UNIVERSIDADE DE LISBOA

FACULDADE DE FARMÁCIA

Patterns of polypharmacy and potential overtreatment in elderly people with type 2 diabetes mellitus using real-world data

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Orientadores: Professora Doutora Carla de Matos Torre
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Tese especialmente elaborada para obtenção do grau de Doutor em Farmácia, Especialidade em Farmacoepidemiologia

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Declaration

The research presented in this thesis was conducted under the umbrella of the Faculty of Pharmacy, University of Lisbon, Portugal, under the supervision of Professor Carla de Matos Torre, Invited Assistant Professor at the Faculty of Pharmacy, University of Lisbon, Professor Ana Paula Martins, Assistant Professor at the Faculty of Pharmacy, University of Lisbon, and Professor Helder Mota Filipe, Associate Professor at the Faculty of Pharmacy, University of Lisbon. Labib AL-Musawe participated in the conception and implementation of all studies as well as in the analysis, interpretation of data, and preparation of all the manuscripts forming the present dissertation. Full acknowledgements have been made where the work of others has been cited or used.

To

My Father & My Mother

Ana Paula Martins

“Never was anything great achieved without danger”

Niccolò Machiavelli

Acknowledgement

Firstly, I thank God for all of his blessings and virtues since the beginning of my life; without him, I would not have reached what I reached in this advanced stage of my scientific and practical life in good health and wellness. May praise and thanks always and forever throughout my life.

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Contents

Publications

- AL-Musawe L, Martins AP, Raposo JF, Torre C. The association between polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients; a systematic review and meta-analysis. *Diabetes Research and Clinical Practice*. 2019;155(107804):1-8. doi:10.1016/j.diabres.2019.107804
- AL-Musawe L, Torre C, Guerreiro JP, et al. Polypharmacy, potentially serious clinically relevant drug-drug interactions, and inappropriate medicines in elderly people with type 2 diabetes and their impact on quality of life. *Pharmacology Research & Perspectives*. 2020;8(4):1-9. doi:10.1002/prp2.621
- AL-Musawe L, Torre C, Guerreiro JP, Rodrigues AT, Raposo JP, Filipe H, Martins AP, Drug-Drug-Drug interactions and inappropriate medicines impact on glycemic control and kidney function in older adults with diabetes attending specialty care institution. (*accepted for publication in the European Journal of Clinical Pharmacology,* January 2021).
- AL-Musawe L, Torre C, Guerreiro JP, Rodrigues AT, Raposo JP, Filipe H, Martins AP, Overtreatment and undertreatment in a sample of elderly people with diabetes. (*submitted*).

RESUMO

O **Capítulo 1** apresenta os principais desafios clínicos em idosos com diabetes tipo 2 e enfatiza a lacuna de conhecimento a respeito de duas das síndromes geriátricas mais importantes, a polifarmácia e o tratamento excessivo em ensaios clínicos randomizados e diretrizes de prática clínica. Para preencher essa lacuna de conhecimento na prática clínica de rotina, uma revisão sistemática e metanálise de estudos observacionais, de coorte e de desenho transversal, seguido por três estudos de desenho observacional e transversal, com os critérios de inclusão de ser idosos com tipo 2 diabetes e com 65 anos ou mais foram todos conduzidos e implementados no **Capítulo 2.** Uma breve descrição dos métodos de pesquisa foi apresentada no **Capítulo 2.1.** Os resultados da revisão sistemática e da meta-análise (**Capítulo 2.2**) mostraram que a polifarmácia em idosos com diabetes tipo 2 foi associada de 62%, 96%, 33% e 72% de probabilidade de mortalidade, enfarte do miocárdio, acidente vascular cerebral e hospitalização, respectivamente. A análise de dados baseados em farmácia (Capítulo 2.3) revela que a polifarmácia, interações medicamentosas potencialmente graves e clinicamente relevantes e medicamentos potencialmente inadequados foram associados a 80%, 34% e 57% de chances de menor qualidade de vida relacionada à saúde em idosos adultos com diabetes tipo 2, respectivamente. A análise de uma base de dados administrativa (**Capítulo 2.4**) mostrou que a polifarmácia e medicamentos potencialmente inadequados foram associados a probabilidades 2 a 2.5 vezes maiores de alteração do controle glicêmico, e os medicamentos potencialmente inadequados também podem estar associados a 5.5 vezes maior probabilidade de alterações da função renal graves em adultos idosos com diabetes tipo 2. Além disso, a análise de dados administrativos de instituições especializadas em tratamento de diabetes (**Capítulo 2.5**) também conclui que mais de 60% dos adultos mais velhos com diabetes tipo 2 foram potencialmente supertratados e mais de 12% foram potencialmente subtratados. Os doentes com sobretratamento, mostraram ser mais homens, pré-obesos, têm maior compromisso macrovascular, neuropatia e pé diabético, e associados estão a uma maior prevalência de doença renal crônica grave. Os doentes, e potencialmente subtratados eram maioritariamente do sexo feminino, obesos, com uma maior prevalência de dislipidemia , doenças vasculares periféricas, infecções e pé diabético, e usavam mais insulina em comparação com aqueles que cumpriam os objectivos terapêuticos. No capítulo (**Capítulo 3**), apresenta-se uma discussão compreensiva dos resultados. Os estudos realizados mostraram que a polifarmácia e o sobretratamento em idosos com diabetes tipo 2 podem estar associados a vários resultados relacionados com a saúde na prática clínica do mundo real, onde estes conceitos são subestimados em ensaios clínicos randomizados e diretrizes de prática clínica, que podem induzir mais danos do que benefícios. A terapia individualizada dos doentes e a otimização da medicação podem ser a maneira de reduzir o risco dessas importantes síndromes geriátricas.

Palavras-chave: Polifarmácia, Sobretratamento e subtratamento, Mortalidade, Doenças cardiovasculares, Hospitalização, Qualidade de Vida, Controle Glicêmico de Idosos, Função Renal, Diabetes tipo 2

ABSTRACT

Chapter 1 introduces the major clinical challenges in older adults with type 2 diabetes and emphasizes the knowledge gap of the two important geriatric syndromes: the polypharmacy, and the overtreatment in randomized controlled trials and clinical practice guidelines. To bridge this knowledge gap in routine clinical practice, **Chapter 2** conducts a systematic review and meta-analysis of observational, cohort and cross-sectional design studies, and then followed by three observational, cross-sectional design studies. The latter implements data which include the criteria of being older adults (aged 65 years old or more) with type 2 diabetes. A brief description of research methods is presented in **Chapter 2.1**. The results of the systematic review and meta-analysis (**Chapter 2.2**) show that polypharmacy in older adults with type 2 diabetes has been associated with 62%, 96%, 33%, and 72% of having odds of mortality, myocardial infarction, stroke, and hospitalization, respectively. The analysis of pharmacy-based data (**Chapter 2.3**) reveals that polypharmacy, potentially serious clinically relevant drug-drug interactions and potentially inappropriate medicines were associated with 80%, 34% and 57% of odds of lower health-related quality of life in older adults with type 2 diabetes, respectively. The analysis of administrative-based data of specialized diabetes care institution (**Chapter 2.4**) concludes that polypharmacy and potentially inappropriate medicines were associated with 2 to 2.5 greater odds of alteration of glycemic control, and that potentially inappropriate medicines can be also associated with 5.5 greater odds of severe kidney function in older adults with type 2 diabetes. Further, the analysis of specialized diabetes care institution administrative-based data (**Chapter 2.5**) also concludes that more than 60% of older adults with type 2 diabetes have found to be potentially overtreated, and more than 12% were found potentially undertreated. The former tends to be composed mostly of males, pre-obese, who have higher macrovascular, neuropathy, and diabetic foot, as well as being associated with a higher prevalence of severe chronic kidney disease; whereas the latter tend to be females, obese, with a higher prevalence of dyslipidemia, peripheral vascular disease, infections, and diabetic foot, along with using more insulin compared to those appropriately on target. **Chapter 3** then discusses these results. Overall, the conducted research shows that polypharmacy and overtreatment in older adults with type 2 diabetes can be associated with several health-related outcomes in real-world clinical practice. These two concepts are underestimated in randomized controlled trials and clinical practice guidelines, possibly inducing more harm than benefits. The individualized therapy of patients and the optimization of medication could be the way to reduce the risk of these important geriatric syndromes.

Keywords: Polypharmacy, Overtreatment, Undertreatment, Mortality, Cardiovascular diseases, Hospitalization, Quality of Life, Glycemic Control Elderly, Kidney Function, Type 2 diabetes.

List of abbreviations

ACC/AHA: American College of Cardiology/American Heart Association

ACCORD: Action to Control Cardiovascular Risk in Diabetes

ADA: American Diabetes Association

ADVANCE: The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

ADE: Adverse drug event

ADR: Adverse drug reaction

AF: Arial Fibriliation

APDP: Associação Protectora dos Diabéticos de Portugal (*Portuguese Diabetes Association*)

BMI: Body mass index

CBV: Cerebrovascular disease

CDA: Canadian Diabetes Association

CHD: Coronary heart disease

CI: Confidence interval

CKD: Chronic kidney disease

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

DDIs: Drug-drug interactions

DPP-4: Dipeptidyl peptidase 4 inhibitors

EASD: European Association for the Study of Diabetes

EDWPOP: The European Diabetes Working Party for Older People

eGFR: Estimated glomerular filtration rate

EMA: European Medicines Agency

EQ-5D: Euroqol 5-D-3L

ESRD: End-stage renal disease

FBG: Fasting blood glucose

FDA: U.S. Food and Drug Administration

HbA1c: Glycated hemoglobin

HDL: High-density lipoprotein

HR: Hazard ratio

GLDs: glucose lowering drugs

GLP-1: Glucagon-like peptide-1 receptor agonist

IDF: International Diabetes Federation

LDL: Low-density lipoprotein

MI: Myocardial infarction

MOMI: Modelo Observacional de Monitorização Intensiva (*Intensive Monitoring Observational Model)*

NICE: The National Institute for Health and Care Excellence

OR: Odds ratio

PAD: Peripheral arterial disease

RCT: Randomized controlled trial

RR: Relative risk

RWD: Real-world data

RWE: Real-world evidence

SBP: Systolic blood pressure

SGLT-2: Sodium-glucose transport protein 2 inhibitors

STOPP: Screening tool of older people's prescriptions

TC: Total cholesterol

T1D: Type 1 diabetes

T2D: Type 2 diabetes

TG: Triglycerides

VADT: Veterans Affairs Diabetes Trial

WHO: World Health Organization

CHAPTER ONE

GENERAL INTRODUCTION

CHAPTER 1.1

MAJOR CLINICAL CHALLENGES IN OLDER PEOPLE WITH TYPE 2 DIABETES

In the recent decades, the worldwide prevalence of diabetes has especially risen among the older population aging 65 years or more. The aging of the population is thought to be one of the most important contributors to the prevalence of diabetes, since the increase in age is itself a substantial risk factor for the development of type 2 diabetes (T2D) (1)(2), along with obesity and physical inactivity (3). T2D is a major and costly health concern worldwide, often resulting in high morbidity, disability, mortality, and impaired quality of life (4).

1.1.1 Pathophysiology of T2D in elderly people

T2D is a progressive disease, and glucose levels are known to increase with age. However, there is evidence for differences in the pathophysiology of T2D in the elderly when compared with younger adults. It is unclear whether the degree of T2D in older adults primarily results from an age-related deterioration in β-cell function (5). Since it was suggested that impaired insulin secretion, rather than insulin resistance, commonly led to T2D in elderly adults compared with young adults (5,6). The divergence in body composition related to aging includes the reduction of the fat-free mass (muscle, bone, water) and the relative increase of fat mass, with visceral obesity leading to alterations in insulin sensitivity (8,9).

Other studies found that most cases regarding older adults with T2D are due to a combination of increased insulin resistance and impaired insulin secretion. Insulin resistance which is associated with advanced age is believed to be due to a combination of adiposity, sarcopenia, and physical inactivity. Impaired pancreatic β-cell adaptation to insulin resistance appears to be an important contributing factor to age-related glucose intolerance and risk of T2D (10,11).

1.1.2 Prevalence of T2D in elderly people

Around 20-25% of the elderly population is diagnosed with diabetes and the vast majority of those elderly (more than 90%) have T2D (7,12,13). Predictably, the incidence of diabetes could reach two-fold in the next decades; accordingly, the prevalence of diabetes is to be more than two times higher among the elderly compared to middle age or young adults (14,15). A major shift in the epidemiology of diabetes has been to those aged 60–79 years old (16). Those who are more likely to remain undiagnosed, that is, 45.6% of the total elderly population with diabetes, tend to be men with a more stable rate of health status (15,17). In Europe, the prevalence data shown an average of 20% (18). Nevertheless, there are some differences across the European countries, where it ranges 14%–16% in Denmark, 15%–18% in the UK, 19%–31% in Greece, 15%–26% in Italy, and 25.5%-27.1% in Portugal (19–23).

A very high prevalence of T2D in older adults is not only seen in the western globe, where the economic standards are high, but also in developing countries, such as Brazil and China. In Brazil, almost 3 million of the 12 million people with T2D are aged over 65 years old, whereas in China, 35 million of the 92 million adults with diabetes are aged over 60 years old, and 20 million are aged over 70 years old (24,25). It was estimated that the incidence of diabetes mellitus increases with age nearly until the age of 65, which means that elderly adults with diabetes may either be diagnosed at or after the age of 65, or the onset of the disease happened in their middle or earlier age (26).

1.1.3 Diabetes complications

The elderly people with T2D represent a diverse population with varied cultural, health, and social care needs. Although many elderly people with T2D will continue to live well and independently, with a good quality of life and high life expectancy, self-managing their diabetes without undue difficulty; others may suffer progressive physical or mental health, frailty, cognitive decline or disability, which increases dependency and vulnerability, and poses ground for added social isolation and loneliness (27). In general, the objective of T2D treatment in older adults is to maintain functional abilities and quality of life, as well as to prevent diabetic complications. However, older adults must endure not only problems related to the treatment of T2D, but also the additional burden related to aging and associated co-morbidities (28).

One of the biggest clinical challenges of managing elderly people with T2D is that the disease rarely occurs in isolation. Many chronic conditions can be associated with it, such as hypertension, dyslipidemia, arthritis, and kidney disease. Chronic conditions are very common among the elderly with diabetes for nearly 60% of older adults with T2D have at least one coexisting chronic illness, and almost 40% of them have four or more (29–31). Compared to young adults, elderly people with T2D are at a higher risk of having a wide range of severe long-standing T2D complications, which are usually divided into macrovascular and microvascular ones (32). With a greater proportion of diabetes cases present in the older population, who are mostly vulnerable, it is not judicious to consider how this population compares to younger patients regarding the development of diabetes complications due to the potentially longer duration of the disease (33).

1.1.3.1 Macrovascular complications

Cardiovascular diseases (CVDs) are a common complication in people with T2D and its prevalence has been growing overtime (34). CVDs represent the principal cause of death and morbidity among older people with diabetes, especially in those with T2D. It can be associated with a 75% increase in mortality rate in older adults and accounts for a large part of the excess mortality (35). It was estimated that 77% of hospitalizations for chronic complications of diabetes were attributable to CVDs (36), with substantial global impact on direct medical costs of T2D, both at patient and population levels (37).

Between 2007 and 2017, a global systematic literature review estimated the prevalence of CVDs among elderly people with T2D found that out of 4,549,481 individuals with T2D, 52% were male, 47% were obese, aged 63.6 ± 6.9 years old, with T2D duration of 10.4 ± 3.7 years. CVDs affected 32.2% of the population overall; 29.1% had atherosclerosis, 21.2% had coronary heart disease (CHD), 14.9% heart failure, 14.6% angina, 10% myocardial infarction (MI) and 7.6% stroke. CVDs were the cause of death in 9.9% of T2D individuals (representing 50.3% of all deaths) (38).

Elderly people with T2D and CVDs have a 4-fold higher incidence rate of cardiovascular events (CVEs) and an 8-fold higher incidence rate of vascular interventions compared to high-risk elderly people without T2D and CVDs (39). However, most elderly patients with T2D are unaware they have CVDs. In a population-based autopsy study including 293 elderly patients with diabetes without clinically known coronary heart problems, nearly 75% had high-grade coronary disease and more than half had the multivessel disease (40). Silent myocardial ischemia (SMI) is another serious problem among elderly patients with T2D. A French study found that SMI with significant lesions occurs in 20.9% of T2D elderly male adults who are asymptomatic for coronary artery disease (41).

Elderly people with T2D are also at higher risk of morbidity and mortality from cerebrovascular diseases (CBVs). Nearly 20% to 40% of patients with T2D suffer from cerebral blood vessel diseases, which can be induced by T2D with sugar, fat and a series of nutrient substance metabolic disorders, resulting in intracranial large and small vessel diseases (42). Another Italian study found the prevalence of CBVs in elderly patients with a history of T2D was 10.6% (43). However, the pathophysiological reasons for this association between CBVs and T2D are not fully elucidated, particularly in elderly people (44). In CBVs, the presence of T2D increases the risk of ischemic cerebral infarction, which accounts for more than three-quarters

of all strokes, but is not the risk of cerebral haemorrhage (45). A prospective cohort study of 375 elderly people with T2D with a mean age of 75 demonstrated that lower scores on the Geriatric Morale scale and Elderly Diabetes Burden scale were predictors for CBVs (HR 2.6 95%CI 1.1–6.5). This suggests psychosocial factors may be associated with stroke events among elderly patients with diabetes (46).

Comparisons of epidemiological data on diabetic and nondiabetic subjects in the general population have clearly demonstrated that T2D is an independent risk factor for ischemic stroke (47), as seen in a prospective cohort study of 14,432 individuals with T2D, for which the average age was ≥ 65 years old, with and without a history of cardiovascular disease, and during a 4-year follow-up, 296 incident stroke events were recorded. In persons with no history of cardiovascular disease, the age-standardized incidence of stroke (per 1000 person-years) was 5.5 (95%CI 4.2 to 6.8) in men, and 6.3 (95%CI 4.5 to 8.2) in women. In people with a history of cardiovascular disease, it was 13.7 (95%CI 7.5 to 19.8) in men and 10.8 (95%CI 7.3 to 14.4) in women (48).

The peripheral arterial disease (PAD) is another of the most common macrovascular complications in elderly patients with T2D. It presents broad clinical characteristics and various consequences and is known as one of the major macrovascular complications of T2D. Although the global prevalence of the latter is knowingly rising (49). the prevalence of PAD in the T2D elderly population is still unclear. However, in the Framingham heart study, 20% of symptomatic PAD patients were associated with diabetes disease (50). Moreover, a German study including people with T2D aged ≥ 65, found that the prevalence of PAD by low ankle-brachial index in those elderly adults with diabetes was 15.3% (51).

Among U.S. elderly people aged 60 years and more the prevalence of PAD for people with diabetes was almost twice as high compared to those without diabetes (52). A multicenter study estimated the prevalence of PAD to be 60.6% among a cohort of 1,430 diabetes people aged 70 years and older (53). Another Indonesian study has shown that elderly adults with T2D aged between 70 and 80 years old were 7.4 times more likely to develop PAD compared to adults with T2D aged between 60 and 69 years old (54). The elevation of PAD prevalence is related to several risk factors such as diabetes, hypertension, dyslipidemia, age, and smoking (55,56).

1.1.3.2 Microvascular complications

Retinopathy is considered the most common microvascular complication and the leading cause of blindness in elderly people with T2D (57). According to the World Health Organization (WHO), diabetic retinopathy is responsible for 4.8% of the number of cases of blindness (37 million) worldwide (58). The overall prevalence of retinopathy in T2D is estimated to be 25.2% (59). The prevalence of retinopathy is considered slightly higher in elderly adults with T2D compared to those younger than 65 years old (29.5% *vs*. 28%) in the U.S. (33). In Japan, the prevalence of retinopathy reached 43% in elderly people with T2D aged 65 or more (60). A Swedish study has shown that the prevalence reached 34.6% in the T2D population with a mean age of 70.3 years, compared with those without diabetes (8.8%) with a mean age of 75 years (61).

Nephropathy is another critical microvascular complication with elderly people with T2D and is considered the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (62). Nearly 25% to 30% of T2D patients exhibit a renal disease, usually expressing as typical diabetic glomerulosclerosis, but sometimes as prominent vascular nephropathy. These two forms of renal lesions are usually intricate. Chronic pyelonephritis, which is particularly frequent in elderly people with T2D with recurrent urinary tract infections, can also contribute to decreased renal function (63).

An Italian study investigating the association of clinical variables and quality of care measures in 157,595 T2D individuals (more than 63% of them aged ≥ 65 years old) found that the prevalence of both estimated glomerular filtration rate (eGFR) and Albuminuria increase with age. Diabetic kidney disease is associated with the poor cardiovascular risk profile and a lower quality of care, although these associations are influenced by the type of renal abnormality and by aging (64). The impact of T2D on renal impairment changes with increasing age. Serum markers of glomerular filtration rate and microalbuminuria identify a renal decline in different segments of the diabetic population (65).

The prevalence of nephropathy in elderly people with T2D is higher than in those with type 1 diabetes (T1D) (63). In the U.S., comparing the elderly people with diabetes with those without diabetes, the prevalence of CKD was higher in individuals older than 65 diagnosed with diabetes. The analysis was conducted through three data sources: the Kidney Early Evaluation Program (KEEP), the National Health and Nutrition Examination Survey (NHANES), and the

billing codes in the Medicare (KEEP 48.2% *vs*. 40.4%, NHANES 58.3% *vs*. 41.4%, Medicare 14.2% *vs*. 4.4%) (66).

The increase in diabetes-related to end-stage kidney disease correlates with the increased burden of diabetes. The elderly population with diabetes remains a large group of those receiving dialysis for diabetic nephropathy (67). The European Renal Association—European Dialysis and Transplant Association Registry Annual Report (2014) showed that 70,953 individuals commenced kidney Replacement Therapy (KRT) in 2014, equating to an overall unadjusted incidence rate of 133 per million population. Of the patients commencing KRT, almost two-thirds were men, more than half aged ≥ 65, and a quarter had diabetes as their primary kidney diagnosis (68). The proportion of ESRD in people with T2D who are considered elderly is currently the fastest-growing segment of incident ESRD population. Despite the fast growth of this group, it is poorly characterized in current literature (69). ESRD with diabetes can be associated with an increased risk of dementia (70).

Moreover, this older population may be more likely to have arteriovenous fistula complications. Among a cohort of elderly adults with T2D aged 65 years and older, 28.6% of patients with diabetes had fistula failure compared to only 10.3% of patients without diabetes (71). Diabetic neuropathy affects both peripheral and autonomic nervous systems and causes considerable morbidity and mortality in T2D patients. Diabetic neuropathy is the most common form of neuropathy, accounting for more hospitalizations and resulting in 50% to 75% of non-traumatic amputations (72,73).

