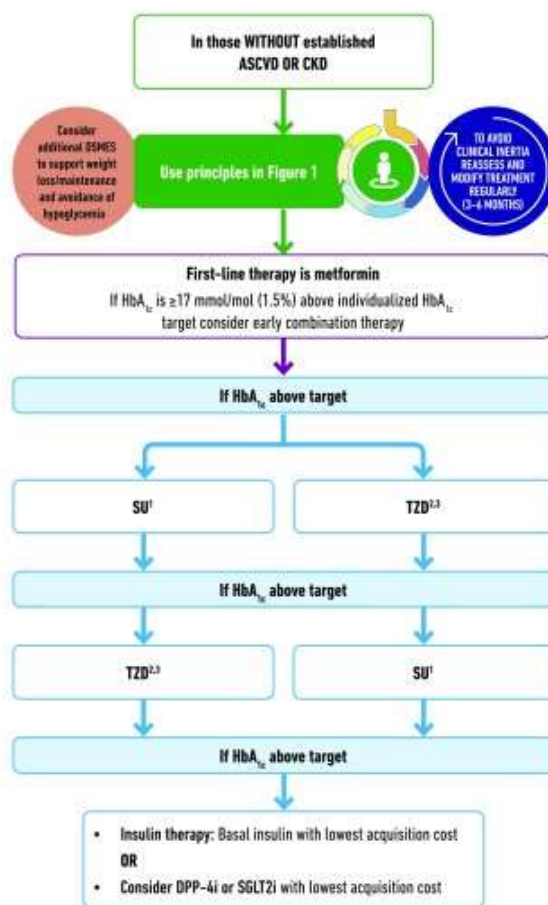
2. Low dose TZDs are better tolerated

3. Degludec / glargine U300 - glargine U100 / detemir - NPH insulin

DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor.

Figure A4 – Choosing glucose-lowering medication if compelling need to minimize hypoglycemia according to the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])

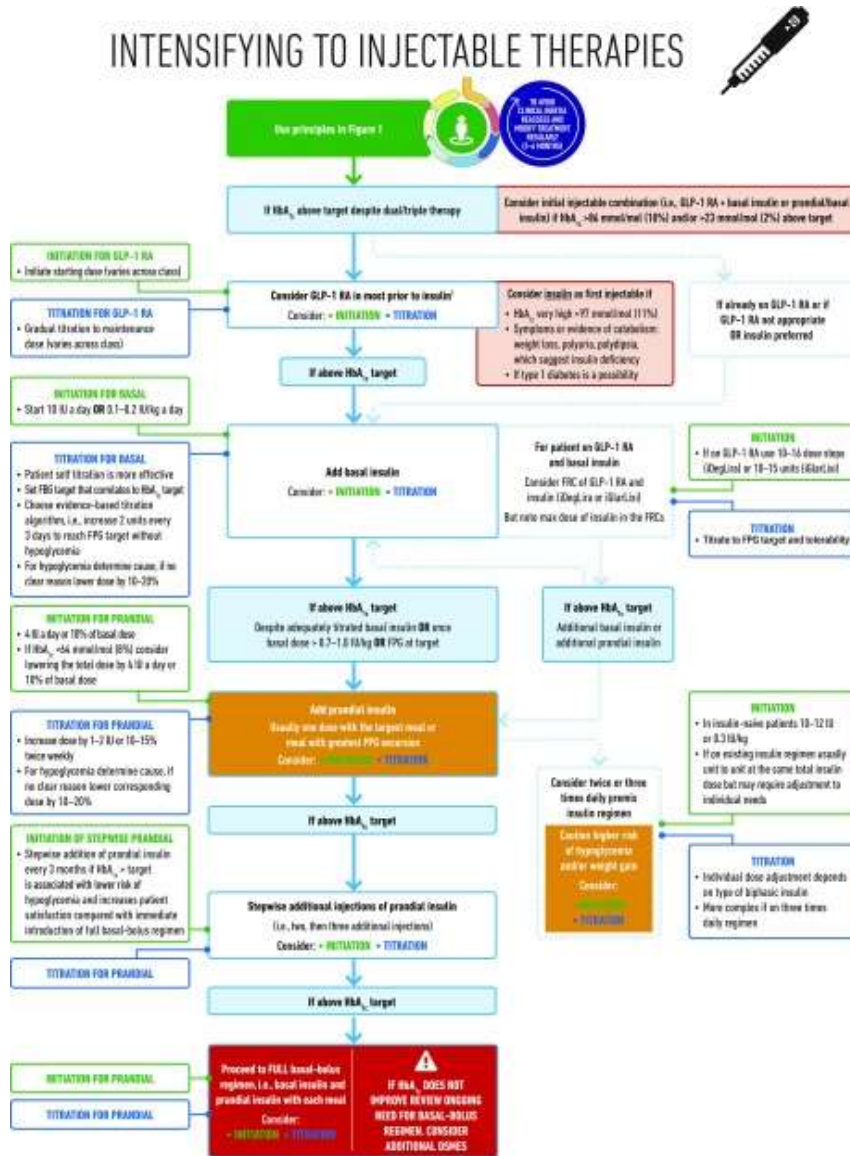
CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



1. Choose later generation SU to minimize risk of hypoglycemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated

DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea

Figure A5 – Choosing glucose-lowering medication if cost is a major issue according to the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])



1. Consider choice of GLP-1 RA considering patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.

FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; FBG, fasting blood glucose; FPG, fasting plasma glucose; max, maximum; PPG, postprandial glucose.

Figure A6 – Intensifying to injectable therapies according to Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])

CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN



Continue treatment with metformin

SGLT2i



If on SGLT2i, continue treatment

Consider adding SGLT2i if

- Established CVD
- If HbA_{1c} above target or as weight reduction aid

TZD¹



Stop TZD when commencing insulin OR reduce dose



Beware

- DKA (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

SULFONYLUREA



If on SU, stop or reduce dose by 50% when basal insulin initiated



Consider stopping SU if prandial insulin initiated or on a premix regimen

DPP-4i



Stop DPP-4i if GLP-1 RA initiated

1. Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Figure A7 – Considering oral therapy in combination with injectable therapies according to the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Source: <http://www.diabetesjournals.org/content/license>. [48])

FACULDADE DE MEDICINA