In elderly people with T2D, peripheral neuropathies are especially troublesome due to their detrimental effects on stability, sensorimotor function, gait, and activities of daily living. As the severity of neuropathy increases, the functional impairment worsens and the quality of life of elderly adults with T2D can be affected (74–76). The clinical diagnosis of diabetic neuropathy is often difficult in elderly adults with T2D. The relationship between symptoms and neuropathy and that between neuropathy and diabetes are more difficult to ascertain in elderly patients, due to age changes in the peripheral and autonomic nervous system and associated diseases frequently encountered in this population (77).

Identification of diabetic neuropathy signals a high risk of foot complications, such as ulcers and gangrene, often resulting in amputation, whereas cardiovascular autonomic neuropathy is associated with an increased risk of postural hypotension and coronary events. All these risks increase markedly with elderly people with T2D (78–80). Therapeutic clinical trials in elderly people with T2D with diabetic neuropathy are insufficient, and clinical complications of diabetic neuropathy in the elderly population are frequently severe. Moreover, there is a lack of treatment options targeting the neuropathic disease state (81,82). The causal pathways leading to diabetic foot ulceration include several components causes, the most important of which is peripheral neuropathy. Foot ulcers have been estimated to affect 1–4% and may be as high as 6%, affecting as many as 25% of the individuals with diabetes over their lifetimes (83,84), This is present to some degree in more than 50% of diabetic persons older than 60 years (85). Once a foot ulcer has developed, there is an increased risk of wound progression that may ultimately lead to amputation; for diabetic ulceration has been shown to precede amputation in up to 85% of cases (86).

1.1.4 Co-morbidities and geriatric syndromes

In addition to the macrovascular and microvascular complications associated with T2D, there is also an increased risk of multiple coexisting medical conditions in older adults, as well as other critical problems which can develop, usually referred to as the geriatric syndromes. This emphasizes that 'one size fits all' treatment strategies are not convenient for this population (87) and can impact the ability of patients to self-manage as well as affect their health-related quality of life, in addition to other health outcomes (88).

The geriatric syndrome can be defined as "clinical condition taken in a very broad sense (personal history and complaints of the patient, clinical examination, and results of complementary examinations) that does not fit into a discrete disease category"(89). Notwithstanding, the concept of geriatric syndrome remains poorly defined. Despite the heterogeneity of elderly T2D population, geriatric syndromes share many common features. They are highly prevalent in older adults with T2D, especially those with a frailer health. Their impact on the quality of life and disability is fundamental (90,91). Some researchers suggest that geriatric syndromes can be considered "medical errors" for reasons which can be associated with an increased risk of mortality. The literature also has declared that geriatric syndromes can be preventable through a systematic approach of care (92,93).

1.1.4.1 Cognitive dysfunction

Cognitive dysfunction is a common and often underdiagnosed syndrome in older people with T2D (94). Alzheimer's disease and vascular dementia are proportionally twice as likely to occur in elderly people with T2D compared with the non-diabetic elderly. The cognitive impairment can vary from one patient to another, from subtle executive dysfunction to clear dementia and memory loss (95), as the prevalence of cognitive impairment and dementia increases with age. The presence of comorbidities in diabetes can contribute to this association. Dementia affects up to 16% of the elderly with diabetes aged >65 and 24% of those aged >75 (96). Additionally, it was found that insulin resistance is a critical risk factor for cognitive impairment in older people with T2D (97).

Mild to moderate cognitive impairment and dementia can be observed more often in elderly people with diabetes (98,99), and it was estimated that at least half of older people with T2D will become cognitively impaired and functionally disabled (100). Furthermore, several studies have shown an association between hyperglycemia and cognitive dysfunction. Hypoglycemia is highly connected to cognitive dysfunction in a way that cognitive impairment may increase the additional risk of hypoglycemia, and the presence of a history of severe hypoglycemia is also linked to the incidence of dementia (101–103).

Since cognitive dysfunction affects treatment adherence and diabetes self-management, the resulting poor glycaemic control and an increased rate of severe hypoglycemia contribute to a vicious cycle. Overall, individuals with cognitive dysfunction have difficulty performing self-care (such as patients not being able to recognize or treat hypoglycemia, or to remember and administer their insulin regime correctly), leading to a significantly reduced quality of life (104). Furthermore, a study of 1,617 elderly people with T2D in the U.S. evaluated the association of diabetes with the incidence of dementia and cognitive impairment without dementia, while accounting for competing risk from death. The study found that in models adjusted for competing risk of death, those with treated and untreated T2D had an increased risk of dementia/cognitive impairment without dementia (HR 2.05 95%CI 1.41-2.97) and (HR 1.55 95%CI 0.93-2.58) compared with those without diabetes (105). Additionally, the presence of retinopathy (a microvascular complication) and stroke (a macrovascular complication) in older adults with T2D were also associated with worsening memory and even memory loss in this population (106,107).

1.1.4.2 Functional impairment

A functional situation involves the ability to undergo simple daily tasks required for routine living. Advanced age and diabetes itself can be recognized as risk factors for functional impairment (108). Functional decline and physical disabilities are an important clinical and public health problem in older adults because they are associated with the loss of independence (109). Generally, diabetes patients have two-to-three times greater difficulty in performing tasks of daily living when compared to patients without diabetes (52). A study in Hong-Kong including elderly people with T2D examined the relationship between diabetes and impairments in functional and cognitive status, as well as depression, and found that the elderly with T2D may be less capable of managing the disease than younger patients as a result of increased risk of both physical (odds ratio (OR) 1.65 95%CI 1.51-1.80) and cognitive impairment (OR 1.28 95%CI 1.11-1.48) (110).

The causes of functional impairment in elderly people with T2D can include the interaction between coexisting comorbid conditions namely, peripheral neuropathy, vision, and hearing difficulties, as well as gait and balance problems. The presence of peripheral neuropathy in almost (50-70%) of elderly people with T2D can lead to postural instability, balance problems, and muscle atrophy (111–113). A long duration of diabetes increases the loss of muscle function in elderly people with T2D and this may contribute to the underlying pathophysiological changes in frailty, disability, and sarcopenia. There is also a gradient effect of functional decline on mortality in the elderly with diabetes, and among those with other chronic conditions, as functional decline was associated with a greater burden of mortality (114–116).

1.1.4.3 Fall and fall risk

Fall is also a common geriatric syndrome in elderly people with T2D and contributes to morbidity, mortality, and the loss of independence. Elderly people with T2D are at higher risk of falling than those without diabetes (117). Falls are a critical concern for elderly adults with T2D (118,119). The annual incidence of falls in the elderly with T2D reached up to 39% (120). A longitudinal study found that this demographic has an increased risk of recurrent falls (30.6%) compared to those without diabetes (19.4%) (121). Elderly people with diabetic peripheral neuropathy are at a high-risk of falling and of declines in sensory function, which is not only caused by neuropathy but also *in* presence of retinopathy, possibly leading to increased risk of falls in the elderly with T2D (74,122). In addition, intensive glycemic control associated with hypoglycemia may be associated with risk falls (123,124).

A systematic review and meta-analysis evaluated the impact of diabetes mellitus on the risk of falls in older adults found that in subgroup analysis, the risk of falls seemed more pronounced among both gender groups (relative risk (RR) 1.81 95%CI 1.19–2.76) than among women (RR 1.52 95%CI 1.04–2.21). Risk of fall increased 94% (RR 1.94 95%CI 1.42–2.63) in insulin-treated patients and 27% (RR 1.27 95%CI 1.06–1.52) in non-insulin treated patients (125). Another longitudinal study found that, in elderly people with T2D, reducing diabetes-related complications may help prevent falls. Achieving lower HbA1C levels with oral hypoglycemic agents was not associated with more frequent falls, but among those using insulin, HbA1C ≤ 6% increased the risk of falls (126). Other potential factors which could be related to the increased frequency of falls in the elderly with T2D include polypharmacy, pain, lower physical activity, functional limitations, and cognitive impairments (127).

1.1.4.4 Vision and hearing impairment

The decline of vision and hearing may be associated with an increase of the risk of fall in elderly people with T2D, leading to functional disabilities and potentially resulting in older patients feeling isolated and more vulnerable to depression (128). Elderly people with T2D have a higher prevalence of vision impairment than those without diabetes. Among patients aged 60 years and older, the prevalence of self-reported vision impairment was 34.2% for those diagnosed with diabetes compared to 21.4% for those without diabetes (128). The epidemiology of Hearing Loss Study found that T2D was associated with a 41% increased prevalence of age-related hearing loss after controlling for potential confounders (129). Other studies also reported that there is a small but statistically significant association of cardiovascular disease and hearing status in the elderly with T2D that is greater for women than men (130), and those who are not on insulin (131).

1.1.4.5 Depression

Diabetes is associated with a high prevalence of depression. Undiagnosed depression can lead to limitations in self-care activities and implementing a healthy lifestyle, and is associated with a higher risk of mortality and dementia in elderly patients with T2D (132–134). Among elderly people with T2D, up to 30% have a significant number of depressive symptoms and 12% to 18% meet diagnostic criteria for major depression. A meta-analysis has shown that the odds ratio for depression in elderly people with T2D compared with those without was higher in males (OR 1.9 95%CI 1.7-2.1) than in females (OR 1.3 95%CI 1.2-1.4) (135,136). Elderly people with T2D experience a higher risk of comorbid depression compared to those who do not have diabetes.

Having T2D can be associated with increases in the risk of subsequent development or recurrence of depression (137).

Comorbid depression in elderly people with T2D is strongly associated with increased burdens of disease symptoms, the decline in self-management and treatment adherence, as well as an increase in health care services utilization, medical expenditures, and risk of more complications (138–140). The impact of depression was examined by several studies focusing on whether it can be associated with increased risk of mortality in elderly people with T2D. It was found that depression is associated with a 1.5 to 2.6-fold increase in the risk of mortality among this population (141,142). In addition, the total annual health care costs were found to be 4.5 times greater for older adults with both diabetes and depression compared to patients with diabetes only (143).

1.1.4.6 Frailty

Frailty can be defined depending on the presence of three or more of the following factors: weight loss, weakness, decreased physical activity, exhaustion, and slow gait speed. People with diabetes aged ≥ 65 years old are more likely to be frail than older adults without diabetes, where an estimated prevalence of approximately 11% of those elderly people with T2D are considered frail (144,145). Several studies have suggested that insulin resistance, adipose tissue inflammation, and skeletal muscle inflammation and dysfunction are related to the likelihood of accelerated aging process and in the increase of frailty in elderly people with T2D (146,147).

Frailty is a state of increased vulnerability to minor stressors, leading to difficulties in the maintenance of homeostasis, which increases the risk of adverse outcomes, such as disability, falls, sarcopenia, and mortality in elderly people with T2D (148). It was estimated that the median life expectancy for elderly frail T2D people was only 1 year and 11 months (149). Sarcopenia (muscle loss due to aging) is one of the major contributors to frailty syndrome, which can be accelerated with diabetes. In a community study of 3,153 elderly T2D people aged ≥ 65 years or more, appendicular lean mass loss in men with diabetes was twice that of men without diabetes (3% *vs* 1.5%), and in women with diabetes it was 1.8 times that of those without diabetes (3.4% *vs* 1.9%), over four years of follow up (150). In addition, the occurrence of frailty depends on declining cardiopulmonary reserve and loss of executive function, as well as on low HbA1c. This was detected as a factor increasing the risk of frailty (151). Diabetes and frailty are interrelated, with sarcopenia and both hyperglycemia and hypoglycemia implicated

(152–154). Frailty is also strongly associated with the presence of CKD in elderly people with T2D, occurring in 21% of those with an eGFR < 45 ml/min/1.73m² (155).

1.1.4.7 Polypharmacy

With the current change in socio-demographic characteristics in recent decades, and the increase of diabetes in elderly populations, multi-morbid conditions have become a critical, pressing public health issue across the world (156). Further, the foresight of medicines' benefits and harms is asymmetric. Approval of medicines depends mostly on efficacy, while the evaluation of medicines' full safety profile is left to post-marketing studies and spontaneous reporting. The medicines' efficacy is mostly overvalued by the physicians, and sometimes their safety is underestimated as a result of the paucity of safety information, along with the scant understanding of the effectiveness of medicines in real-life (157).

The rising prevalence of multimorbidity leads to several treatment strategies frequently resulting in an increased risk of treatment complexity and uncertain treatment pathways. This consequently leads to high treatment burden and multiple medication usage, or as it is often called, polypharmacy, which can sometimes reduce the benefits and increase the risk or potential harms of the treatment (158). Elderly people with T2D are at high risk of polypharmacy as a result of multiple comorbid conditions associated with diabetes, which also poses ground for the consequence of long-term disease complications when compared with young adults with T2D (159,160). Polypharmacy can increase the risk of clinical complexity, treatment burden, drug-disease or drug-drug interactions, contributing to poor health outcomes, including frailty, falls or increasing the fall risks in the elderly, hospitalization or emergency room visits, functional disability, and/or cognitive decline as a result of treatment in adverse events (161–163).

1.1.4.8 Overtreatment

In addition to polypharmacy, for elderly people with T2D with multiple serious comorbidities and functional decline, treatment intensification to reach optimal glycaemic can result in few or no benefits or even be harmful towards the same end. The glucose-lowering medicines with more risk of causing hypoglycaemia (such as insulin and sulfonylureas) were considered as the second most common medications associated with emergency department visits or hospitalizations reported to the U.S. Food and Drug Administration (FDA) (163). The problem of overtreatment received more attention regarding elderly people with T2D who were diagnosed with dementia, being at a much higher risk of hypoglycemia compared to those without

dementia, as well as the increased risk of detrimental drug interactions due to the presence of polypharmacy (164).

In patients with greater clinical complexity, intensive diabetes treatment could result in a significant increased risk-adjusted probability of severe hypoglycemia from 1.7% with standard treatment to 3% with intensive treatment (165). Given the heterogeneity of elderly people with T2D, an individualized approach is warranted to avoid overtreatment of frail older individuals. Diabetes healthcare management in elderly people with T2D therefore presents a difficult challenge. Clinical and functional complexity and diversity, along with multiple coexisting comorbid conditions in this population are factors demanding special attention. Treatment goals should be formulated with an awareness of the medical, functional, social, and financial environment of the elderly patients. Aspects of the geriatric syndromes that can adversely affect the successful management of diabetes include cognitive dysfunction, depression, physical disabilities, polypharmacy, and overtreatment.

1.1.5 Addressing the current knowledge gap of polypharmacy and overtreatment

Older adults with T2D are heterogeneous in their health status. The scarcity of evidence regarding polypharmacy and overtreatment, as well as their impacts on health outcomes from randomized controlled trials (RCTs) and clinical practice guidelines represent crucial challenges to determining standard intervention strategies suitable to older adults (166).

1.1.5.1 Data from randomized clinical trials

Regarding polypharmacy, only three RCTs (Table 1) were found. Two trials defined polypharmacy as the use of five or more medicines (167)(169). The RCT by Strain *et al* did not consider polypharmacy as part of the study outcomes that need to be measured (168). Whereas a trial by Vanassche *et al* (169), found that polypharmacy was associated with recurrent venous thromboembolism in patients using warfarin, as well as associated with increased risk of bleeding regardless of the treatment used. The analysis risk of bias revealed that the three trials were categorized with good quality. The analysis of the risk of bias can be found in (Supplementary Table 1).

Table 1 Randomized controlled trials that assessed polypharmacy in older people with T2D

Study Reference	Study design	Participants number / mean age ± standard deviation	Objectives of the RCT	Definition and number of participants on polypharmacy	Impact of polypharmacy measured	Quality assessment
Barnett et al. 2013 (167)	Randomized, double-blind, parallel-group, multinational phase 3	Total sample (241) Mean age (74.9±4.3)	Effectiveness of linagliptin in elderly adults with T2D	Using of five or more medicines Number of participants on polypharmacy (171)	The impact of polypharmacy was not examined	Good quality
Strain et al. 2017 (168)	Double blind, placebo control RCT	Total sample (278) Mean age (75.1±4.3; 74.4±4)	Assessment of feasibility of setting individualized glycemic goals and factors influencing targets set in a clinical trial in elderly patients with T2D	Not available Number of participants on polypharmacy (139)	Polypharmacy was not considered by physicians when setting targets	Good quality
Vanassche et al. 2018 (169)	Double blind RCT	Total sample (8240) Mean age <65 years (47.1±11.9) 65-<75 years (69.3±2.9) ≥75 years (79.9±4.2) >80 years (83.5±3.3)	Determination of the effects of advanced age, comorbidities, and polypharmacy on the efficacy and safety of edoxaban and warfarin in patients with VTE	Using of five or more medicines Number of participants on polypharmacy (1805)	Recurrent VTE increased with polypharmacy in warfarin treated patients but not with edoxaban Bleeding increased with polypharmacy regardless of treatment	Good quality

RCT: randomized controlled trial, T2D: type 2 diabetes, VTE: venous thromboembolism

Regarding the RCTs which addressed overtreatment in elderly people with T2D, the mean age was between 60 and 71.7 years old. The definition of overtreatment or treatment intensification based on HbA1c value was between < 6% to < 7%, except for one RCT which used the fasting blood glucose value of <121 mg/dL as a definition of glycemic intensification (175). The prevalence of participants receiving intensification was between 44.4% to 50%. Only the intensive blood glucose control and vascular outcomes in patients with T2D (ADVANCE) achieved a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily because of a 21% relative reduction in nephropathy (173). The

Veterans Affairs Diabetes (VADT) trial shows that a slow progression of albuminuria had little benefit from overtreatment (174).

The other RCTs failed to find any significant benefit either in a reduction of a major cardiovascular event (172)(173)(174)(175), restenosis (176), or risk of death from cardiovascular events (171) (173)(174) (177), death from hypoglycemia/hyperglycemia or from microvascular events (177), or reduction in microvascular complications (170). Furthermore, The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that the use of intensive therapy increased mortality (172) (Table 2). The analysis risk of bias revealed that the three trials were categorized with good quality, two with fair quality, and two with poor quality. The analysis of the risk of bias can be found in (Supplementary Table 2).

Table 2 Randomized controlled trials that assessed overtreatment in older people with T2D

Study Reference	Study design	Participants number / mean age ± standard deviation	Trial end points	Definition of overtreatment or glycemic intensification	Implications	Quality assessment
VA CSDM trial 1999 (170)	Prospective, RCT	Total sample (153) Mean age (60±6)	Effects of intensive glycemic control on peripheral and autonomic neuropathy	HbA1c < 7% Number of participants received intensification (75)	No reduction in overall prevalence of peripheral or autonomic neuropathy.	Poor quality
PROactive trial 2005 (171)	Prospective, RCT	Total sample (5238) Mean age (61·9±7·6; 61·6±7·8)	Composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle	HbA1c < 6.5% Number of participants received intensification (2605)	No significant difference in reduction of the risk of death from any cause, non-fatal MI, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg.	Good quality
ACCORD trial 2008 (172)	Randomized, multicenter, double 2 x 2 factorial design	Total sample (10,251) Mean age (62.2±6.8)	Reduction of nonfatal MI, nonfatal stroke, or death from cardiovascular causes.	HbA1c < 6% Number of participants received intensification (5128)	the use of intensive therapy increased mortality and did not significantly reduce major cardiovascular events	Good quality
ADVANCE trial 2008 (173)	Randomized, multicenter, double 2 x 2	Total sample (11,140) Mean age	Reduction of microvascular events (nephropathy and	HbA1c ≤ 6.5% Number of participants	a 10% relative reduction in the combined outcome of major macrovascular and	Good quality

	factorial design	(66 ± 6)	retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death).	received intensification (5571)	microvascular events, primarily because of a 21% relative reduction in nephropathy	
VADT trial 2009 (174)	Open-label RCT	Total sample (1791) Mean age (60.5 ± 9)	Time from to first occurrence of a major cardiovascular event, a composite of MI, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene	HbA1c < 6% Number of participants received intensification (892)	No significant effect on the rates of major cardiovascular events, death, or microvascular complications, except for progression of albuminuria	Fair quality
HEART2D trial 2009 (175)	Prospective, open-label, randomized, two-arm parallel design	Total sample (1115) Mean age (61.1 ± 9.7; 60.9 ± 9.8)	If diabetes treatment that targets abnormalities of the post-meal period reduces excess CV mortality and morbidity in patients with T2D and recent MI	FBG < 121 mg/dL Number of participants received intensification (557)	Similar levels of HbA1c achieved, and no difference in risk for future cardiovascular event rates	Fair quality
IDA trial 2009 (176)	RCT	Total sample (99) Mean age (66;62)	improved glucose control, achieved by adding or optimizing insulin treatment, will reduce the rate of restenosis after PCI in patients with T2D.	HbA1c < 6.5% Number of participants received intensification (44)	Intensified treatment did not influence the rate of restenosis	Poor quality
JEDI trial 2012 (177)	Randomized, controlled, multicenter, prospective intervention	Total sample (1173) Mean age (71.7 ± 4.7)	To evaluate long-term, multiple risk factor intervention on physical, psychological, and mental prognosis, and development of complications and cardiovascular disease in elderly people with T2D	HbA1c < 6.9% Number of participants received intensification (585)	No significant differences in fatal events (MI, sudden death, stroke, death due to renal failure, death due to hyper/hypoglycemia, malignancy and pneumonia) or non-fatal events (MI, angina pectoris, coronary revascularization, hospitalization due to heart failure, stroke, diabetic ulcer or gangrene	Poor quality

VA CSDM: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes, PROactive: Prospective Pioglitazone Clinical Trial In Macrovascular Events, ACCORD: The Action to Control Cardiovascular Risk in Diabetes, ADVANCE: Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation, VADT: Veterans Affairs Diabetes Trial, HEART2D: Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes, IDA: Insulin Diabetes Angioplasty study, JEDI: Japanese Elderly Diabetes Intervention Trial. RCT: randomized controlled trial, HbA1c: glycated hemoglobin, MI: myocardial infarction, CV: cardiovascular, T2D: type 2 diabetes, PCI: Percutaneous Coronary Intervention, FBG: fasting blood glucose

1.1.5.2 Data from clinical practice guidelines

In the European Diabetes Working Party for Older People with T2D guidelines (EDWPOP), the potential overtreatment was defined as an HbA1c level below 7.6%. This definition only included those who are frail, dependent, associated with chronic comorbid diseases, care home residents, and at high risk for hypoglycemia (178). The standards of medical care in diabetes published by the American Diabetes Association (ADA) discussed whether older adults with diabetes are at a higher risk than any other elderly population for several geriatric syndromes, including polypharmacy, which may have an effect on their self-management abilities (179). ADA mentioned that polypharmacy in older adults with diabetes in the long-term care settings such as in nursing homes and skilled nursing facilities are at high risk for hypoglycemia, along with their higher number of complications, comorbid conditions, and other risk factors (179). ADA also debated whether narrow glycemic control in the elderly with diabetes is considered as overtreatment, increasing the risk of hypoglycemia, which was regrettably shown to be a common clinical practice, suggesting the de-intensification of regimens in patients taking non-insulin glucose-lowering medicines (179).

The European Association for the Study of Diabetes (EASD) and ADA in their joint statement addressed polypharmacy to the extent that it represents an additional important consideration alongside patient preferences, glycaemic targets, and comorbid conditions for the process of glucose-lowering medication selection. No specific recommendations were mentioned in the statement regarding polypharmacy or overtreatment for older adults (180). The International Diabetes Federation (IDF) guideline for the elderly with T2D included polypharmacy as one of the most important factors which can contribute to increasing the risk of adverse drug events and proposed to reduce it wherever possible (182). In addition, the IDF identified polypharmacy as one of the risk factors for hypoglycemia in the elderly with T2D, as well as one of the risk factors for falls in this population. Furthermore, IDF proposed HbA1c level < 7% / 53 mmol/l as a threshold measure of potential overtreatment of older people who are at high risk for hypoglycemia (182).

The National Institute for Health and Care Excellence (NICE) recommends the implementation of an individualized approach for the management of adults with T2D, taking into consideration the risk of polypharmacy and their impact on risk and benefit of the drug treatment, with no specific recommendations for the elderly population (184). Finally, the recent Canadian Diabetes Association (CDA) guidelines recommended that in a selected elderly

population with T2D, such as those who are frail and residents of long-term care settings and at higher risk of hypoglycemia due to polypharmacy and other risk factors, deprescribing should be taken into consideration (185). The CDA also recommends that certain medicines such as statins and sulfonylureas be the first to deprescribe, due to the lack of benefit from these medicines for those with reduced life expectancy and at risk of hypoglycemia (Table 3).

Table 3 Clinical Recommendations from clinical practice guidelines regarding polypharmacy and overtreatment

Clinical practice guideline	*Definition of polypharmacy*	*Clinical recommendations*	*Definition of overtreatment*	*Clinical recommendations*
EDWPOP[1] 2011(178)	N.A.	N.A.	Potential overtreatment HbA1c < 7.6%	For frail (dependent; multisystem disease; care home residency including those with dementia) patients where the hypoglycaemia risk is high and symptom control and avoidance of metabolic decompensation is paramount, the target HbA1c range should be 7.6–8.5%
ADA[2] 2019 (179)	N.A.	Screening for geriatric syndromes may be appropriate in older adults experiencing limitations in their basic and instrumental activities of daily living as they may affect diabetes self-management and be related to health-related quality of life	N.A.	Overtreatment of diabetes is common in older adults and should be avoided Deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia, if it can be achieved within the individualized HbA1c target
ADA-EASD[3] position statement 2018-2019 (180)*(181)*	N.A.	N.A.	N.A.	Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost. Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin
IDF[4] 2013 (182)	N.A.	Consideration of polypharmacy as one of factors that contribute to medicine related adverse events Consider the medicine burden and	Proposed definition as An HbA1c < 7% / 53 mmol/l	An HbA1c < 7% / 53 mmol/l should be used as a warning of possible overtreatment

		reduce polypharmacy, the complexity of the dose regimen, and consider stopping medicines where possible and safe.		
ACC/AHA[5] 2019 (183)	N.A.	N.A.	N.A.	N.A.
NICE[6] 2015 (184)	N.A.	Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment on the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy	N.A.	N.A.
CDA[7] 2018 (185)	N.A.	Older people with diabetes are frequently on multiple medications, many of which may be inappropriate in the setting of complex comorbidity and limited life expectancy In selected populations, deprescribing should be considered to reduce complexity of therapy, side effects and adverse drug interactions Drugs that can be considered first for deprescribing in these individuals include statins and sulfonylureas, because of lack of benefit in people with limited life expectancy and concerns about hypoglycemia, respectively.	N.A.	N.A.

1 European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus, 2 American Diabetes Association, 3 American Diabetes Association ‐ European Association for the Study of Diabetes, 4 International Diabetes Federation, 5 American College of Cardiology/American Heart Association, 6 The National Institute for Health and Care Excellence, 7 Canadian Diabetes Association, N.A.: not available

The evidence stemming from the clinical trials that reported the knowledge and/or the impact of polypharmacy in elderly people with T2D are scarce and limited. The definition of polypharmacy solely used in the RCTs is the use of five or more medicines. The primary

objective of these RCTs was not focused on the impact or the influence of polypharmacy, as there was no description of the population in those studies and only one trial which measured or reported the impact of polypharmacy on clinical, humanistic, or economic outcomes (169). RCTs that assessed or measured the impact of overtreatment in this population were very few. The risk of intensifying glycemic management in such RCTs outweighed the benefits, with the exception of two trials which found some benefit in reducing the microvascular complications (173)(174).

The clinical practice guidelines for the management of older adults with diabetes were not much different from the RCTs in the paucity of the evidence or in recommendations regarding polypharmacy and overtreatment. None of the major clinical practice guidelines defined the concept of polypharmacy, nor of overtreatment, except the EDWPOP and IDF's guideline which potentially considered them as HbA1c < 7.6% (60 mmol/mol) and as HbA1c < 7% (53 mmol/mol), respectively, signaling a possible overtreatment threshold (178)(182).

Some of these guidelines recommended checking for polypharmacy in elderly people with T2D as it could be a possible reason affecting their self-care management, reducing health-related quality of life (179), and increasing the risk of adverse drug events (182). However, there was no clear methodology proposed by these guidelines for screening and detecting polypharmacy and overtreatment, or specific criteria for the elderly people with T2D to follow for screening. Additionally, there was no clear procedure or criteria for control and management of polypharmacy in most of the guidelines, except for NICE's guideline recommendation for the individualized approach in managed care, which also discussed the benefits and risk of medicines (184). Moreover, IDF recommended the reduction of polypharmacy by reducing the dosage complexity and deprescribing medicines whenever safe and possible (182). The CDA guideline suggested that deprescribing should occur in selected elderly subgroups, especially those with complex comorbidities and limited life expectancy, starting firstly with statins and sulfonylureas (185).

No management methodology or clinical procedure was suggested by most clinical practice guidelines on how to avoid overtreatment, except for the considerations (Table 4) suggested by ADA's guideline through the de-intensification or simplification of treatment (179), and the evidenced-based recommendations algorithm (Figure 1) by EDWPOP's guideline for frail elderly people with T2D to avoid unnecessary overtreatment and polypharmacy (43).

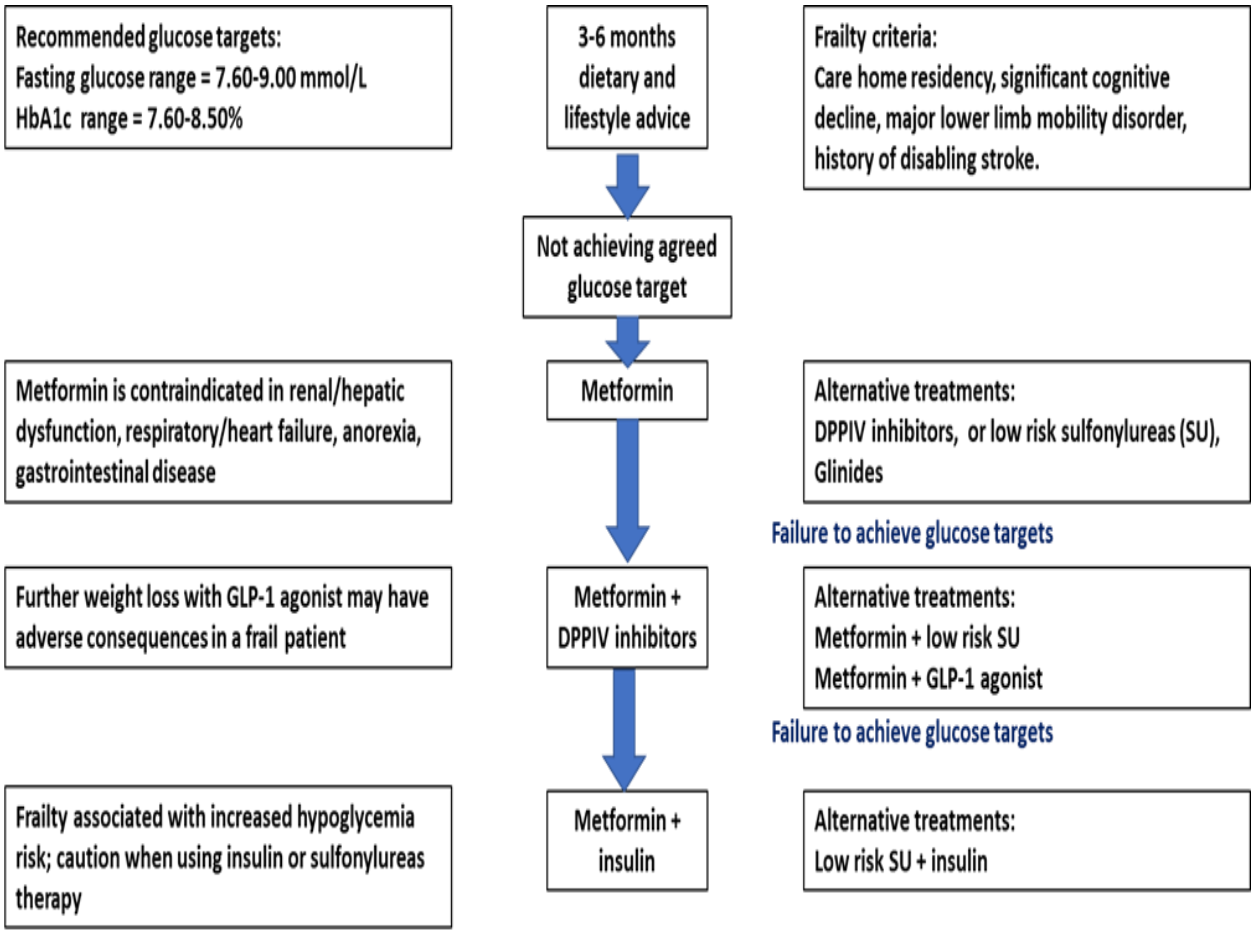
Table 4 Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes

Patient characteristics/ health status	Reasonable A1C/ treatment goal	Rationale/considerations	When may regimen simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	A1C < 7.5% (58 mmol/mol)	• Patients can generally perform complex tasks to maintain good glycemic control when health is stable • During acute illness, patients may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	A1C < 8% (64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication regimen	• If unable to manage complexity of an insulin regimen • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling patients receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C Glucose target: 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic control is important for recovery, wound healing, hydration, and avoidance of infections • Patients recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the patient will receive at home	• If treatment regimen increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication regimen during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (long-term care or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	A1C < 8.5% (69 mmol/)	• No benefits of tight glycemic control in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin regimen and the patient would like to decrease the number of injections and fingerstick blood glucose monitoring events each day • If the patient has an inconsistent eating	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern

			pattern	• If taking any medications without clear benefits
Patients at end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or fingersticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Adapted from the Older Adults: Standards of Medical Care in Diabetes—2019, American Diabetes Association, Diabetes Care 2019 Jan; 42(Supplement 1): S139-S147. https://doi.org/10.2337/dc19-S012

Figure 1 Glucose lowering algorithm for frail, older people with T2D



Adapted from European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus. Executive Summary, Volume 37, Supplement 3, November 2011, Pages S27-S38, https://doi.org/10.1016/S1262-3636(11)70962-4

1.1.5.3 Bridging the knowledge gap using real-world data

Elderly people with T2D are often under-represented in RCTs, despite shouldering a disproportionate onus of T2D and consumption of prescribed medicines and therapies, limiting treatments' generalizability, effectiveness, and safety (186). This evidence gap hinders clinical decision-making for elderly patients, as the risks and benefits of treatment are unclear (26). Treatment of elderly patients with T2D is challenging because of the high prevalence of comorbidities, the use of polypharmacy, overtreatment, frailty, and age-related reduction in pancreatic islet function. Safety is therefore an important consideration for treatment, especially the avoidance of iatrogenic hypoglycemia which occurs frequently in elderly patients and can have severe consequences (187). Yet, there are no clinical practice guidelines that address the appropriateness of polypharmacy among the whole of the elderly adult population registering T2D therapeutic regimens; equally, there is a rarity of RCTs examining the health-related outcomes associated with the use of polypharmacy in this population (188).

Despite the strong evidence of harms for certain types of medicines classes outweighing their benefits- as is the case for benzodiazepines or psychotropic medicines - there is an absence of strong evidence supporting the benefit-risk assessment of important classes, such as for anti-diabetic medicines (189). Moreover, the deprescribing considerations developed by the clinical practice guidelines for the management of elderly people with T2D are opaque and varied due to uncertainty originating in the lack of data from routine clinical practice (190). Real-world data plays an important role in the evaluation of short- and long-term medicines' safety through the evaluation of polypharmacy risks. These can range from drug-drug interactions, potentially inappropriate medicines influencing patients' health-related quality of life in clinical practice for the elderly populations with T2D, to other outcomes including the risk of disease complications, hospitalization, and mortality (191).

Real-world data can also be used to assess the effectiveness of therapy in elderly people with T2D and to understand how diabetes therapy intensification can add the risk of severe hypoglycemia, and higher therapy cost through overtreatment (192). Clinical guidelines are mostly based on a single disease, with little attention paid to how such guidelines overlap or conflict with each other. For older people with multiple conditions, applying multiple sets of guidelines leads to a treatment burden, polypharmacy, and frankly conflicting advice.

RCTs and regulatory approval processes focus on whether medicines work under ideal conditions. They may not provide enough information on how well the drug works under real-world conditions, such as in the context of polypharmacy amongst the elderly patient populations, which limits the detection of drug-drug interactions and adverse drug reactions (193). Real-world studies are increasing the amount of information which healthcare providers can use for clinical decision-making by adding information that is not collected as part of RCTs, such as benefit-risk in underrepresented elderly people with T2D with several comorbidities and on polypharmacy (194).

In the era of real-world data, elderly people with T2D on polypharmacy are one of the patients' groups in the greatest need of personalized medication therapy in routine clinical practice. Individual differences in drug response are wide-ranging and difficult to predict in this group. For these patients, it is clear that "one size does not fit all" (195). RCTs frequently assess a single distinguished intervention in a specific point in time and setting. They have limited possibility to investigate the complex treatments which are common in real life, such as polypharmacy and/or overtreatment, especially in the complex elderly population with T2D and comorbid conditions (196). Because of the ethical and feasibility reasons preventing the RCTs, one way forward might be to use a translational design with integration of clinical and epidemiological research to improve medication strategies for the T2D elderly population with polypharmacy and overtreatment (148).

Optimal management of T2D in elderly people who are not always included in RCTs currently represents a real challenge for the clinicians. The optimal glycemic target to achieve for elderly diabetic patients is still a point of contention in the presence of several factors such as frailty, limited life expectancy, falls, dementia, and risks from polypharmacy and overtreatment. More studies are required to provide strong evidence for the assessment of benefit and harm of polypharmacy, and equally, for overtreatment. More studies are required to provide strong evidence for the assessment of benefit and harm of polypharmacy and overtreatment derived from real-world observational studies may differ from the experienced by elderly people with T2D.

Polypharmacy is criticized for being a concept that is inherently too general and imprecise. In clinical routine practice, polypharmacy raises concerns, given that the net effects of multiple medicine use are unpredictable and can be harmful to an already impaired older adult with T2D, organ failure, and functional decline. The topic of polypharmacy and overtreatment research requires new directions to gain more robust evidence. This includes observational

studies and translational research, which requires interdisciplinary collaboration from both academics and healthcare professionals.

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Supplementary Tables

Supplementary Table 1 Assessment of risk of bias for the randomized controlled trials concerning polypharmacy

Study Reference	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS	Quality assessment
Barnett *et al.* 2013 (167)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Good quality
Strain *et al.* 2017 (168)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Vanassche *et al.* 2018 (169)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality

Supplementary Table 2 Assessment of risk of bias for the randomized controlled trials concerning overtreatment

Study Reference	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS	Quality assessment
VA CSDM trial (170)	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Poor quality
Proactive trial (171)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Good quality
ACCORD trial (172)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
ADVANCE trial (173)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
VADT trial (174)	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Fair quality
HEART2D trial (175)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk	Fair quality
IDA trial (176)	low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Poor quality
JEDI trial (177)	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk	Poor quality

VA CSDM: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes, PROactive: Prospective Pioglitazone Clinical Trial In Macrovascular Events, ACCORD: The Action to Control Cardiovascular Risk in Diabetes, ADVANCE: Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation, VADT: Veterans Affairs Diabetes Trial, HEART2D: Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes, IDA: Insulin Diabetes Angioplasty study, JEDI: Japanese Elderly Diabetes Intervention Trial.

CHAPTER 1.2

THESIS OUTLINE AND OBJECTIVES

As life expectancy continues to increase, so does the number of elderly people with diabetes, with more than 90% of people aged over 65 diagnosed with type 2 (T2D). Treatment of elderly people with T2D has its unique challenges, because of the high prevalence of comorbidities, polypharmacy, overtreatment, frailty, and other age-related syndromes. There is also the further burden of associated chronic conditions and disease-related complications, placing additional and often competing demands on T2D management.

The literature relating to polypharmacy and overtreatment has been expanded over recent decades. Despite this progress and its growing, the data relating to the spectrum of polypharmacy and overtreatment is conflicting in what regards elderly people aged 65 years or more with T2D. The concepts of polypharmacy and overtreatment are not clearly defined themselves, which inhibits the understanding of their impact on benefit-risk assessment of treatment in this population whose needs ultimately demand the restructuring of routine clinical practice.

This thesis is divided into three chapters. **Chapter 1** introduces the major clinical challenges in elderly people with T2D and addresses the rationale behind the need to investigate the impact of polypharmacy and overtreatment in routine clinical practice **Chapter 2** conducts a systematic review and meta-analysis of observational, cohort and cross-sectional design studies, and is followed by three observational, cross-sectional design studies. The latter implements data which include the criteria of being older adults (aged of 65 years old or more) with T2D.

Chapter 2.1 presents a brief description of research methods. **Chapter 2.2** investigates the global view on the impact of polypharmacy on major clinical outcomes by systematically reviewing the available literature and critically appraising the available evidence through meta-analysis.

Chapter 2.3 examines the prevalence of polypharmacy and describes the socio-demographic profile, identifying and addressing the potentially serious clinically relevant drug-drug interactions, and potentially inappropriate medicines. It then determines the impact of polypharmacy, potentially serious clinically relevant drug-drug interaction, and potentially inappropriate medicines on health-related quality of life using data from nationwide, pharmacy-based intensive monitoring of glucose-lowering medicines in Portugal (MOMI database).

Chapter 2.4 replicates this framework, determining the impact of polypharmacy, potentially serious clinically relevant drug-drug interaction and potentially inappropriate medicines on glycemic control and kidney function using data from the administrative database of the Portuguese Diabetes Association (APDP).

Chapter 2.5 investigates the prevalence, characteristics, and factors associated with potential overtreatment and undertreatment for older people with T2D, using the data from administrative database of the Portuguese Diabetes Association (APDP).

Chapter 3 encompass a general discussion where results of studies conducted are summarized and discussed as well as future recommendations on optimizing polypharmacy and overtreatment in elderly people with T2D.

CHAPTER TWO

METHODOLOGIES AND RESULTS

CHAPTER 2.1

RESEARCH METHODS

This chapter provides the general outline of the research methodology that was used to answer the research questions, including study designs, the settings where each study took place, the participants selected to be included, the data collected, and the ethical obligation required. The specific data analysis and outcomes are described in detail in the methods section of each study conducted.

2.1.1 Research designs

The research conducted using a systematic review of cross-sectional and cohort designs with meta-analysis of cohort designs, followed by three studies with cross-sectional design. The research designs, main outcomes, and settings (databases) are presented in Table 1**.**

Table 1 Research designs, main outcomes, and settings (databases)

Study Number	I	II	III	IV
Design	Systematic review and meta-analysis	Cross-sectional	Cross-sectional	Cross-sectional
Main outcomes	Association between polypharmacy and all-cause mortality, myocardial infarction, stroke, and hospitalization	Association between polypharmacy, potentially serious clinically relevant DDIs and PIMs with health-related quality of life	Association between polypharmacy, potentially serious clinically relevant DDIs and PIMs with glycemic control, and kidney function	Characteristics and factors associated with potential overtreatment and undertreatment
Settings (Databases)	PubMed/Medline, ScienceDirect, and Web of Science	MOMI (Modelo Observacional de Monitorizacao intensiva)	APDP (Associação Protectora dos Diabéticos de Portugal)	APDP (Associação Protectora dos Diabéticos de Portugal)

DDIs: drug-drug interactions, PIMs: potentially inappropriate medicines

2.1.2 Research settings (Databases)

The description of the three research settings (databases) is described in detail in Table 2

Table 2 Research settings

Databases	PubMed/Medline, ScienceDirect, and Web of Science	MOMI (Modelo Observacional de Monitorizacao intensive)	APDP (Associação Protectora dos Diabéticos de Portugal)
Description	• Free electronic search engine databases provides access to a large scientific and medical research articles worldwide.	• Pharmacy-based database of nationwide, intensive monitoring study that monitored a specific glucose lowering drugs (GLDs), conducted between 15th November 2014 and 30th November 2015 in Portugal (1)(2)(3) • MOMI Conducted at the Centre for Health, Evaluation & Research (CEFAR) of the National Association of Pharmacies (ANF) and was fully funded by ANF. • 670 community pharmacies (33.9% of total Portuguese community pharmacies), and 1328 participants (760 of these participants aged ≥ 65 years) included in MOMI. • Population consisted of T2D adult patients, first users (defined as who did not take the inception monitored drug	• Administrative and consultation database of the Portuguese Diabetes Association (APDP). • APDP has been founded in 1926, being the oldest member of the International Diabetes Federation (IDF). • APDP aids in the different fields of diabetes (diabetology, cardiology, urology, psychology, psychiatry, ophthalmology, and pathology) to approximately 6,000 diabetics per year, from which 1,600 are new individuals. • These individuals usually sent by the Health Centers of the National Health Services and by practitioners of other institutions which collaborate with the Association.

	within 6 months prior to recruitment, as self-reported by the patients) of the recently launched GLDs that were reimbursed in Portugal at the time of enrolment: dipeptidyl peptidase-4 inhibitors (DPP-4) (sitagliptin, vildagliptin, saxagliptin and linagliptin) alone or in fixed-dose combination with metformin, glucagon-like peptide-1 (GLP-1) (liraglutide and exenatide) or sodium-glucose co-transporter 2 inhibitors SGLT-2 (dapagliflozin), cohort was divided into two subgroups: incident new users (participants who were using one of the monitored drugs for the first time and had no current or prior experience with DPP-4, GLP-1 or SGLT2) and prevalent new users (participants who had previously used/current use at least one drug of the monitored treatment classes: DPP-4, GLP-1 or SGLT2, but not the inception GLD) • MOMI data collected through 1) baseline questionnaire by trained pharmacist during a	• The APDP database regulated by APDPSoft, which is a software developed since 1999, accompanies the evolution of the services provided by the APDP. Currently, this software supports and monitors several valences, especially in terms of clinical data file, markings management, laboratory parameters, invoicing the health subsystems, integration of numerous diagnosis equipment as well as an effective liaison with the electronic services of the Ministry of Health in Portugal (6–8). • The APDP database does not contain mortality, hypoglycemic episodes, frailty score, emergency visits, or hospitalization records. • APDP database did not reported the patients'' signs or symptoms, medicines dosage form, concentration, frequency, method of administration, and medicines use history.

	structured face-to-face interview; 2) telephone questionnaires and 3) pharmacy records. • MOMI database included socio-demographic, anthropometrics, age at time of T2D diagnosis, usual diabetes outpatient clinical care, co-morbidities and diabetes related conditions/complications and concomitant therapy and T2D treatment, baseline and 6 months follow up data of health-related quality of life, data regarding GLDs adverse drug events and hypoglycemic episodes at 2 weeks, 3 months and 6 months, and data regarding persistence and adherence of GLDs. • All concurrent diseases were classified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), and all co-medication therapy and T2DM treatment were coded according to the Anatomic Therapeutic	• The percentages of missing data related to some outcome variables are calculated. Multiple imputation procedure in SAS statistical software used to impute the missing data.

	Classification (ATC) (4)(5) • Participants' informed written consents and questionnaires data were stored in specific designed Microsoft Office Access® databases • All errors were appropriately corrected in the database, based on information written on the questionnaires. The percentage of missing data was calculated. • The data collected in MOMI did not include any patients' signs, symptoms, or lab results, as well as the reported outcomes except for quality of life, only related to the specific GLDs.

2.1.3 Research participants

Eligible participants included if they are: elderly people (aged 65 years or more), diagnosed with T2D, and have medical history/medicines records available.

2.1.4 Data collection

In the (***Chapter 2.2***), the data collected from each study included author name, publication year, study design, study setting, study location, study outcomes, the definition of Polypharmacy, subjects' demographic data, sample size, study duration and the statistical

model used. Individual data for the prevalence of polypharmacy were derived either directly or indirectly from each study. Polypharmacy defined as the use of a discrete definition and categorical thresholds (9). Studies were identified by searching electronic databases of PubMed/Medline, ScienceDirect, and Web of Science, through April 2019. No limit was set for the study setting or time frame. No limitation was considered for the date of acceptance or publication. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to standardize the conduct and reporting of this systematic review and meta-analysis (10).

In the (***Chapter 2.3***), the data collected were sociodemographic data, body mass index (BMI), clinical care setting, T2D treatment and, T2D related complications, co-morbidities, and chronic conditions concomitant therapy. All elderly people with T2D from the MOMI study are included (N=670). **Polypharmacy** was defined as the use of five or more medicines (11). The medicines used checked for the **potentially serious clinically relevant drug-drug interactions** using IBM Micromedex drug interaction Platform (IBM® Corporation, 2019) (12). **Potentially inappropriate medicines** identified using Screening Tool of Older Persons' Prescriptions (STOPP) criteria version 2, the final list included 80 STOPP criteria, was agreed after two rounds of Delphi validation, which arranged according to the physiological systems of the body for ease of use and rapid application (13).

The **quality of life** was measured using the three-level EuroQol five-dimensional (EuroQol 5-D-3L) questionnaire. The EQ-5D encompasses five dimensions influencing health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each with three levels of functioning (first level; no problem, second level; some problems, third level; severe problems) (14). The summary scores were computed to Portuguese preference weighted EQ-5D index scores using Portuguese values set. After that, the study participants finished the EQ-5D visual analog a scale (VAS). In the VAS, the patients evaluated their current health state on scale between zero

(worst possible health state) to one hundred (best possible health state), the high scores index together high VAS suggest best health state (15).

In the (***Chapter 2.4***), Socio-demographic data, BMI, diabetes duration, diabetes-related complications, last lab data including glycated hemoglobin (HbA1c), fasting blood glucose (FBG), creatinine, and last reading of systolic (SBP) and diastolic blood pressure (DBP), medicines used for treatment of both T2D and associated comorbidities were all collected. Participants were considered hypertensive if they have blood pressure ≥ 140/90 mmHg or they are on anti-hypertensive medicines. For **kidney function**, we calculated the estimated glomerular filtration rate (eGFR) based on participant characteristics and serum creatinine using Modification of Diet in Renal Disease Study equation (MDRD-GFR)(16). **Glycemic control** refers to the typical levels of blood sugar (glucose) in a person with diabetes evaluated using HbA1c (17). The study included all the elderly people with T2D who registered during the year of 2018 at APDP (N=444). **Polypharmacy** was defined as the use of five or more medicines (11). The medicines used were analysed to identify the **potentially serious clinically relevant drug-drug interactions** using IBM Micromedex Platform (IBM® Corporation 2019) (12). **Potentially inappropriate medicines** were identified using STOPP criteria version 2 (13).

In the (***Chapter 2.5***), Socio-demographic data, BMI, diabetes duration, diabetes complications, last lab results including HbA1c, FBG, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), total cholesterol (TC), creatinine, sodium, and potassium), as well as the last blood pressure record including both SBP and DBP, medicines used for the treatment of both T2D and associated comorbidities were retrieved from the administrative database of APDP. The study included all the elderly people with T2D who registered during the year of 2018 at APDP (N=444). Participants were considered hypertensive if they have blood pressure ≥ 140/90 mmHg or they were on anti-hypertensive medicines. For kidney function, we calculated the eGFR based on participant characteristics and serum creatinine using the

modification of diet in renal disease study equation (MDRD-GFR) (16). Polypharmacy was defined as the use of five or more medicines (11).

According to the action to control cardiovascular risk in diabetes (ACCORD) trial (18) a review by *Lipska and colleagues* (19), and the recommendations from European diabetes working party for older people with T2D clinical guideline (20), the majority of older people with T2D aged 65 years old or more, the harm from HbA1c target lower than 7.5% or higher than 9% are likely to outweigh the benefit. Therefore, the **potential overtreatment** defined as HbA1c target of (<7.5%), **appropriately on target** HbA1c of (≥7.5%-≤9%), and **potential undertreatment** HbA1c target of (>9%) and were on treatment with glucose-lowering medicines in mono or combination therapy.

2.1.5 Research statistical analysis

OpenMeta[Analyst] a cross-platform software for meta-analysis was used (21). All other statistical analysis performed using SAS software (22).

2.1.6 Ethical obligations

The ethical approval for the original MOMI study (Modelo Observacional de Monitorizacao intensiva) was obtained from the Portuguese Data Protection Authority (5339/2014) and by the Ethics Committee of the Institute of Public Health of the University of Porto (CE14021) and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. A written, signed informed consent form was obtained from all participants prior to initiation of any study procedures. This study was registered in the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance E-register of studies (ENCEPP/SDPP/8433). In addition, Ethical approval was also obtained from the Portuguese Diabetes Association (APDP) ethics committee for health, official number (70/2019) to use the data of elderly people with type 2 diabetes from in their administrative database.

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CHAPTER 2.2

THE ASSOCIATION BETWEEN POLYPHARMACY AND ADVERSE HEALTH CONSEQUENCES IN ELDERLY TYPE 2 DIABETES MELLITUS PATIENTS; A SYSTEMATIC REVIEW AND META-ANALYSIS

2.2.1 Abstract

Aim To summarize the existing literature concerning the association between polypharmacy and adverse health consequences in elderly patients with type 2 diabetes mellitus.

Methods We searched four literature databases (PubMed/Medline, ScienceDirect and Web of Science) through April 2019. We included all studies that addressed the association between polypharmacy and all-cause of mortality, glycemic control, macrovacular complications, hospitalization, potentially inappropriate medicines, drug-drug interactions and fall. A statistical program OpenMeta [Analyst] was used. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with a random effects model. I^2 statistics was performed to assess heterogeneity.

Results Out of sixteen studies, three studies were used for meta-analysis. A statistically significant association was found between polypharmacy and all-cause mortality (OR= 1.622, 95% CI (1.606-1.637) P<0.001), and myocardial infarction (OR=1.962, 95% CI (1.942-1.982), P<0.001. Non-statistically significant association with evidence of moderate heterogeneity was found between polypharmacy and stroke (OR=1.335; 95% CI (0.532-3.346), P=0.538, I^2=45%), and hospitalization (OR= 1.723; 95% CI (0.983-3.021), P=0.057, I^2=57%).

Conclusions Pooled risk estimates reveal that polypharmacy is associated with increased all-cause mortality, macrovacular complications and hospitalization using categorical definitions. These findings assert the need for interventions that optimize the balance of benefits and harms in medicines prescribing.

Keywords: type 2 diabetes mellitus; polypharmacy; elderly; multimorbidity

2.2.2 Introduction

Type 2 diabetes mellitus is highly prevalent chronic condition among adults, being estimated that more than 500 million people diagnosed in 2018 worldwide with gradual elevation with aging and life expectancy (1). Elderly patients are usually associated with more chronic conditions such as hypertension, dyslipidemia, coronary heart disease, and chronic kidney disease (2)(3). Polypharmacy appears to be highly prevalent and important lineament. A cross-sectional study in Canada found that (48%) of elderly frail patients with type 2 diabetes mellitus were taking ≥ 9 medications daily (4). Another study in Greece found that (43.4%) were using ≥ 7 medications daily (5). Since multiple medications are needed to control the disease and associated comorbid conditions, those patients often require to take more than dozen of different classes of medications (6).

Polypharmacy can be associated with adverse outcomes, such as increase the risk of hypoglycemia, decline in medication adherence, risk of drug-drug interactions, and probability of worsen quality of life which can result in higher risk of hospitalization, mortality rate and healthcare costs (7). Management of those patients is a complex process due to patients characteristics, which require individualize medication regimen to balance the pressing to control the diabetes as well as other comorbid conditions and/or complications and minimizing and/or preventing medications related risks (8).

The international diabetes federation (IDF) guideline recommends to consider reducing polypharmacy, suggesting to perform comprehensive medication review, consider deprescribing when its safe and possible, dose titration, identify adherence difficulties, apply medications lists such as Beer's or (STOPP) and screening tool to alert to right treatment (START), implementation of non-pharmacological options, providing individualized medication education, and involve family/caregivers in the care plan (8). On the other hand, the American diabetes association guideline recommends the avoidance of polypharmacy and undergoing

deintensification of complex regimen whenever possible, taking into consideration special attention while prescribing and monitoring of pharmacological therapies, medications costs and presence of other comorbidities (9)(10).

When researching the literature on adverse health consequences of polypharmacy, it was noteworthy that there is no available synthesis of data examining multiple patient outcomes. It is therefore important to examine the available literature to determine the risk of adverse health consequences from polypharmacy among those patients (8). Greater knowledge about this problem is important, and early interventions should be designed and implemented (9).

Aim

To summarize the existing literature concerning the association between Polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients.

2.2.3 Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to standardize the conduct and reporting of this systematic review and meta-analysis (11).

Study Characteristics

Observational studies (cross-sectional studies, cohort studies, case series, and case-control studies), interventional studies (randomized controlled trials, and quasi-experimental studies) designs were considered. Only studies published in English were included.

Types of Participants

Participants who were aged ≥ 65 years old and diagnosed with type 2 diabetes mellitus. We included studies that defined polypharmacy as a discrete definition and studies using categorical thresholds (12)(13).

Primary outcomes

All-cause of mortality (risk of death)

Glycemic control, for the purpose of the this review we considered the following categories of elderly patients' glycemic target according to IDF global guideline for managing older people with type 2 diabetes mellitus. (A) Functionally independent (HbA1c target is 7.0-7.5%), sub-category (A) frail (HbA1c target up to 8.5%). (B) Functionally dependent (HbA1c target is 7.0-8.0%), sub-category (B) dementia (HbA1c target up to 8.5%) (8).

Macrovascular complications which including coronary artery diseases (CAD), heart failure (HF), cerebrovascular disease (CVD) and stroke (10).

Hospitalization or hospital Re-admission (including all-cause hospital admissions and unplanned re-hospitalization) (14).

Secondary outcomes

Studies were reported the association between polypharmacy and potentially inappropriate medicines (15), drug–drug interaction (16), and fall or fall risk (17).

Information Sources

Studies were identified by searching electronic databases of PubMed/Medline, ScienceDirect, and Web of Science, through April 2019. No limit was set for the study setting or time frame. No limitation was considered for date of acceptance or publication.

Search Strategy

The full search strategy is included in supplementary data

Study Selection

All titles and abstracts identified in the databases above were screened for eligibility by one author (L.M). Two review authors independently evaluated full texts of all potentially eligible studies for appropriateness for inclusion without prior consideration of the results (AP.M, L.M). Any disagreements were resolved by discussion or feedback from a third and fourth authors (JF. R, C.T).

Data Item

The following information was extracted: author name, publication year, study design, study setting, study location, study outcomes, definition of Polypharmacy, participants demographic data: age groups (if applicable), gender, sample size, study duration and statistical model used.

Quality (Risk of Bias) assessment for the individual studies

Two review authors independently assessed the quality for each study. Any disagreements were resolved by discussion or a third author (JF. R). We used the Newcastle-Ottawa Scale (NOS) for observational cohort and modified version for cross-sectional studies which was used in previous studies (18). Using a point" Star" system to judge on the three broad perspectives, a maximum of one 'star' for each h item within the 'Selection' and 'Exposure/Outcome' categories; maximum of two 'stars' for 'Comparability' for cohort studies.

For the modified tool for cross-sectional studies, a maximum five stars for the selection category, two stars for the comparability category and three stars for outcome category. The scale scores varied depending on the study design: for cross-sectional studies it ranged from 0 (lowest grade) to 9 (highest grade) and for cohort studies from 0 (lowest grade) to 10 (highest grade), Studies with scores above the median were classified as good quality studies, for cross-sectional studies > 5 and for cohort studies > 6.

Data Synthesis

Individual data for prevalence of polypharmacy were derived either directly or indirectly from each study. To address the association of polypharmacy with adverse health consequences, we calculated the odd ratio (OR) and their respective 95% confidence intervals, and *P* value was set to be < 0.05. Meta-analysis was implemented when there were two or more studies with same design identified the same outcome using random-effect model, and I^2 test was used to identify the heterogeneity. OpenMeta[Analyst] a cross-platform software for meta-analysis was used (19).

2.2.4 Results

Study selection

The search of the electronic databases provided a total of 1859 citations. After screening the titles and abstracts for duplicates, 1823 were remained. Of these, 1663 were removed due to either the full text copy was not available, or the papers did not publish in English. The full texts of the remaining 160 citations were examined in more detail. Of these, 143 studies did not meet the inclusion criteria. Finally, sixteen studies were included in the systematic review and three studies were included in the meta-analysis**.** Figure 2 The PRISMA flow diagram for the included studies

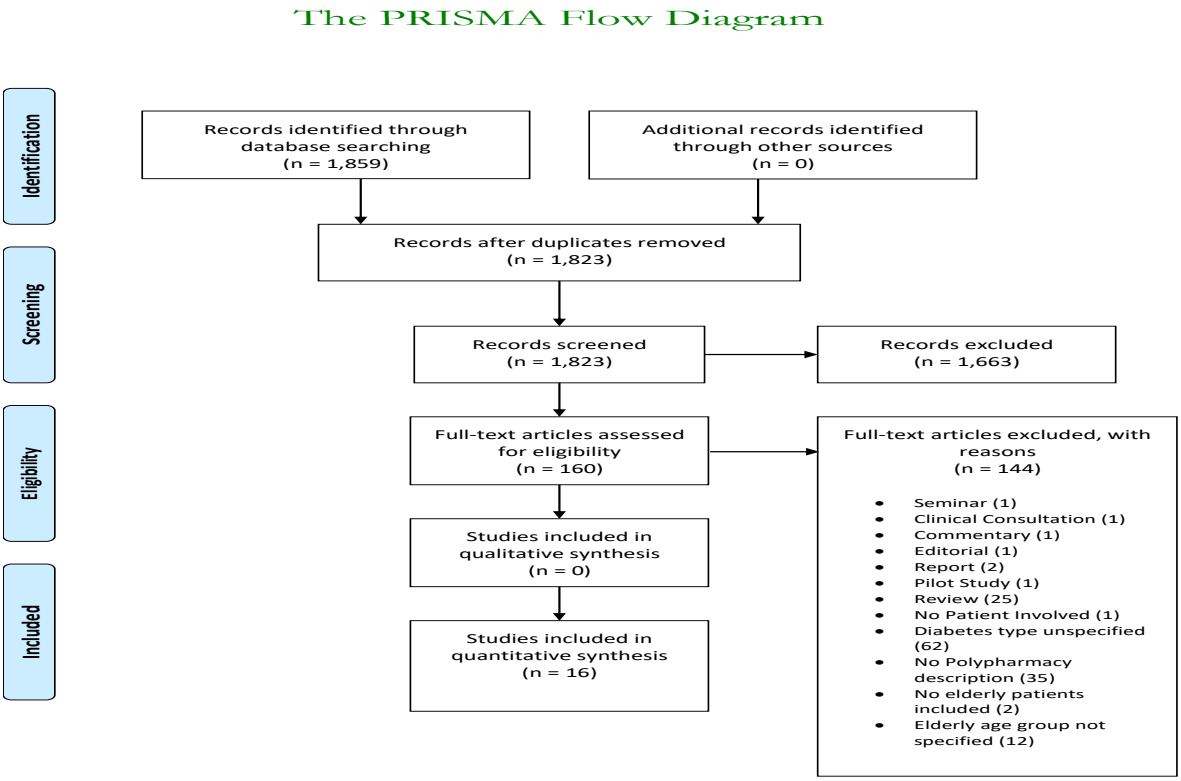


Figure 2 The PRISMA flow diagram for the included studies

The studies publication date was 2018 (n=1), 2017 (n=1), 2016 (n=3), 2015 (n=5), 2013 (n=3), 2012 (n=2), and 2010 (n=1). The studies duration was between 4 months to 10 years. The studies conducted mainly in USA (n=7), Australia (n=2), Malaysia (n=2), UK (n=1), Chile (n=1), Brazil (n=1), Italy (n=1), and Japan (n=1).

The total number of patients included in this review was 1,205,821, in which 50.22% of these were females. 1,179,325 (97.80% of the total number of patients) were elderly. The most common definition of polypharmacy was using five or more medications found in 50% of the studies and the prevalence was between (6.25 to 93.4%). The extracted data summarized in Table 1

Table 1 Characteristics of the Included Studies

Source	Study location	Study Setting	Sample size	Age group (%)	Female N (%)	Study Frame	Study outcomes	Statistical analysis	Definition of PolyPharmacy
Cohort Studies									
Yashkin, 2018	USA	The US Centers for Medicare and Medicaid Services	910,880	≥ 65 (100)	455,440 (50)	2003-2012	Risk of all-cause mortality Risk of diagnosis congestive heart failure (CHF) Hospitalization for myocardial infarction (MI) Hospitalization for stroke or transient ischemic attack (TIA)	Cox-proportional hazard model	Using more than five medicines
Tan, 2015	USA	National Medicare claims data	37,086	65-74 (16.1) 75-84 (16.9) 85+ (19.4)	22,953 (61.89)	2008-2010	Co-administration of cotrimoxazole with glyburide or glipizide Emergency room visits for hypoglycemia after coadministration of co-trimoxazole or a reference antibiotic with glyburide or glipizide	logistic regression model	Using of five or more of oral medicines
Caughey, 2017	Australia	Administrative claims data from the Department of Veterans' Affairs for hospitalized patients	876	> 75 Years (100)	366 (41.8)	Jan-Dec 2012	Prevalence of Potentially high risk prescribing that associated with poor outcomes before/after hospitalization Treatment conflicts associated with diabetes and medicines for comorbid conditions that affects blood glucose level (sulfonylureas, corticosteroids, anti-psychotics, and NSAIDs) Potentially inappropriate medicines issues 4 months before/after admission using Beer's criteria	McNemar's chi-squared test and Relative differences	Using of 10 or more medicines

HAMADA, 2016	UK	Primary care database	5324	> 80 (100)	2668 (50)	2011-2013	Proportion of Patients prescribed different classes of drug during the first quarter Q1 (9-12months before death) and last quarter Q4 (3 months before death) of last year of life	Frequencies and proportions	Using five or more medicines
Patel, 2012	USA	Electronic health records database	324	≥ 65 (100)	205 (63.27)	Jun 2006–Jun 2007	Risk of MI, stroke, hospitalization and death	Bivariate analysis and multivariate logistic regression	Under-Polypharmacy (< 5 medicines), Polypharmacy (> 5-<10 medicines), Severe-Polypharmacy (> 10 medicines)
Huri, 2013	Malaysia	tertiary hospital database	208	≥ 65 (43.3)	112 (53.85)	Jan 2009-Mar 2014	Identification and assessment of drug related problems (DRPs) Assessment of Potentially inappropriate medicines using Beer's criteria	Chi-squared test	Using six or more medicines
Ajmera, 2015	USA	Humana Medicare Advantage Prescription Drugs plan database	16,653	65-74 (63.8) ≥ 75 (36.2)	8110 (48.7)	Jan 2007-Feb 2012	Association between time to treatment intensification and elderly patient specific complexities	Multivariable Cox-proportional hazards regression	Using more than six medicines
Raval, 2015	USA	Humana Medicare with Prescription Drug (MAPD) plan database	202,496	65-74 (48.32) ≥ 75 (51.68)	104,461(51.59)	Jan 2007-Aug 2011	All-cause of hospital readmission	Multivariable logistic regressions	Using of more than thirteen medicines
Arellano, 2016	Chile	Public teaching hospital	138	≥ 65 (100)	74 (53.62)	May-Aug 2015	Prevalence of potentially inappropriate medicines using Beer's and STOPP criteria Determination of clinical variables associated with potentially inappropriate medicines	Multivariate logistic regression	Using four or more medicines
LIPSKA, 2013	USA	Kaiser Permanente Northern California healthcare	9094	≥ 70 (18)	819 (50)	2005-2006	Association between HbA1c level and self-reported severe	Poisson regression models	Using more than four medicines

		delivery system					hypoglycemia		
Cross-Sectional Studies									
Araújo, 2013	Brazil	Public primary care institutions	579	70-79 (20.1) 80-92 (9.3)	407 (70.3)	Mar-Jul 2009	Prevalence of Drug Interactions Association with medication adherence and capillary glucose	non-parametric x^2	Using five or more medicines
Caughey, 2010	Australia	Prescription dispensing database at Vartan affairs department	18,968	≥ 79 (100)	8364 (44.1)	Apr-Jul 2007	Prevalence of comorbid conditions Potentially inappropriate medicines using Beer's criteria	Frequencies and proportions	Using five or more medicines
Huri. 2015	Malaysia	Premier teaching hospital	242	≥ 65 (56.2)	124 (51.2)	Jan 2008–Mar 2014	Prevalence of anti-diabetic medicines Factor associated with glycemic control with different chronic kidney disease (CKD) stages	Chi-square test	Using five or more medicines
Weiss, 2012	USA	National Health and Examination Survey	1443	≥ 65 (47.8)	779 (54)	1999-2004	association between Treatment effect modifiers patterns and number of hospitalizations	Multivariable negative binomial regression model	Using five or more medicines
Noale, 2016	Italy	diabetes centers	1342	≥ 65 (100)	638 (47.54)	Sep 2010-Oct 2011	Characteristics associated with Polypharmacy	Logistic regression models	Using five or more medicines (Unadjusted odd ratio)
Chiba, 2015	Japan	Outpatient diabetes clinic at geriatric hospital	168	≥ 65 (100)	109 (64.9)	Dec 2009 – Apr 2011	Risk factors of falls	Multiple logistic regression	Using more than five medicines

The review found that between 26% to 48.7% of elderly diabetes type 2 patients had HbA1c between (8.0% to ≥ 8.5%) despite receiving treatment intensification. Median time to treatment intensification was shorter in those on polypharmacy (18.5 months) than those without polypharmacy (20.4 months). No association found between HbA1c and polypharmacy (20)(21)(22).

The prevalence of potentially inappropriate (PIMs) medicines was varied among the studies, ranging from 22.7% to 79% using Beer's and 48% using STOPP criteria. The most common identified PIMs were using of metformin in elderly patients with type 2 diabetes mellitus aged ≥ 85 years old, benzodiazepines, tricyclic anti-depressants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and beta-blockers. Polypharmacy was associated with presence of PIMs (23)(24)(25).

Severe hypoglycemia was reported from the interaction between sulfonylureas (glyburide and glipizide) with co-trimoxazole antibiotic more in patients on polypharmacy. Interactions between oral hypoglycemic agents (metformin, glyburide, metformin plus glyburide and acarbose) with hydrochlorothiazide, furosemide, angiotensin-converting enzyme inhibitors (ACEIs), simvastatin and prednisolone were also reported (26)(27). No association was reported between fall or fall risk and polypharmacy (28)

Risk of bias assessment

Assessment of risk of bias is found in Table 2

Table 2 Assessment of Quality/Risk of Bias in the Cohort & Cross-sectional Studies

	Selection				Comparability	Outcome			Analysis score
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Yashkin 2017	+	+	+	+	+	+	+	+	8
Tan (2015)	+	+	+	+	++	+			7
Caughey (2017)	+	+	+	+	++	+			7
Hamada (2016)	+	+	+	+	+	+	+		7

Patel (2012)	+	+	+	+	+	+	+	+	8
Huri (2013)	+	+	+	+	+	+			6
Ajmera (2015)	+	+	+	+	++	+	+	+	9
Raval (2015)	+	+	+	+	+	+	+	+	8
Arellano (2016)	+	+	+	+	+	+			6
Lipska (2013)	+	+	+	+	+	+			6

	Selection				Comparability	Outcome		Quality score
Study	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on the design and analysis	Assessment of outcome	Statistical test	
Araújo, 2013	+	+	+	+	+	++	+	8
Caughey, 2010	+			+	+	++		5
Huri, 2015	+	+	+	+	+	++	+	8
Weiss, 2012	+	+	+	+	+	++	+	8
Noale, 2016	+	+	+	+	+	++	+	8
Chiba, 2015	+		+	+	+	++	+	7

Table 3 summarizes the estimated ORs (95% CIs) obtained from each study for the association between polypharmacy with all-cause mortality, myocardial infarction, stroke, and hospitalization.

Table 3 ORs and 95% CIs for the association between polypharmacy with all-cause mortality, myocardial infarction, stroke, and hospitalization

Outcome	Study reference	Study design	Odd ratio (95% CI)
All-cause mortality	Yashkin et al. 2018	Cohort	1.622 (1.606 to 1.637)
	Patel et al. 2012	Cohort	1.169 (0.468 to 2.918)
	Noale et al. 2016	Cross-sectional	4.569 (3.056 to 6.829)
Myocardial infarction	Yashkin et al. 2018	Cohort	1.962 (1.942 to 1.982)
	Patel et al. 2012	Cohort	1.544 (0.526 to 4.596)
	Noale et al. 2016	Cross-sectional	4.67 (3.01 to 7.25)
Stroke	Yashkin et al. 2018	Cohort	1.718 (1.701 to 1.735)

	Patel et al. 2012	Cohort	0.559 (0.109 to 2.860)
	Noale et al. 2016	Cross-sectional	1.56 (0.96 to 2.52)
Hospitalization	Raval et al. 2015	Cohort	1.438 (1.371 to 1.509)
	Patel et al. 2012	Cohort	2.714 (1.197 to 6.149)

The association between polypharmacy and all-cause of mortality was reported in two cohort studies (29)(30) and one cross-sectional study (31). When combining the estimated effects based on cohort studies, polypharmacy was significantly associated with all-cause mortality (pooled OR, 1.622; 95% CI 1.606 to 1.637, P<0.001, I^2=0%) **figure 2.** Including the cross-sectional study, a non-statistically significant association with evidence of high heterogeneity was observed (pooled OR, 2.151; 95% CI 0.971 to 4.765, P=0.059, I^2=92%).

Figure 3. Meta-analysis of cohort studies of polypharmacy and all-cause mortality, ordered by date of publication

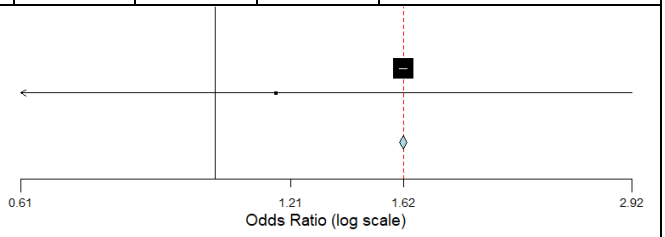
Study	No of patients had all-cause mortality risk in polypharmacy group	Total no of subjects in polypharmacy group	No of patients had all-cause mortality risk in control group	Total no of subjects in control group	Odd ratio	Lower 95% CI	Upper 95% CI	Weight %
Yashkin, 2018	358,456	445,222	358,456	499,165	1.622	1.606	1.637	99.989
Patel, 2012	16	105	8	60	1.169	0.468	2.918	0.011

Heterogeneity

Tau² Q (DF=1) I² Het. P value

0.000 0.493 0% 0.483

Overall effect OR=1.622, 95% CI (1.606 to 1.637), P<0.001



The association between polypharmacy and myocardial infarction was reported in two cohort (29)(30) and one cross-sectional study (31). When combining the estimated effects based on cohort studies, polypharmacy was significantly associated with myocardial infarction (pooled OR, 1.962; 95% CI 1.942 to 1.982, P<0.001, I^2=0%) **figure 3**. Including the cross-sectional study, a significant association was also observed, with evidence of level of heterogeneity (pooled OR, 2.790; 95% CI 1.140 to 6.828, P=0.025, I^2=94%).

Figure 4 Meta-analysis of cohort studies of polypharmacy and MI, ordered by date of publication

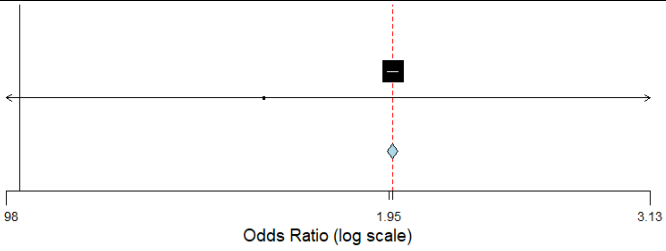
Study	No of subjects had MI in polypharmacy group	Total no of subjects in polypharmacy group	No of subjects had MI in control group	Total no of subjects in control group	Odd ratio	Lower 95% CI	Upper 95% CI	Weight %
Yashkin, 2018	339,212	412,534	339,212	483,081	1.962	1.942	1.982	99.99
Patel, 2012	13	105	5	60	1.544	0.526	4.596	0.009

Heterogeneity

Tau² Q (DF=1) I² Het. P value

0.000 0.177 0% P=0.674

Overall effect (OR=1.962, 95% CI (1.942 to 1.982), P<0.001



Data on the association between polypharmacy and stroke was reported in two cohort (29)(30) and one cross-sectional study (31). When combining the estimated effects based on cohort studies, a non-significant association between polypharmacy and stroke was observed (pooled OR, 1.335; 95% CI 0.532 to 3.346, P=0.538, I^2=45%) **figure 4**. Including the cross-sectional study, a significant association was observed, with evidence of high level of heterogeneity (pooled OR, 1.929; 95% CI 1.164 to 3.199, P=0.011, I^2=76%).

Figure 5 Meta-analysis of cohort studies of polypharmacy and stroke, ordered by date of publication

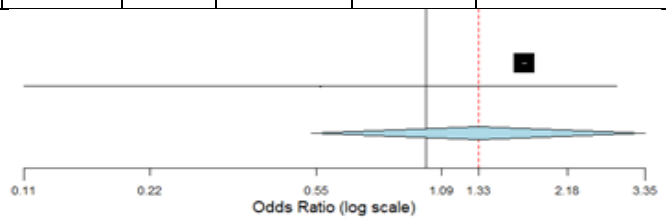
Study	No of subjects had stroke in polypharmacy group	Total no of subjects in polypharmacy group	No of subjects had stroke in control group	Total no of subjects in control group	Odd ratio	Lower 95% CI	Upper 95% CI	Weight %
Yashkin, 2018	341,610	420,981	341,610	477,977	1.718	1.701	1.735	77.508
Patel, 2012	3	105	3	60	0.559	0.109	2.860	22.492

Heterogeneity

Tau^2 Q (DF=1) I^2 Het. P value

0.284 1.818 45% 0.178

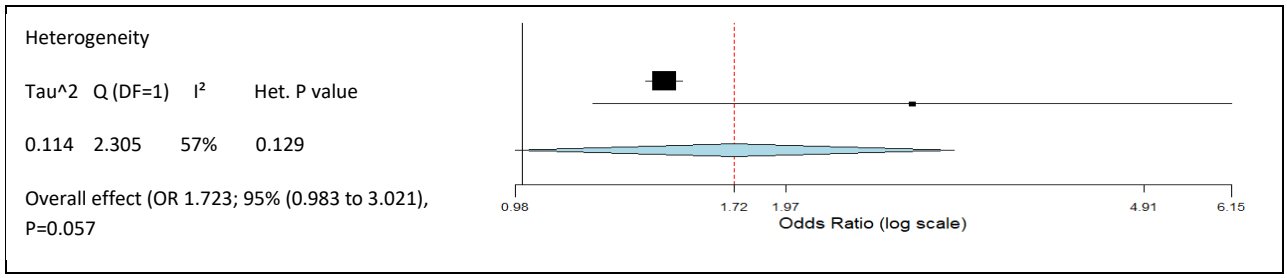
Overall effect (OR 1.335, 95% (0.532 to 3.346), P=0.538



Data regarding the association between polypharmacy and hospitalization was reported in two cohort studies (30)(32). When combining the estimated effects of these studies, a non-sgnificnat association between polypharmacy and hospitalization with moderate evidence of heterogenity was observed (pooled OR, 1.723; 95% CI 0.983 to 3.021, P=0.057, I^2=57%) **figure 5**

Figure 5 Meta-analysis of cohort studies of polypharmacy and hospitalization, ordered by date of publication

Study	No of subjects hospitalized in polypharmacy group	Total no of subjects in polypharmacy group	No of subjects hospitalized in control group	Total no of subjects in control group	Odd ratio	Lower 95% CI	Upper 95% CI	Weight %
Raval, 2015	2222	12,653	24,488	189,843	1.438	1.371	1.509	71.547
Patel, 2012	34	105	9	60	2.714	1.197	6.149	28.453



2.2.5 Discussion

The increase in categorical threshold from 5 or more medicines was associated with high risk of by 62% in all-cause mortality, 96% with myocardial infarction, 33% with stroke and 72% with hospitalization. The risk did not increased in dose-dependent manner, which can be explained by low number of elderly patients with type 2 diabetes mellitus using 10 or more medicines per day (33)(34). These findings were not agreed with previous systematic reviews, which found that the association between polypharmacy and mortality (33), as well as dementia (35) increased in a dose-dependent patterns when the threshold values for the number of medicines defining polypharmacy increased.

A meta-analysis of five prospective randomized controlled trials of intensive glucose lowering therapy (but not polypharmacy) effect on cardiovascular outcomes and death in elderly patients with type 2 diabetes mellitus found that, 17% reduction in events of non-fatal MI (OR=0.83, 95% CI (0.75-0.93), 15% reduction in events of coronary heart disease (OR=0.85, 95% CI (0.77-0.93) and no significant effect on events of stroke (OR=0.93, 95% CI (0.81-1.06) or all-cause mortality (OR=1.02, 95% CI (0.87-1.19) (36).

The review found between 26% to 48.7% of elderly diabetes mellitus type 2 patients received treatment intensification. Despite that, these patients mostly had higher HbA1c value between (8.0% to ≥ 8.5%). large real-world observational study of 17493 type 2 diabetes

mellitus patients, found that treatment intensification was less likely the older the patient, and more likely the higher the first HbA1c value, up to an HbA1c threshold of 9% (37)

Clinical inertia, which is defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines, greater comorbidity, long duration of diabetes, aging, and higher use of oral hypoglycemic agents can be a key reason for uncontrolled hyperglycemia (38). it can be also applied for the failure of clinician to stop or reduce therapy no longer needed (reverse clinical inertia) (39).

A review found that clinical inertia can be occur at all stages of diabetes treatment. Medication non-adherence to glucose lowering medicines may range from 53% to 65% at 1 year, can be responsible for higher HbA1c values in about 23% of cases (40).

Our findings agreed with clinical guidelines for the treatment of older adults with Type 2 diabetes mellitus in which the HbA1c in those population should be up to 8.5% whenever appropriate, treatment intensification should be used at appropriate time with caution especially with elderly to avoid the risk of hypoglycemia and other adverse events (38).

Polypharmacy was also found associated with risk of potentially inappropriate medicines, with prevalence between 22.7% – 79% Beer's criteria and 48% using STOPP criteria. These results in agreement with previous reviews conducted in Europe and United States (41)(42)(43). Principle PIMs identified were similar to those found in previous reviews (43)(44).

The review did not found any association between polypharmacy and fall or fall risk only in one study. Previous review and large cohort study found that older adults with type 2 diabetes mellitus are associated with greater risk of falls, especially in insulin-treated patients, without measuring the impact of polypharmacy (45)(46).

Another large cohort study of type 2 diabetes mellitus found that using four or more (not a definition of polypharmacy in the study) can be associated increasing risk of fall, with no

specific glucose lowering drug involvement in fall risk. The study revaled that examining the relationship between medications and falls would benefit from using formal definition of polypharmacy and what mechanisms link polypharmacy to adverse events (47).

Even most of studies included in this review were of good quality, these studies are observational, and number of medications cannot be assigned to patients, since those who are on polypharmacy are associated with adverse health consequence more than those who are taking fewer medicines.

Therefore, risk of confounding, follow up, and sampling bias cannot be ignored and particularly important. However, other types of bias may be present. Presence of these biases result in apparent evidence of heterogeneity in the studies used in meta-analysis.

Because of concerns regarding confounding and complexity between polypharmacy and adverse health outcomes, it is more suggested to conduct randomized controlled trials that may provide more definitive solutions regarding to these issues.

The meta-analysis has several limitations; the quality of meta-analysis was affected by the quality of included studies. Firstly, studies used several definitions of polypharmacy and non-polypharmacy (for example: in non-polypharmacy definition, patients may be classified as using 4 or less, 5 or less, less than 13 medicines), based on the definition of polypharmacy.

The definition of polypharmacy that most studies used did not provide any information on duration, definition of number of medications and if non-prescription medicines were used. Moreover, information regarding all comorbid conditions and/or diabetes complications was not fully reported, also some studies were excluded patients had specific complications, and presence of other risk factors can also affect these associations.

The number of studies that involved in meta-analysis for assessment of overall effect of the association between polypharmacy and adverse health consequences in elderly with type 2 diabetes melllitus was low; this can be associated with several explanation, little information is available in the literature about such associations in those population, most of studies evaluated these adverse health consequences did not consider polypharmacy as risk factor.

Poor representation of elderly population in clinical trials, even they are more prone to adverse effects due to comorbidities and polypharmacy. Moreover, a few large prospective cohort studies seek to overcome these limitations from clinical trials which can be considered as representative of patients on polypharmacy, but they were limited by either small sample size or follow up periods.

In addition, studies weighted with high percentage were accounted for the overall effect of meta-analysis, as well as using of unadjusted estimates of risk of association with polypharmacy can exceeded the adjusted estimates. Many studies were excluded for this review because either reported exposure or outcome, were not of interest.

2.2.6 Conclusion

Distinguishing the potential risks of polypharmacy in elderly type 2 diabetes mellitus patients is clinically important. Our goal was to summarize the existing knowledge regarding this topic, which may reveal support for a statistical association between polypharmacy and several adverse health outcomes.

Polypharmacy has been and always will be common among those patients due to the need to control diabetes and other comorbid conditions. Unfortunately, with this increase in the use of multiple medicines may come with an increased risk for negative health outcomes. The results of this systematic review were mixed, with some studies demonstrated the association

between polypharmacy and adverse health consquences, and other studies failed to find this association.

This can raise the question of whether polypharmacy is solely a marker of inappropriate medicines use, and whether it is also a marker of underprescribing, which may lead to underuse of appropriate medicines, and increase the risk of adverse health consquences in those population, in addition to Multimorbidity, aging, scarcity of scientific evidence, risk of adverse events and economic issues (48).

Appropriate monitoring should be implemented, including necessary laboratory testing and patient education regarding how to monitor themselves for potential adverse events and what to do when they occur. Interventions designed for improvement of medication appropriateness, which includes a deprescribing, are generally effective at improving surrogate clinical markers, but the effect on long-term outcomes, such as mortality, is not well established.

Conflict of interest

All authors declare that there is no conflict of interests

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Supplementary data

Search Strategy

PubMed/Medline

Search	Query
#11	("medication errors"[MeSH Terms] OR ("medication"[All Fields] AND "errors"[All Fields]) OR "medication errors"[All Fields] OR ("medication"[All Fields] AND "error"[All Fields]) OR "medication error"[All Fields]) AND ("polypharmacy"[MeSH Terms] OR "polypharmacy"[All Fields]) AND "AND "[All Fields] AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "AND "[All Fields] AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields])
#10	"Falls"[All Fields] AND "Polypharmacy"[All Fields] AND "diabetes"[All Fields] AND "Elderly"[All Fields]
#9	"Potentially inappropriate medication"[All Fields] AND "Polypharmacy"[All Fields] AND "diabetes"[All Fields] AND "Elderly"[All Fields]
#8	Search Polypharmacy[Title] AND Diabetes[Title] AND type[Title] AND 2[Title] AND Medication[Title] AND Adherence[Title]
#7	Search (("Polypharmacy") AND "Diabetes type 2") AND "Hospitalization"
#6	Search (("Polypharmacy") AND "Diabetes type 2") AND "Adverse events" Schema: all
#5	Search (("Polypharmacy") AND "Diabetes type 2") AND "Adverse events"
#4	Search (("Polypharmacy") AND "Diabetes Type 2") AND "Drug-Drug Interactions Schema: all
#3	Search (("Polypharmacy") AND "Diabetes Type 2") AND "Drug-Drug Interactions
#2	Search Polypharmacy[Title] AND Diabetes[Title] AND Type[Title] AND 2[Title] AND Glycemic[Title] AND control[Title]
#1	Search (("Polypharmacy") AND "Diabetes Type 2") AND "Glycemic control"

Science Direct

"Polypharmacy" AND "Diabetes Type 2" AND "Glycemic Control" OR "Polypharmacy" AND "Diabetes" AND "Glycemic control" OR "Polypharmacy" AND "Diabetes Type 2" AND "Drug-Drug Interactions" OR "Polypharmacy" AND "Diabetes" AND "Drug-Drug Interactions" OR "Polypharmacy" AND "Diabetes Type 2" AND "Adverse event" OR "Polypharmacy" AND "Diabetes" AND "Adverse events" OR "Polypharmacy" AND "Diabetes" AND "Hospitalization" OR "Polypharmacy" AND "Diabetes Type 2" AND "Hospitalization" OR "Potentially inappropriate medication" AND "Polypharmacy" AND

"diabetes" AND "Elderly" OR "Falls" AND "Polypharmacy" AND "diabetes" AND "Elderly" OR "Medication Error AND "Polypharmacy" AND "diabetes" AND "Elderly".

Web of Science

TOPIC: ("Polypharmacy" AND "Diabetes" AND "Elderly" AND "Glycemic Control") Refined by: Open Access: (OPEN ACCESS), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC. TOPIC: (Polypharmacy AND Diabetes type 2 AND Glycemic Control), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

TOPIC: ("Polypharmacy" AND "Diabetes" AND "Elderly" AND "Drug-Drug Interactions") Refined by: Open Access: (OPEN ACCESS), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC. TOPIC: (Polypharmacy AND Diabetes type 2 AND Drug-Drug Interactions), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

TOPIC: ("Polypharmacy" AND "Diabetes" AND "Elderly" AND "Adverse Events"), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC. TOPIC: (Polypharmacy AND Diabetes type 2 AND adverse events), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

TOPIC: ("Polypharmacy" AND "Diabetes" AND "Elderly" AND "Hospitalization"), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC. TOPIC: (Polypharmacy AND Diabetes type 2 AND Hospitalization), Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

TOPIC: ("Potentially inappropriate medication" AND "Polypharmacy" AND "diabetes" AND "Elderly")Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

TOPIC: ("Falls" AND "Polypharmacy" AND "diabetes" AND "Elderly")Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC.

CHAPTER 2.3

POLYPHARMACY, POTENTIALLY SERIOUS CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS, AND INAPPROPRIATE MEDICINES IN ELDERLY PEOPLE WITH TYPE 2 DIABETES AND THEIR IMPACT ON QUALITY OF LIFE

2.3.1 Abstract

The aim of the study is to investigate the patterns of polypharmacy, clinical-relevant drug-drug interactions (DDIs) and potentially inappropriate medicines (PIMs), and whether polypharmacy, potential serious clinically-relevant DDIs or PIMs can be associated with low quality of life (QoL) index scores of older adults with type 2 diabetes (T2D). A cross-sectional study was conducted using data of 670 elderly T2D sub-cohort from a nationwide pharmacy-based intensive monitoring study of inception cohort of T2D in Portugal. 72.09% were found on polypharmacy (≥ 5 medicines). Participants on polypharmacy were mostly females (p=0.0115); more obese (p=0.0131); have more comorbid conditions (p<0.0001); more diabetes complications (p<0.0001); and use more of glucose lowering drugs (p=0.0326); insulin (p<0.0001);chronic medicines (p<0.0001); and have higher diabetes duration (p=0.0088) than those without polypharmacy. 10.59% of the participants found to have potential serious clinically relevant DDIs. The most frequent drug-combinations were angiotensin-converting enzyme (ACE) inhibitors with angiotensin-receptor blockers (ARBs), aspirin with Selective serotonin reuptake inhibitors (SSRIs) and clopidogrel with calcium channel blockers. PIMs found in 36.11% of the participants. The most common PIMs were benzodiazepines, long-acting sulfonylureas, and iron overdose. The adjusted multivariate models show that Polypharmacy and PIMs and potential serious clinically relevant DDIs were associated with lower QoL index scores (OR 1.80 95% CI 1.15-2.82) and (OR 1.57 95% CI 1.07-2.28), (OR 1.34 95% CI 0.73-2.48), respectively. The study shows that polypharmacy, potential serious clinical-relevant DDIs and PIMs may correlate with risk of reduced health related quality of life outcome of older adults with T2D.

2.3.2 Introduction

The prevalence of elderly people with type 2 diabetes (T2D) has been increasing globally. In 2018, it was estimated that there were more than 500 million people diagnosed with T2D (1), and more than half were elderly (2). Elderly people with T2D are at higher risk of polypharmacy as result of multimoridity and aging (3).

Polypharmacy can be associated with several unintended therapeutic outcomes such as increasing the incidence of potential serious drug-drug interactions (DDIs) that can be harmful and life-threatening and use of potentially inappropriate medicines (PIMs) (4,5,6,7). Despite that, there is a paucity in addressing the risk of potential clinicaly relevant serious DDIs and PIMs. Only one study found that at least one potential serious clinically relevant DDIs was found (7.10%)[8], and two studies found that the prevalence of PIMs was found between (22.70%-68.10%) (9,10). Moreover, there is a lack of evidence on whether the presence of polypharmacy and its consequences can impact quality of life (QoL).

Therefore, the aims of this study was to investigate the patterns of polypharmacy, clinical-relevant drug-drug interactions (DDIs) and potentially inappropriate medicines (PIMs), and whether polypharmacy, potential serious clinically-relevant DDIs or PIMs can be associated with low QoL index scores of older adults with T2D.

2.3.3 Methods

A cross-sectional study was conducted using the baseline data of elderly (aged 65 years or more) cohort from a nationwide pharmacy-based intensive monitoring study of inception cohort of T2D patients using the recently launched glucose lowering drugs (GLDs). Pharmacists and participants recruitment procedures have been described in detailed elsewhere (11). Invitation letters were sent to all pharmacies from the National Association of Pharmacies that satisfied the inclusion criteria. The pharmacists who agreed to participate were invited to attend a training session in which the study was explained.

The eligible study population consisted of first users of the new GLD (defined as users who did not take the inception-monitored drug within the 6 months prior to recruitment, as self-reported by the patients) that were that were reimbursed in Portugal at the time of enrollment: dipeptidyl peptidase-4 inhibitor (DPP-4) alone or in fixed-dose combination with metformin, glucagon like peptide 1 receptor agonists (GLP-1 ra) or sodium-glucose transport protein 2 (SLGT-2). In this context, the inception drug corresponded to the GLD within the monitored therapeutic classes (DPP-4, GLP-1 ra or SLGT-2) which the patient was identified with at cohort entry.

The cohort was divided into two subgroups according to participants' T2D treatment experience: incident new users; participants who were using one of the monitored drugs for the first time and had no current or prior experience with DPP-4, GLP-1 ra or SGLT2 and prevalent new users; participants who had previously used or were still using least one drug of the monitored treatment classes: DPP-4, GLP-1 ra or SGLT2, but not the inception GLD.

At recruitment, participants had a structured face-to-face interview with a trained pharmacist to collect the sociodemographic data (birth date, gender, highest educational level completed, co-residence status, and number of people living in the subject's household), anthropometric (weight and height were measured by pharmacy staff to calculate the body mass index (BMI)) which categorized as (underweight < 18.50 Kg/m^2), (normal: 18.50-24.99 Kg/m^2), (overweight: 25.00-29.99 Kg/m^2) and (obese: ≥30 Kg/m^2). Self-reported data was collected on clinical characteristics (age at time of T2D diagnosis, clinical care setting), T2D treatment, T2D related complications, co-morbidities, and concomitant therapy.

Data Analysis

Study participants were divided into two subgroups according to the presence or absence of polypharmacy. Polypharmacy was defined as the use of five or more medicines, which is the most widely accepted definition in the literature (12).

The medicines used were checked for the DDIs using IBM Micromedex Platform (IBM® Corporation, 2019) (13). This platform classify them according to their severity as: ***contraindicated***-the drugs are contraindicated for concurrent use; ***major*** interaction potential life-threatening and/or requiring medical intervention to minimize or prevent serious adverse effects; ***moderate*** interaction - may result in exacerbation of the patient's condition and/or require an alteration in therapy; and ***minor*** interaction-would have limited clinical effects, and generally would not require a major alteration in therapy. Micromedex platform also addresses the potential adverse effect of the interaction, mechanism of the interaction, onset of the interaction, rate of scientific evidence (Excellent/Good/Fair/Unknown), and the proposed clinical management of the interaction.

We defined potentially serious clinically relevant DDIs as those having a severity of ***major*** drug-drug interaction or when the drug combination is ***contraindicated*** with scientific evidence rating of ***excellent*** (defined as controlled studies that have clearly established the existence of the interaction) according to Micromedex. PIMs were identified using STOPP criteria version 2, the final list included 80 STOPP criteria, was agreed after two rounds of Delphi validation, which arranged according to the physiological systems of the body for ease of use and rapid application (14). In terms of predictive validity, it modestly discriminates for outcomes such as adverse drug events, emergency department visits, and hospital admissions. The STOPP criteria version 2 has a high sensitivity in detecting PIMs and good inter-rater reliability (15,16,17).

The QoL was measured using the three-level EuroQol five-dimensional (EuroQol 5-D-3L) questionnaire. The EQ-5D encompass five dimensions influencing health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each with three levels of functioning (first level; no problem, second level; some problems, third level; severe problems). The summary scores was computed to Portuguese preference weighted EQ-5D index scores using Portuguese values set (18). After that, the study participants finished the EQ-5D visual analogue scale (VAS). In the VAS, the patients evaluated their current health state on scale between **zero** (worst

possible health state) to **one hundred** (best possible health state), the high scores index together high VAS suggest best health state (19).

Statistical Analysis

A database was created including information on socio-demographic characteristics, comorbidities, and prescribed medicines including both T2D and other chronic medicines, potential (contraindication, serious, moderate, and minor) DDIs, and PIMs. Data were described as absolute and relative counts and means (± standard deviation).

A multivariate binary logistic regression model to assess the adjusted associations between polypharmacy, potential serious clinically relevant DDIs, potentially inappropriate medicines and lower quality of life scores. Based on Portuguese elderly population preferences, mean index score of QoL was considered 0.60 as cutoff value (20). Results of this analysis were presented as adjusted odds ratios (ORs) and their respective 95% confidence intervals (CIs). Data analysis was performed using SAS® software.

2.3.4 Results

Characteristics of Study Population

Of the 1328 adults with T2D recruited in the original cohort, 670 were elderly people with T2D included in the current study. Of these, 483 (72.09%) were on polypharmacy. Among those on polypharmacy, 75.57% (n=365) and 24.43% (n=118) were using 5-9 and ≥10 different medicines, respectively. Participants on polypharmacy were significantly more females (p=0.0115), more obese (p=0.0131), had a higher duration of diabetes (p=0.0088), more comorbid conditions (p<0.0001), more diabetes complications (p<0.0001), using more GLDs treatment (p=0.0326), insulin use (p<0.0001), and more chronic medicines (p<0.0001) compared to those without polypharmacy (Table 1).

Table 1 Descriptive characteristics of study population according to polypharmacy

Characteristics	Total sample (N=670)	T2D on Polypharmacy (N=483)	T2D Not on Polypharmacy (N=187)	*P* value
Gender M/F (%)	338/332 (50.45/49.55)	229/254 (47.41/52.59)	109/78 (58.29/41.71)	P=0.0115
Age (Mean ± SD)	73.01 ± 6.22	73.21 ± 6.22	72.50 ± 6.22	P=0.2606
65-74 (%)	432 (64.48)	303 (62.73)	129 (68.99)	
75-84 (%)	203 (30.30)	152 (31.47)	51 (27.27)	
≥ 85 (%)	35 (5.22)	28 (5.80)	7 (3.74)	
BMI (%)				P=0.0131
Underweight (< 18.5 kg/m²)	2 (0.29)	2 (0.41)	0 (0)	
Normal (18.5 – 24.99 Kg/m²)	108 (16.12)	77 (15.94)	31 (16.58)	
Pre-obese (25 – 29.99 Kg/m²)	277 (41.34)	185 (38.30)	92 (49.20)	
Obese (≥ 30 K/m²)	265 (39.55)	207 (42.86)	58 (31.02)	
	NR = (18)	NR = (12)	NR = (6)	
Educational Level (%)				P=0.7507
No Education	128 (19.10)	95 (19.67)	33 (17.65)	
Primary (1-9 Years)	425 (63.43)	304 (62.94)	121 (64.71)	
Secondary (10-12 Years)	54 (8.06)	42 (8.70)	12 (6.42)	
Superior (> 12 Years)	41 (6.12)	29 (6)	12 (6.42)	
	NR = (22)	NR= (13)	NR= (9)	
Occupation (%)				P=0.9262
Employed	21 (3.13)	16 (3.31)	5 (1.04)	
Unemployed	4 (0.60)	3 (0.62)	1 (0.53)	
Retired	605 (90.29)	434 (89.86)	171 (91.44)	
Domestic	37 (5.52)	28 (5.80)	9 (4.81)	
	NR = (3)	NR= (2)	NR= (1)	
Living alone				P=0.5906
Yes	135 (20.14)	100 (20.70)	35 (18.71)	
No	531 (79.25)	381 (78.88)	150 (80.21)	
	NR = (4)	NR= (2)	NR= (2)	
Duration of Diabetes (%)				P=0.0088
Less than one year	57 (8.50)	34 (7.04)	23 (12.30)	
≥1-<3 years	52 (7.76)	32 (6.63)	20 (10.70)	
≥3-<6 years	85 (12.68)	64 (13.25)	21 (11.23)	
≥6-<10 years	77 (11.49)	54 (11.18)	23 (12.30)	
≥10 years	348 (51.94)	272 (56.31)	76 (40.64)	
	NR = (44)	NR = (20)	NR = (24)	
Healthcare Setting (%)				P=0.1821
Primary Care	469 (70.00)	331 (68.53)	138 (73.80)	
Non-Primary care	201 (30.00)	152 (31.47)	49 (26.20)	
Comorbidities (%)				P<0.0001
Yes	629 (93.88)	470 (97.31)	159 (85.03)	
No	41 (6.12)	13 (2.69)	28 (14.97)	
Comorbid conditions (%)				
Hypertension	531 (79.25)	409 (84.68)	122 (65.24)	P<0.0001
Renal Failure	72 (10.74)	63 (13.04)	9 (4.81)	P=0.0200
Heart Failure	125 (18.65)	108 (22.36)	17 (3.52)	P<0.0001
Dyslipidaemia	398 (59.40)	326 (67.49)	72 (14.91)	P<0.0001
Thyroid gland	24 (3.58)	21 (4.35)	3 (1.60)	P=0.0865
Respiratory system	25 (3.73)	21 (4.35)	4 (2.14)	P=0.1760
Digestive system	31 (4.62)	27 (14.44)	4 (2.14)	P=0.0565
Musculoskeletal system	19 (2.83)	17 (3.52)	2 (1.07)	P=0.0866
Prostate hyperplasia	21 (3.13), NR = (332)	13 (2.69); NR= (254)	8 (4.28); NR= (78)	P=0.5539
Neoplasms	23 (3.43)	14 (2.90)	9 (4.81)	P=0.2222
Depression	11 (1.64)	7 (1.45)	4 (2.14)	P=0.5286
Hyperuricemia	16 (2.38)	15 (3.11)	1 (0.53)	P=0.0506
Other	79 (11.79)	67 (13.87)	12 (6.42)	P=0.0073
Diabetes Complications (%)				P<0.0001
Yes	179 (26.71)	151 (31.26)	28 (14.97)	
No	482 (71.94)	326 (67.49)	156 (83.42)	
	NR = (9)	NR = (6)	(NR = 3)	
Retinopathy (%)	120 (17.91)	103 (21.33)	17 (9.09)	P=0.0002
Nephropathy (%)	74 (11.04)	65 (13.46)	9 (4.81)	P=0.0014
Diabetic Foot (%)	39 (5.82)	35 (7.25)	4 (2.14)	P=0.0116
Diabetes Medicines (%)				
Oral GLD treatment	670 (100)	483 (100)	187 (100)	P=0.0326

Insulin	**117 (17.46)**	**106 (21.95)**	**11 (5.88)**	**P<0.0001**
Chronic Medicines (%)				**P<0.0001**
Yes	**458 (68.35)**	**365 (75.57)**	**93 (49.73)**	
No	**193 (28.80), NR = (19)**	**118 (24.43)**	**75 (40.11); NR= (19)**	
Renin-angiotensin system medicines	**458 (68.35)**	**365 (75.57)**	**93 (49.73)**	**P<0.0001**
Beta-blocking agents	**173 (25.28)**	**161 (33.33)**	**12 (6.42); NR= (19)**	**P<0.0001**
Diuretics	**172 (25.67)**	**160 (33.13)**	**12 (6.42); NR= (19)**	**P<0.0001**
Calcium channel blockers	**144 (21.49)**	**130 (26.92)**	**14 (7.49); NR= (19)**	**P<0.0001**
Lipid lowering medicines	**398 (59.40)**	**343 (71.01)**	**55 (29.41)**	**P<0.0001**
Anti-thrombotic	**259 (38.65)**	**239 (49.48)**	**20 (10.70); NR= (19)**	**P<0.0001**
Acid related disorders medicines	**212 (31.64)**	**196 (40.58)**	**16 (8.56); NR= (19)**	**P<0.0001**
Psycholeptics	**167 (24.92)**	**153 (31.68)**	**14 (7.49); NR= (19)**	**P<0.0001**
Psychoanaleptics	**114 (17.01)**	**102 (21.12)**	**12 (6.42); NR= (19)**	**P<0.0001**
Potentially serious clinically relevant drug-drug interactions	**71 (10.59)**	**70 (14.49)**	**1 (0.53)**	**P<0.00001**
Potentially inappropriate medicines	**242 (36.11)**	**219 (45.34)**	**23 (12.30)**	**P<0.00001**

BMI body mass index; N.R. non-respondents to the questionnaire in the original study; GLD: glucose lowering drugs, these includes: Gliptins (either alone or in combination), GLP-1 agonists, SGLT2-inhbitors, or any combination of any two diabetes study medicines.

Identification of potentially serious clinically relevant DDIs

Of 670 elderly adults with T2D, 71 (10.59% of total cohort) had potential serious clinically relevant DDIs. Among the most frequent drug-combinations that contributed to potential serious clinically relevant DDIs were angiotensin-converting enzyme (ACE) inhibitors with angiotensin-receptor blockers (ARBs) (24.71%), aspirin with selective serotonin reuptake inhibitors (SSRIs) (19.10%) and clopidogrel with calcium channel blockers (13.84%) (Figure 1). The full description of these DDIs presented in (Table 2).

Figure 1 The prevalence of drug combinations that contributed to the potentially serious clinically relevant drug-drug interactions

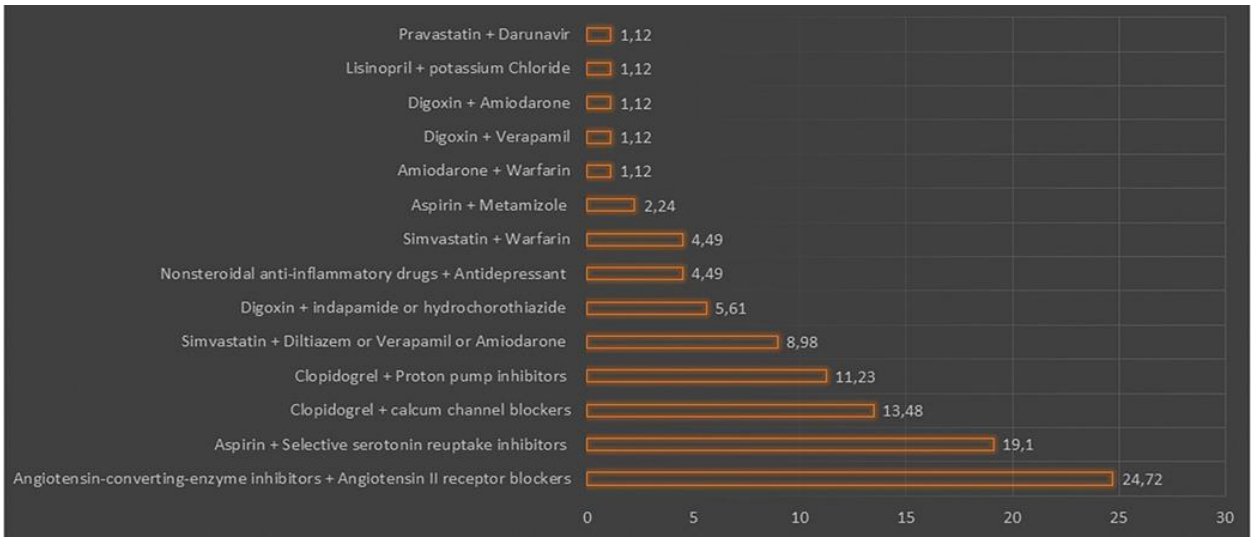

Table 2 Description and frequency of potential serious clinically relevant drug-drug interactions

Drug\medicines class	Drug\medicines class	Potential adverse effect	Mechanism	Onset	N (%)
ACE inhibitors[1] (C09AA)	ARBs (C09CA)[2]	Risk of Hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure	dual blockade of the renin-angiotensin-aldosterone system	Out specified	22 (24.71)
Aspirin (B01AC06)	Selective serotonin reuptake (SSRIs) inhibitors (N06A)	Risk of bleeding	depletion of platelet serotonin by SSRI; additive effects	Not specified	17 (19.10)
Clopidogrel (B01AC04)	Dihydropyridine derivatives (C08CA), SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS (C08D)	Risk of decreased antiplatelet effect and increased risk of thrombotic events	inhibition of CYP3A-mediated clopidogrel activation	Not specified	12 (13.48)
Clopidogrel (B01AC04)	Proton pump inhibitors (A02BC)	Risk of reduced antiplatelet activity	decreased inhibition of platelet aggregation of clopidogrel by PPIs	Rapid	10 (11.23)
Simvastatin (C10AA01)	Diltiazem (C08DB01), Verapamil (C08DA01) Amiodarone (C01BD01)	increased risk of myopathy, including rhabdomyolysis	inhibition of CYP3A4-mediated simvastatin metabolism	Rapid	8 (8.98)
Digoxin (C01AA05)	Hydrochlorothiazide (C03AA03), indapamide (C03BA11)	Risk of digitalis toxicity (nausea, vomiting, arrhythmias)	diuretic-induced hypokalemia and hypomagnesemia enhance Na-K-ATPase inhibition by cardiac glycosides	Delayed	5 (5.61)
NSAIDs (M01A)[3]	Antidepressant (N06A)	increased risk of bleeding	Unknow	Not specified	4 (4.49)
Simvastatin (C10AA01)	Warfarin (B01AA03)	increased risk of bleeding and an increased risk of rhabdomyolysis	competition for cytochrome P450 3A4-mediated metabolism	Delayed	4 (4.49)
Aspirin (B01AC06)	Metamizole (N02BB02)	Risk of reduced efficacy of aspirin	attenuated antiplatelet effect of aspirin	Not specified	2 (2.24)
Amiodarone (C01BD01)	Warfarin (B01AA03)	increased INR and an increased risk of bleeding	increased exposure to warfarin	Delayed	1 (1.12)
Digoxin (C01AA05)	Verapamil (C08DA01)	increased serum digoxin concentrations, risk of digitalis toxicity and increased risk of complete heart block	inhibition of renal and/or extrarenal digoxin clearance; additive effects on AV node conduction	Rapid	1 (1.12)
Digoxin (C01AA05)	Amiodarone (C01BD01)	result in digoxin toxicity and potentiated effects of amiodarone	inhibition of p-glycoprotein by amiodarone, and reduction of digoxin clearance; interference with amiodarone by digoxin	Not specified	1 (1.12)
Lisinopril (C09AA03)	Potassium chloride (A12BA01)	Risk of hyperkalemia	lowered aldosterone levels	Delayed	1 (1.12)
Pravastatin (C10AA03)	Darunavir (J05AE10)	increased exposure to pravastatin	inhibition of CYP3A-mediated pravastatin metabolism by darunavir	Not specified	1 (1.12)

1 angiotensin converting enzyme inhibitors; 2 angiotensin receptor blockers, 3 non-steroidal anti-inflammatory drugs

Identification of potentially inappropriate medicines

Of the study cohort, 242 (36.11%) had at least one PIMs. Of these, 176 (72.72%) had one PIM, 49 (20.24%) had two PIMs, and 17 had more than two PIMs (7.02%). The mean of PIMs was (1.36 ± 0.78) per patient. The most prevalent PIMs were benzodiazepines (43.50%), long-acting sulfonylureas, glibenclamide or glimepiride (9.37%), and higher dose of iron supplements (4.83%) (Figure 2). The full description of potentially inappropriate medicines presented in (Table 3).

Figure 2 The prevalence of potentially inappropriate medicines according to organ system or medicines class

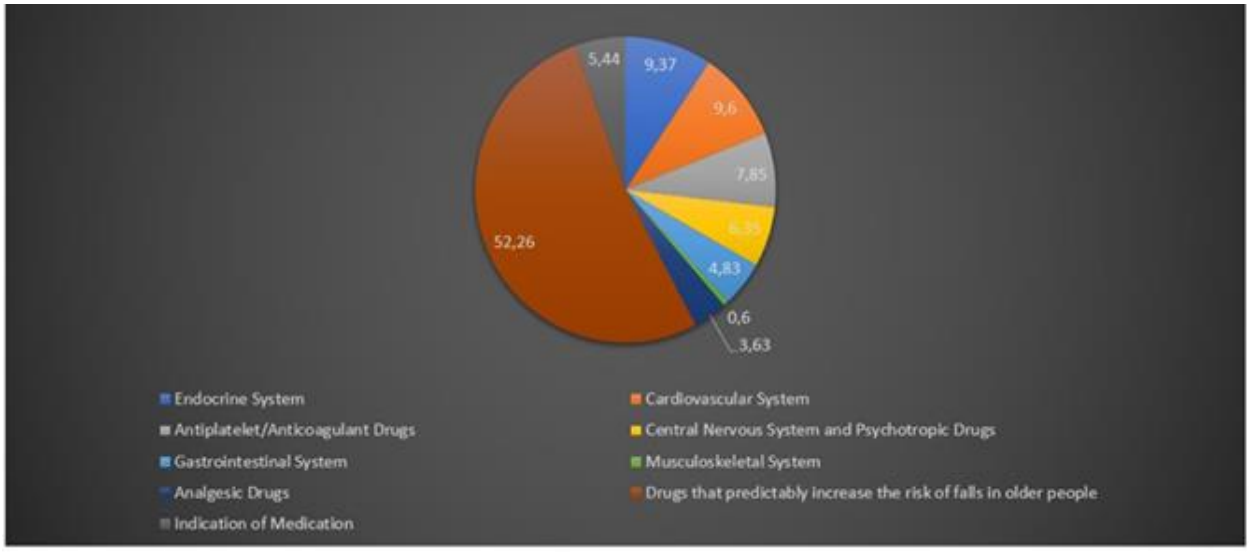

Table 3 Description and frequency of potentially inappropriate medicines detected in the study using STOPP criteria

Section	STOPP Criteria	N (%)
Endocrine System	Sulphonylureas with a long duration of action with type 2 diabetes mellitus	31 (9.37)
Cardiovascular System	Using of Centrally acting antihypertensives	15 (4.53)
	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	10 (3.02)
	Loop diuretic as first-line treatment for hypertension	5 (1.51)
	Beta-blocker in combination with verapamil or diltiazem	1 (0.30)
	Verapamil or diltiazem with NYHA[1] Class III or IV heart failure	1 (0.30)
Antiplatelet/Anticoagulant Drugs	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease	2 (0.60)
	Long-term aspirin at doses greater than 160mg per day	8 (2.42)
	NSAID[2] and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	5 (1.51)
	NSAID[2] with concurrent antiplatelet agent(s) without PPI[3] prophylaxis	5 (1.51)
	The use of Ticlopidine	6 (1.81)
Central Nervous System	Initiation of Tricyclic Antidepressants (TCAs) as first-line antidepressant treatment	12 (3.63)

and Psychotropic Drugs	**Use of first-generation antihistamines**	**9 (2.72)**
Gastrointestinal System	**Oral elemental iron doses greater than 200 mg daily**	**16 (4.83)**
Musculoskeletal System	**COX-2 selective NSAIDs with concurrent cardiovascular disease**	**2 (0.60)**
Analgesic Drugs	**Use of oral or transdermal strong opioids**	**12 (3.63)**
Drugs that predictably increase the risk of falls in older people	**Benzodiazepines**	**144 (43.50)**
	Hypnotic Z-drugs e.g., zopiclone, zolpidem, zaleplon	**13 (3.93)**
	Neuroleptic drugs	**16 (4.83)**
Indication of Medication	**Duplication drug class prescription**	**18 (5.44)**
	Total	**331**

1 New York Heart Association Functional Classification; 2 Non-steroidal anti-inflammatory drugs; 3 proton pump inhibitors

Quality of life

Elderly patients with T2D in the study who were on polypharmacy have some to more severe problems in mobility (p=0.0004), usual activity (p=0.0001), personal care (p=0.0001), pain (0.0007), and anxiety and depression (p=0.0365), low mean VAS score (63.19±21.24 vs. 69.30±19.97, p<0.0001) and low mean index score (0.58±0.32 vs. 0.72±0.24, p<0.0001), compared with those not on polypharmacy. The elderly people with T2D with potential serious clinically relevant DDI have less problems in all EuroQol 5-D-3L dimensions, but with low mean VAS score (62.00±20.56 vs. 65.16±21.11, p=0.3466) and low index score (0.54±0.37 vs. 0.63±0.29, p=0.0637) compared with those without potential serious clinically relevant DDIs. Elderly people with T2D with at least one PIM have some to severe problems in mobility (p=0.0346), and pain (p=0.0031), with low mean VAS score (62.32±21.89 vs. 66.33±20.45, p=0.0387) and low mean index score (0.57±0.30 vs. 0.65±0.30, p=0.0003) compared with those without any PIM (Table 4).

Table 4 Descriptive analysis of patients with\without polypharmacy, with\without potential clinically relevant drug interactions and with\without potentially inappropriate medicines according to their EuroQol 5-D-3L

Patient Classification	Mobility [1]			Personal care[2]			Usual activity[3]			Pain[4]			Anxiety and depression[5]			VAS[6] score (mean ±SD)	Index score (mean ± SD)
	No problem	Some problems	Severe problems	No problem	Some problems	Severe problems	No problem	Some problems	Severe problems	No problem	Some problems	Severe problems	No problem	Some problems	Severe problems		
Polypharmacy	231 (35.59)	229 (35.29)	9 (1.39)	375 (57.78)	69 (10.63)	25 (3.85)	299 (46.07)	128 (19.72)	42 (6.47)	225 (34.72)	195 (30.09)	48 (7.41)	266 (41.24)	157 (24.34)	44 (6.82)	63.19 ± 21.24	0.58± 0.32
no polypharmacy	122 (18.80)	55 (8.47)	3 (0.46)	166 (25.58)	7 (1.08)	7 (1.08)	145 (22.34)	29 (4.47)	6 (0.92)	108 (16.67)	68 (10.49)	4 (0.62)	107 (16.59)	65 (10.08)	6 (0.93)	69.30 ± 19.97	0.72± 0.24
P value	0.0001			0.0004			0.0001			0.0007			0.0365			<0.0001	<0.0001
Potentially Serious clinically relevant DDIs	29 (4.47)	34 (5.24)	2 (0.31)	50 (7.70)	8 (1.23)	7 (1.08)	39 (6.01)	17 (2.62)	9 (1.39)	32 (4.94)	25 (3.86)	8 (1.23)	38 (5.89)	20 (3.10)	7 (1.09)	62.00 ± 20.56	0.54 ± 0.37
No Potentially serious clinically relevant DDIs	324 (49.92)	250 (38.52)	10 (1.54)	491 (75.65)	68 (10.48)	25 (3.85)	405 (62.40)	140 (21.57)	39 (6.01)	301 (46.45)	238 (36.73)	44 (6.79)	335 (51.94)	202 (31.32)	43 (6.67)	65.16 ± 21.11	0.63 ± 0.29
P value	0.2161			0.0681			0.0852			0.4071			0.5673			0.3466	0.0657
PIM	112 (17.26)	118 (18.18)	5 (0.77)	187 (28.81)	36 (5.55)	12 (1.85)	147 (22.65)	68 (10.48)	20 (3.08)	101 (15.59)	107 (16.51)	26 (4.01)	129 (20.00)	81 (12.56)	23 (3.57)	62.32 ± 21.89	0.57 ± 0.30
No PIM	241 (37.13)	166 (25.58)	7 (1.08)	354 (54.55)	40 (6.16)	20 (3.08)	297 (45.76)	89 (13.71)	28 (4.31)	232 (35.80)	156 (24.07)	26 (4.01)	244 (37.83)	141 (21.86)	27 (4.19)	66.33 ± 20.45	0.65 ± 0.30
P value	0.0346			0.0929			0.0524			0.0031			0.2852			0.0387	0.0003

1-number of non-respondents = 21, 2-number of non-respondents =21, 3-number of non-respondents for =21, 4-number of non-respondents =22, 5-number of non-respondents=25, 6-number of non-respondents for=88.

On the adjusted multivariate analysis, polypharmacy, potential serious clinically relevant DDIs and potentially inappropriate medicines were associated with lower index scores (OR 1.80 95% CI 1.15-2.82), (OR 1.34 95% CI 0.73-2.48) and (OR 1.57 95% CI 1.07-2.28), respectively (Table 5)

Table 5 Results of adjusted multivariate models analyzing polypharmacy with QoL, potential serious clinically relevant drug-drug interactions and potentially inappropriate medicines with QoL

Model 1			Model 2			Model 3		
Parameter	**OR**	**95% CI**	**Parameter**	**OR**	**95% CI**	**Parameter**	**OR**	**95% CI**
Polypharmacy	1.80	1.15-2.82	**Potential serious clinically relevant DDIs**	1.34	0.73-2.48	**PIM[1]**	1.57	1.07-2.28
Male	0.47	0.32-0.68	**Male**	0.45	0.31-0.66	**Male**	0.47	0.33-0.69
Age (74-85)	1.63	1.08-2.47	**Age (74-85)**	1.66	1.10-2.50	**Age (74-85)**	1.66	1.10-2.52
Obesity	1.89	1.09-3.27	**Obesity**	1.92	1.11-3.32	**Obesity**	1.97	1.14-3.41
Chronic conditions	3.44	1.24-9.58	**Chronic conditions**	4.25	1.56-11.59	**Chronic conditions**	4.04	1.47-11.09
Complications	2.06	1.34-3.16	**Complications**	2.14	1.40-3.28	**Complications**	2.18	1.42-3.35

1 potentially inappropriate medicine

2.3.5 Discussion

This study show high prevalence of polypharmacy in a cohort of elderly people with T2D when comparing to other countries such as Sweden (56.70%) (21), Italy (57.10%) (22), and Greece (22.50%) (23). This can be explained by a higher overall prevalence of polypharmacy in older population with chronic diseases in Portugal (24). Polypharmacy was more prevalent in the elderly women with T2D. this finding was reported in previously studies (25,26,27). It can be explained that women tend to be more concerned about their health and seek health services more often (27). Obesity was associated with polypharmacy, a finding also in agreement with pre-existing literature (22,28), which could be due to the presence of multimorbid conditions (28,29).

Duration of diabetes, presence of comorbid conditions and diabetes complications were associated with polypharmacy. T2D itself with wide array of comorbidities such as hypertension, dyslipidaemia and heart failure, in addition to renal complications can increases the chance of multiple medicines use (30).

10.59% of the study cohort were found to have potentially serious clinically relevant DDIs, which considered higher than previously reported (7.10%) (8). However, a direct comparison is unattainable due to the differences in comorbid conditions and medicines prescribed and different platforms used for assessing DDIs. These harmful potential interactions may result in increased risk of thrombotic events from decreased antiplatelet effect or bleeding, followed by hypotension or renal failure from cardiovascular medicines, myopathy with statin therapy and increased digoxin concentrations causing risk of toxicity.

Our results were different from previously reported study by *Dumbreck and colleagues* whom selected three clinical guidelines produced by the National Institute for Health and Care Excellence (NICE) including T2D, and systematically looked for potentially serious drug-drug interactions in relation to another 11 NICE guidelines found that the most common category was cardiovascular related harm such as significant hypotension or bradycardia, followed by increased lithium or digoxin concentrations causing risk of toxicity, myopathy with statin treatment, and renal or serum potassium associated harms (31).

The most common medicines class combinations involved in potential serious clinically relevant DDIs were ACE inhibitors and ARBs. Prescribers seem to be less aware of the risk from this combination, as it counts for more than (24%) of the total potential serious clinically relevant DDIs. Both (VALIANT) and (ONTARGET) trials revealed that concurrent use of both ACE inhibitors and ARBs was not associated with reduce the risk of death from cardiovascular causes, myocardial infarction, stroke or hospitalization from heart failure but had significantly increased risk of hypotension, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of renal dysfunction requiring dialysis (32,33).

Clopidogrel was the most prevalent interacting medicine involved in potential serious clinically relevant DDIs (24.71%). This can be explained by higher prevalence of heart diseases and use of antiplatelet agents. Concurrent use of clopidogrel and proton pump inhibitors may be associated with high-risk of thrombotic events. A recent meta-analysis found that this

combination associated with increased in composite major adverse cardiac events which is a composite outcome typically comprised of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (HR 1.28; 95% CI 1.24–1.32), myocardial infarction (HR 1.51; 95% CI 1.40–1.62) and stroke (HR 1.46; 95% CI 1.15–1.86) (34).

Interaction between calcium channel blockers and clopidogrel can be also associated with reduced clopidogrel effect. Nevertheless, there are controversies in the literature, since some studies found a reduction in the effect of clopidogrel with this combination (35,36), and other studies could not establish any evidence of reduction in the anti-platelet activity of clopidogrel (37,38).

The prevalence of PIMs was found 36.11%. This finding is in agreement with previous studies (22.70-68.10%) (9,10). Comparing to the literature, our findings show high prevalence of benzodiazepines use (43.50% vs 5.9%-14.80%) (9,10).

Benzodiazepines are associated with a higher risk of falls in older adults (39), A study conducted in Ireland found that, the use of benzodiazepines was associated with serious falls when coupled with polypharmacy (adjusted relative risk (aRR) 1.40, 95% CI 1.04–1.87), and associated with a greater number of falls (adjusted incident rate ratio (aIRR) 1.32, 95% CI 1.05–1.65), independent of polypharmacy (40).

The use of long-acting sulfonylureas was the 2nd major PIMs (9.37%) reported. Previous study found that the use of these long-acting sulfonylureas was associated with increased risk of hip fracture (aOR 1.46, 95 % CI 1.17–1.82) and the risk become higher in those with documented hypoglycemia (aOR 2.42, 95 % CI 1.35–4.34) (41). The use of higher doses of oral elemental iron was also reported in the study (4.83%), which can be associated with abdominal discomfort, nausea, vomiting, changes in bowel movements, and black stools (42).

The study revealed that polypharmacy (using 5 or more medicines) was associated with increased risk of low quality of life. A study in Spain of elderly population (52.50% of them with T2D) found that the of poor quality of life was only associated when polypharmacy defined as the use of 10 or more medicines (43). In addition, the study found that the presence of at least

one potentially inappropriate medicine, and potential clinically relevant DDIs can be associated with increasing the risk of poor health related quality of life in elderly with T2D. To the best of our knowledge, these results have not previously been reported.

Previous study by *Antonio De Vincentis and colleagues* found that only polypharmacy which considered as simple measure surpass PIM and DDI indicators of quality of therapy as it correlate of primary clinical outcomes, that are mortality and rehospitalization (44)

Some limitations were present in the study. Presence of information bias which characterized by inaccuracy of exact comorbid condition diagnosis and data regarding lab results (e.g. estimated glomerular filtration rate) were not reported. The data analysed in the present study were baseline data, and we do not know if the patients were really consumed all dispensed medicines.

The drug-drug interactions found in this study were only potential; in other words, no actual outcomes or consequences were evaluated. Finally, due to the nature of the cross-sectional design, we could not have the opportunity to explore the impact of polypharmacy on symptoms burden or quality of life over time.

This study reveals that polypharmacy is common and highly prevalent in cohort of elderly people with T2D, which can be due to disease burden and presence of multimorbid conditions.

The prevalence of potential serious clinically relevant DDIs are relatively low and the medicines concerned are few. The monitoring of patients treated with clopidogrel and other cardiovascular medicines should be improved. Great attention should be considered while prescribing two different class of cardiovascular medicines with synergism effect that could have potential impact renal function and electrolyte balance, especially in elderly. Precise and updated information on interacting drugs could prevent the occurrence of known interactions, particularly when therapeutic alternatives exist.

Defining the clinical relevance of a DDI is extremely important due to the presence of thousands of theoretically potential DDIs. High-quality evidence to support the existence of many DDIs is required, which can be established through real-world observational studies.
STOPP criteria represent the more common avoidable instances of inappropriate prescribing in older people in day-to-day clinical practice. Based on our results, risk of fall, fracture or fracture risk, hypoglycemia and even gastrointestinal side effects can be avoided if prescribers assessed appropriately those elderly patients' medicines use.

The selection and use of PIM criteria for research or practice should take into consideration considered the circumstances and requirements for each case as the relationships with outcomes can be different substantially between tools (45)

One of the challenges facing healthcare professionals is that the actual harms of both drug-drug interactions and potentially inappropriate medicines which are poorly quantified in real-world populations in which people are typically older, frail, have more comorbid conditions and receiving more medicines. Future studies should have the ability to explore the influence of possible adverse drug events as results of drug-drug interactions and potentially inappropriate medicines due to polypharmacy on elderly with T2D and the impact on quality of life over time in real-world.

2.3.6 Conclusions

The use of polypharmacy is highly prevalent among cohort of elderly people with T2D. This population is at higher risk of potential serious clinically relevant DDIs and PIMs as result of polypharmacy. The prevalence of potential serious clinically relevant DDIs found relatively low and can be associated with increased risk of poorer quality of life, like polypharmacy and potentially inappropriate medicines. Prospective studies are required to observe the clinical outcomes of the potential serious clinically relevant DDIs and presence of PIMs in real-world clinical practice. Health Interventions including pharmacist's medication use review and deprescribing strategies may help to improve patient-centered outcomes.

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CHAPTER 2.4

DRUG-DRUG INTERACTIONS AND INAPPROPRIATE MEDICINES IMPACT ON GLYCEMIC CONTROL AND KIDNEY FUNCTION IN OLDER ADULTS WITH DIABETES ATTENDING SPECIALTY CARE INSTITUTION

2.4.1 Abstract

Purpose to describe and assess the impact of polypharmacy, and its potential adverse reactions; serious clinically-relevant drug-drug interactions (DDIs) and inappropriate medicines (PIMs) on glycemic target, and kidney function in a sample of older adults with type 2 diabetes (T2D)

Methods cross-sectional study was performed in a real-world database included 444 elderly people with T2D from the Portuguese Diabetes Association, aged ≥ 65 years, and registered in 2018. DDIs were analyzed using Micromedex drug-interaction platform and PIMs identified using STOPP criteria version-2

Results polypharmacy was identified in 43.6% of patients. This group of patients shown to be more females (50% vs.39.6%, P=0.0208), higher HbA1c targets (P=0.0275), longer diabetes duration (66.4% vs.54.4%, P=0.0019), more hypertensive (87% vs.62.9%, P<0.0001), using more insulin (38.1% vs.26%, P=0.0062), sulfonylureas (37.1% vs.15.6%, P<0.0001), GLP-1 receptor-agonists (9.7% vs.3.6%, P=0.0077), metformin-DPP-4 inhibitors (41.2% vs.29.2%, P=0.0081), and SGLT2 inhibitors (19% vs.9.6%, P=0.0040)

8.7% of patients had potentially serious clinically-relevant DDIs, mainly due to interacting medicine pairs dexamethasone and fluoroquinolones. Furthermore, 23.4% had PIMs, and cardiovascular medicines accounted for largest therapeutic group associated. Polypharmacy found to be associated with two-fold greater odds of having HbA1c ≤8%. Whereas PIMs associated with 2.5-fold greater odds of having HbA1c ≤9%, and 5.5-folds greater odds of having severe kidney function.

Conclusions these findings suggested that there is a potential association between polypharmacy and PIMs and altered glycemic control, and PIMs with the deterioration of kidney function.

Keywords drug-drug interactions, potentially inappropriate medicines, glycemic control, kidney function, elderly, type 2 diabetes

2.4.2 Introduction

The pharmacological management of elderly people with type 2 diabetes (T2D) represents a major challenge for health care professionals. At least 50% of older adults with T2D have three or more comorbid chronic conditions (1), as well as the presence of diabetes complications and geriatric syndromes (2), which can add more intricacy to the pharmacological therapy, leading to polypharmacy. The presence of polypharmacy in elderly people with T2D may be linked to negative effects, that can result in more harm than benefit (3). This may include severe, life-threatening drug-drug interactions (DDIs), prescription of potentially inappropriate medicines (PIMs), that can be associated with the consequence of the decreased quality of life (4). There are a few studies that addressed the impact of polypharmacy on kidney function in older adults (5). To the best of our knowledge, no previous studies reported the impact of polypharmacy, potentially serious clinically relevant DDIs and PIMs on glycemic target, and kidney function in older people with T2D. Therefore, the study aimed to investigate the association of polypharmacy, potentially serious clinically relevant DDIs and PIMs with glycemic target, and kidney function in older people with T2D.

2.4.3 Methods

A cross-sectional study was conducted using the administrative database of the Portuguese Diabetes Association (APDP). APDP is the eldest member of the International Diabetes Federation (IDF) and is considered a specialty care diabetes institution in Portugal that provides support in the different fields of diabetes (diabetology, cardiology, urology, psychology, psychiatry, ophthalmology, and pathology) (6). Participants were included in the study if they were diagnosed with T2D, aged 65 years or more, and registered in 2018.

Socio-demographic data, body mass index (BMI), diabetes duration, diabetes-related complications, laboratory data including the last measured each of glycated hemoglobin (HbA1c), fasting blood glucose (FBG), serum creatinine, systolic and diastolic blood pressure, medicines used for the treatment of both T2D and associated comorbidities were all collected. Participants were considered hypertensive if they have blood pressure ≥ 140/90 mmHg or they are on anti-hypertensive medicines. For chronic kidney disease (CKD), we calculated the estimated glomerular filtration rate (eGFR) based on participant characteristics and serum creatinine using the Modification of Diet in Renal Disease Study equation (MDRD-GFR)(7). Polypharmacy was defined as the use of five or more medicines (8).

In the current study, potential serious clinical-relevant DDIs defined as those drug-drug interactions that considered contraindicated or may potentially harmful and life-threatening and require medical intervention to minimize or prevent serious adverse effects based on the excellent quality of scientific evidence (defined as those with established controlled studies)(4), using the IBM Micromedex Platform (IBM® Corporation 2019) (9).

PIMs were identified using STOPP criteria version 2. The criteria was developed following an extensive literature review and two rounds of Delphi consensus validation. The STOPP criteria are classified according to organ systems (e.g., cardiovascular system) to facilitate easy and rapid medicines review. For each criterion, the tool contains a brief explanation of why a medicine or a combination of medicines is considered potentially inappropriate (10).

Statistical analysis

Descriptive data were presented as frequencies and percentages or mean ± SD. Comparison of the difference in the mean of each glycemic targets, and kidney function according to the exposure to polypharmacy, potentially serious clinically relevant DDIs, and PIMs was tested for statistical significance using the paired Wilcoxon two-Sample test, the P-value was set to be <0.05. Besides, the association between polypharmacy, potentially serious clinically relevant DDIs and PIMs with HbA1c targets of ≤ 7.00%, ≤ 8.00%, ≤ 9.00%, and > 9.00%, and severe stage kidney function (eGFR <30mL/min/1.73 m^2) was tested using multivariable linear regressions models. SAS statistical program (Cary, NC, USA) was used for all analyses.

2.4.4 Results

A total of 444 elderly people with T2D were included in the study. Polypharmacy was found in 43.6% of the patients. Patients on polypharmacy have shown to be more females (50% vs.39.6%, P=0.0208), with higher HbA1c targets of ≤ 8.00%, ≤ 9.00% (P=0.0275), and longer duration of diabetes (66.4% vs.54.4%, P=0.0019), more hypertensive (87% vs.62.9%, P<0.0001), using more insulin (38.1% vs.26%, P=0.0062), sulfonylureas (37.1% vs.15.6%, P<0.0001), GLP-1 receptor-agonists (9.7% vs.3.6%, P=0.0077), metformin in combination with DPP-4 inhibitors (41.2% vs.29.2%, P=0.0081), SGLT2 inhibitors (19% vs.9.6%, P=0.0040), compared to those not on polypharmacy. Table 1 describes the differences between study participants characteristics according to the exposure to polypharmacy.

Table 1 Descriptive characteristics of study participants according to exposure to polypharmacy

Characteristics n (%) or Mean ± SD	T2D on Polypharmacy (N=194)	T2D Not on Polypharmacy (N=250)	P value
Gender (female)	97 (50)	99 (39.6)	P=0.0286
Age	72.8 ± 6.8	73.0 ± 6.8	P=0.1338
65-74	56 (28.8)	88 (35.2)	
75-84	137 (70.6)	151 (60.4)	
≥ 85	1 (0.5)	11 (4.4)	
BMI			P=0.0607
Underweight (< 18.5 kg/m²)	0 (0)	1 (0.4)	
Normal (18.5 – 24.99 Kg/m²)	25 (12.8)	48 (19.2)	
Pre-obese (25 – 29.99 Kg/m²)	98 (50.5)	94 (37.6)	
Obese (≥ 30 K/m²)	68 (35)	91 (36.4)	
	NR = (3)	(NR = 16)	
Duration of Diabetes			P=0.0019
≥1-<3 years	17 (8.7)	48 (24.7)	
≥3-<6 years	20 (10.3)	40 (16)	
≥6-<10 years	28 (14.4)	26 (13.4)	
≥10 years	129 (66.4)	136 (54.4)	
FBG	184.9 ± 71.4	179.1 ± 68.2	
	(NR=2)	(NR=6)	
HbA1c category			P=0.0275
≤ 6.00%	20 (10.3)	47 (18.8)	
≤ 7.00%	53 (27.3)	76 (30.4)	
≤ 8.00%	67 (34.5)	64 (25.6)	
≤ 9.00%	27 (13.9)	24 (9.6)	
> 9.00%	24 (12.3)	32 (12.8)	
	NR=(3)	NR=(7)	
Comorbid conditions			
Hypertension	168 (86.5), (NR=1)	153 (61.2), (NR=7)	P<0.0001
CKD	144 (74.2), (NR=7)	167 (66.8), (NR=9)	P=0.1610
Dyslipidaemia	97 (50), (NR=27)	123 (49.2), (NR=54)	P=0.3640
Infections	28 (14.4), (NR=1)	18 (7.2)	P=0.0217
CKD category			P=0.6924
1-(estimated GFR ≥ 90mL/min/1.73 m²)	46 (23.7)	74 (29.6)	
2-(estimated GFR 60-89mL/min/1.73 m²)	78 (40.2)	90 (36)	
3A-(estimated GFR 59-45mL/min/1.73 m²)	37 (19)	45 (18)	
3B-(estimated GFR 44-30mL/min/1.73 m²)	21 (10.8)	20 (8)	
4-(estimated GFR 15-29mL/min/1.73 m²)	6 (3)	9 (3.6)	
5-(estimated GFR < 15mL/min/1.73 m²)	3 (1.5)	3 (1.2)	
Diabetes Complications			P=0.8738
Yes	43 (22.1)	57 (22.8)	
No	151 (77.8)	193 (77.2)	
Cardiovascular diseases	45 (23.1)	33 (13.2)	P=0.7957
Peripheral vascular disease	31 (15.9)	38 (15.2)	P=0.8221
Neuropathy	18 (9.2)	22 (8.8)	P=0.8614
Retinopathy	20 (10.3)	28 (11.2)	P=0.7643
Nephropathy	14 (7.2)	21 (8.4)	P=0.6462
Diabetic Foot	19 (9.7)	18 (7.2)	P=0.3267
Diabetes Medicines			
Insulin	74 (38.1)	65 (26)	P=0.0062
Metformin	82 (42.2)	92 (36.8)	P=0.2417
SU	72 (37.1)	39 (15.6)	P<0.0001
GLP-1 ra	19 (9.7)	9 (3.6)	P=0.0077
DPP-4 inhibitors	39 (20.1)	37 (14.8)	P=0.1412
Metformin + DPP-4 inhibitors	80 (41.2)	73 (29.2)	P=0.0081
SGLT2 inhibitors	37 (19)	24 (9.6)	P=0.0040
Metformin + SGLT2 inhibitors	14 (7.2)	9 (3.6)	P=0.0881
Potentially serious clinically relevant DDIs	35 (89.7)	4 (10.3)	P<0.0001
Potentially inappropriate medicines	77 (74)	27 (26)	P<0.0001

BMI: body mass index, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, CKD: chronic kidney disease, GLP-1 ra: Glucagon-like peptide-1 receptor agonist, DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitor, SGLT2 inhibitors: Sodium-glucose Cotransporter-2 Inhibitors, NR: not reported

Among the 444 older people with T2D, 39 (8.7% of total patients) were found to have potential serious clinically relevant DDIs. The most identified interacting medicine pairs were dexamethasone and fluroquinolones (27.2%), followed by clopidogrel and calcium channel blockers (13.6%), and clopidogrel with proton pump inhibitors (13.6%) Figure 1. The full description of the potentially serious clinically relevant DDIs presented in Table 2.

Figure 1 The prevalence of medicines pairs that contributed to potentially serious clinically relevant drug-drug interactions

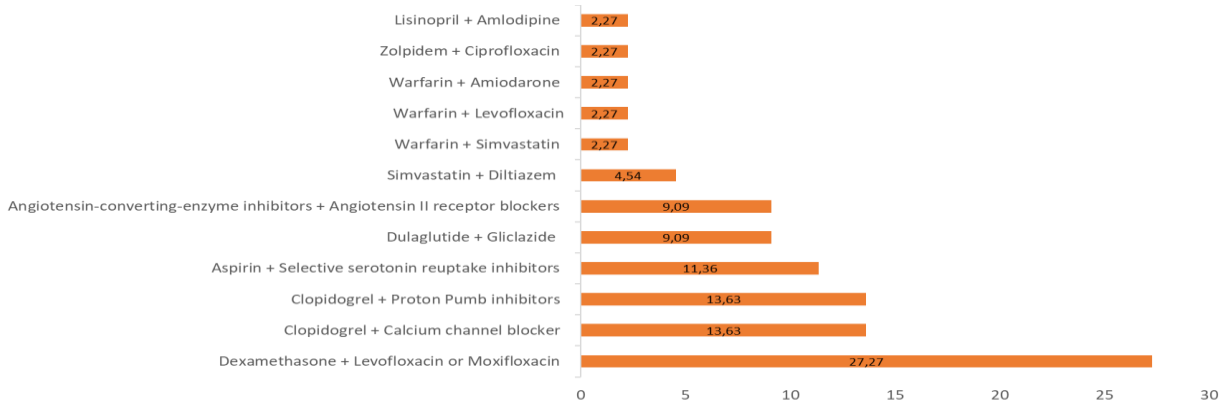


Table 2 Description of the potentially serious clinically relevant drug-drug interactions

(Medication/Class)	(Medication/Class)	Potential adverse reaction	Mechanism of Interaction	Onset	N (%)
Dexamethasone (H02AB02)	Levofloxacin (S01AE05), Moxifloxacin (S01AE07)	increased risk of tendon rupture	additive effect of risk for tendon rupture	Delayed	12 (27.2)
Clopidogrel (B01AC04)	Calcium channel blocker (C08)	decreased antiplatelet effect and increased risk of thrombotic events.	inhibition of CYP3A-mediated clopidogrel activation	not specified	6 (13.6)
Clopidogrel (B01AC04)	Proton pump inhibitors (A02BC)	may result in reduced antiplatelet activity	decreased inhibition of platelet aggregation of clopidogrel	Rapid	6 (13.6)
Aspirin (B01AC06)	Selective serotonin reuptake inhibitors (N06AB)	increased risk of bleeding	depletion of platelet serotonin by SSRI; additive effects	not specified	5 (11.3)
Dulaglutide (A10BJ05)	Gliclazide (A10BB09)	increased risk of hypoglycemia.	additive hypoglycemia	not specified	4 (9)
Angiotensin converting enzyme inhibitor (C09A)	Angiotensin receptor blockers (C09CA)	increased risk of hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure	dual blockade of the renin-angiotensin-aldosterone system	not specified	4 (9)
Simvastatin (C10AA01)	Diltiazem (C08DB01)	increased serum concentrations of simvastatin and increased risk of myopathy, including rhabdomyolysis.	inhibition of CYP3A4-mediated simvastatin metabolism by diltiazem	Rapid	2 (4.5)
Warfarin (B01AA03)	Simvastatin (C10AA01)	increased risk of bleeding and an increased risk of rhabdomyolysis.	competition for cytochrome P450 3A4-mediated metabolism	Delayed	1 (2.2)
Warfarin (B01AA03)	Levofloxacin (S01AE05)	increased risk of bleeding	disruption of vitamin K synthesis	Delayed	1 (2.2)
Warfarin (B01AA03)	Amiodarone (C01BD01)	increased INR and an increased risk of bleeding.	increased exposure to warfarin	Delayed	1 (2.2)
Zolpidem (N05CF02)	Ciprofloxacin (S01AE03)	increased zolpidem plasma concentrations.	Unknown	not specified	1 (2.2)
Lisinopril (C09AA03)	Amlodipine (C08CA01)	increased risk of hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure.	disruption of vitamin K synthesis	not specified	1 (2.2)

According to the STOPP criteria version 2, 133 PIMs were found amongst 104 (23.4%) of the total patients. Of these, 80 patients (76.9%) have one PIM, 20 patients (19.2%) have two PIMs, and four patients (3.8%) have more than two PIMs. The highest frequency of PIMs use related to the cardiovascular system (29.3%), followed by drugs that predictably increase the risk of falls in older people (24.2%), and the endocrine system (14.2%) Figure 2. The full description of the PIMs presented in Table 3.

Figure 2 The prevalence of potentially inappropriate medicines according to the organ system or medicines class

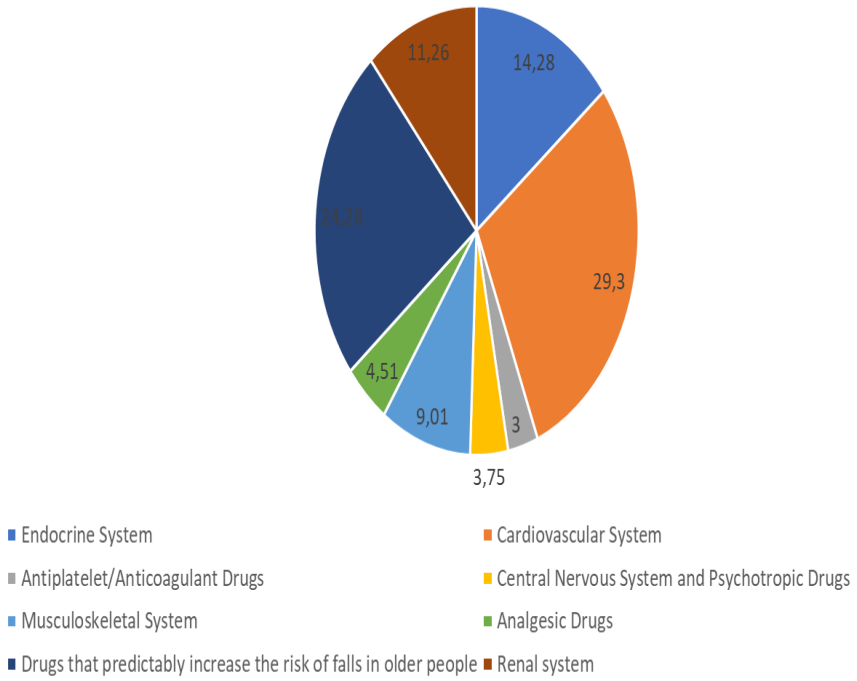


Table 3 The description of potentially inappropriate medicines according to STOPP criteria

Section	STOPP Criteria	N (%)
Endocrine System	Sulphonylureas with a long duration of action with type 2 diabetes mellitus	19 (14.2)
Cardiovascular System	Using of Centrally acting antihypertensives	5 (3.7)
	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	2 (1.5)
	Loop diuretic as first-line treatment for hypertension	3 (2.2)
	ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia	28 (21)
	Aldosterone antagonists with concurrent potassium-conserving drugs without monitoring of serum potassium (risk of dangerous hyperkalaemia)	1 (0.7)
Antiplatelet/Anticoagulant Drugs	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease	1 (0.7)
	Aspirin plus clopidogrel as secondary stroke prevention, (no evidence of added benefit over clopidogrel monotherapy).	2 (1.5)
	NSAID[1] and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	1 (0.7)
Central Nervous System and Psychotropic Drugs	Initiation of Tricyclic Antidepressants (TCAs) as first-line antidepressant treatment	3 (2.2)
	Use of first-generation antihistamines	1 (0.7)
	Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia.	1 (0.7)
Musculoskeletal System	NSAID with concurrent corticosteroids without PPI prophylaxis	10 (7.5)
	NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure	2 (1.5)
Analgesic Drugs	Use of oral or transdermal strong opioids	6 (4.5)
Drugs that predictably increase the risk of falls in older people	Benzodiazepines	23 (17.2)
	Hypnotic Z-drugs e.g., zopiclone, zolpidem, zaleplon	6 (4.5)
	Neuroleptic drugs	4 (3)
Renal system	Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis)	10 (7.5)
	NSAID's if eGFR < 50 ml/min/1.73m2	4 (3)
	Factor Xa inhibitors if eGFR < 15 ml/min/1.73m2	1 (0.7)
	Total	133

NSAIDs: Non-steroidal anti-inflammatory drugs

The comparison among participants' HBA1c, and eGFR according to the exposure to polypharmacy, potentially serious clinically relevant DDIs and PIMs presented in (Figure 3, Figure 4, Figure 5), and the mean difference described in Table 4.

Figure 3 comparison between participants' HbA1c and eGFR according to the exposure to polypharmacy

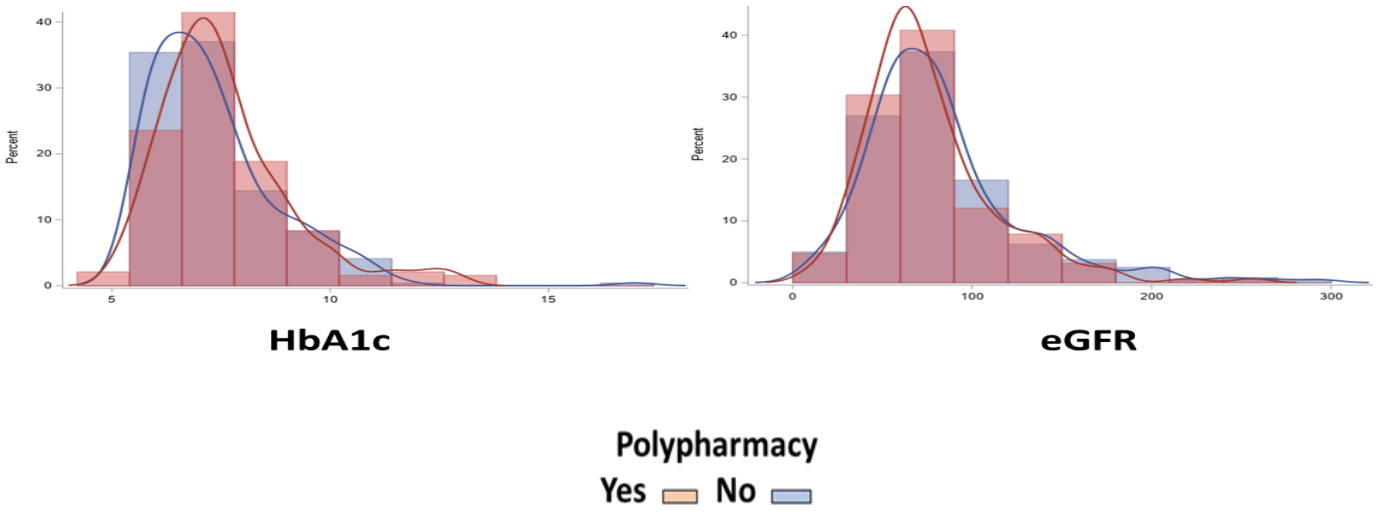


Figure 4 Comparison between participants HbA1c and eGFR according to the exposure to potentially serious clinically relevant drug-drug interactions

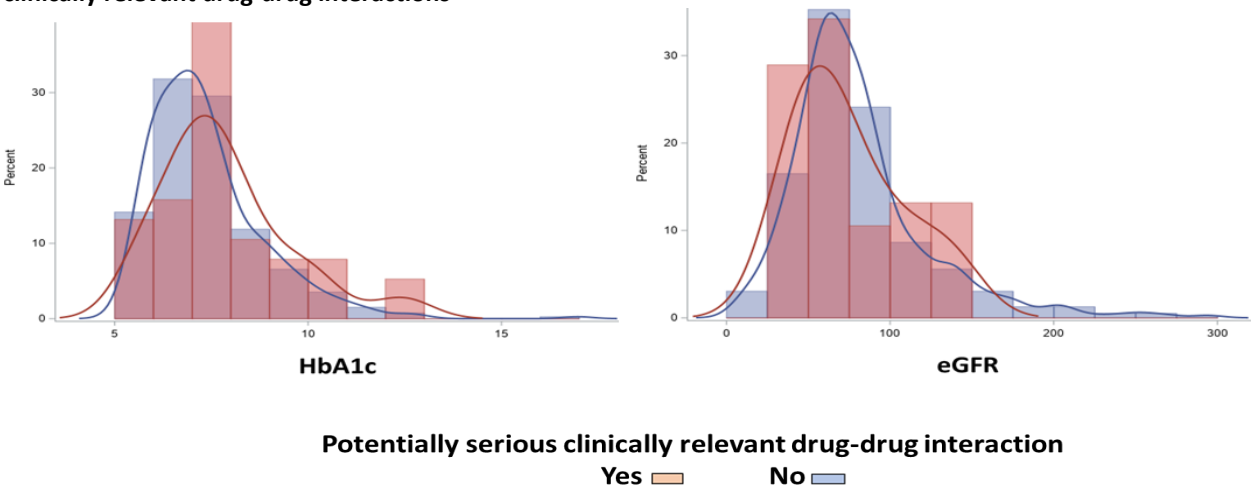
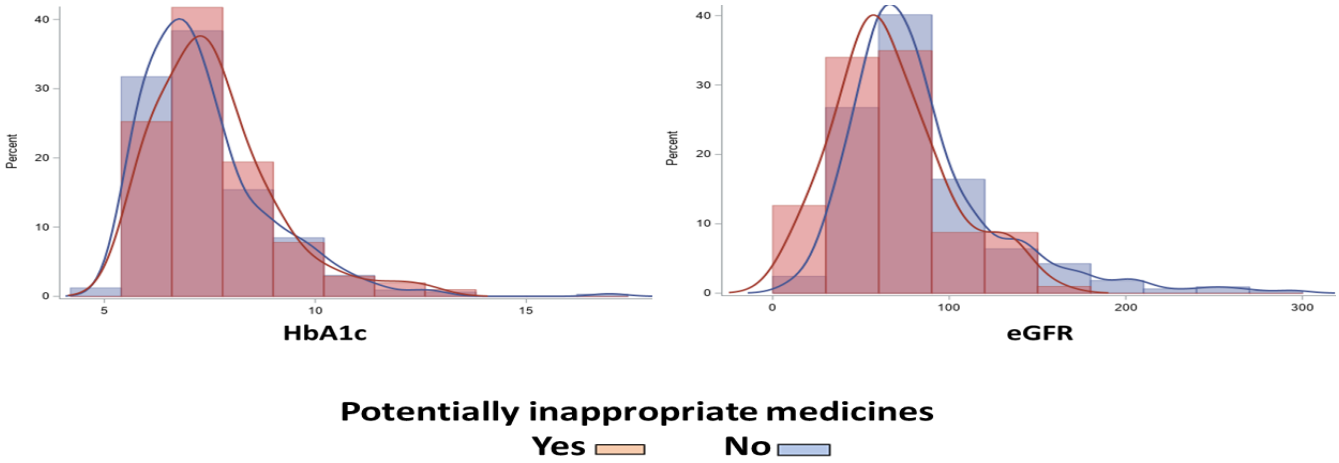


Figure 5 comparison between participants HbA1c and eGFR according to the exposure to potentially inappropriate medicines



The adjusted multivariate logistic regression revealed that the multiple medicines use (polypharmacy) were associated with a higher odd of HbA1c target of ≤ 8% (OR 2, 95% 1-3.9, P=0.0315). On the other hand, the presence of PIMs has associated with a higher odd of HbA1c target of ≤ 9% (OR 2.5, 95%CI 1-6.5, P=0.0490), and severe kidney function (OR 5.5, 95%CI 2.1-14.1, P=0.0003) (Table 5).

Table 4 Mean difference in HbA1c, and eGFR according to exposure to polypharmacy, potentially serious clinically relevant drug-drug interaction, and inappropriate medicines

	HbA1c target	Kidney function
Polypharmacy (Yes vs No)	7.5 ± 1.5 vs 7.3 ± 1.5	76.1 ± 42.6 vs 83 ± 42.5
P value	P=0.0215	P=0.1309
Potentially serious clinically relevant DDIs (Yes vs No)	7.8 ± 1.5 vs 7.3 ± 1.5	74.4 ± 42.8 vs 80.5 ± 42.5
P value	P=0.0651	P=0.3402
PIMs (Yes vs No)	7.5 ± 1.5 vs 7.3 ± 1.5	66.9 ± 42.8 vs 84 ± 42.5
P value	P=0.0527	P=0.0002

PIMs: potentially inappropriate medicines, DDIs: drug-drug interactions

Table 5 The association between polypharmacy, potentially serious clinically relevant drug-drug interactions, and inappropriate medicines with HbA1c target, and eGFR

	Polypharmacy	Potentially serious clinically relevant DDIs	PIMs
	OR (95% CI)	OR (95% CI)	OR (95% CI)
HbA1c target			
HbA1c ≤ 7.00% vs. ≤ 6.00%	1.6 (0.8-3.2)	0.5 (0.1-2)	1.3 (0.5-3)
HbA1c ≤ 8.00% vs. ≤ 6.00%	2 (1-3.9)	1.4 (0.4-4.3)	2.1 (0.9-4.8)
HbA1c ≤ 9.00% vs. ≤ 6.00%	2.1 (0.9-4.7)	1 (0.2-4)	2.5 (1-6.5)
HbA1c > 9.00% vs. ≤ 6.00%	1.3 (0.6-2.9)	1.6 (0.4-5.7)	1.5 (0.5-4)
Severe kidney Function			
eGFR < 30mL/min/1.73 m^2 (Yes vs. No)	0.8 (0.3-2.1)	0.4 (0.05-3.5)	5.5 (2.1-14.1)

PIMs: potentially inappropriate medicines; DDIs: drug-drug interactions

2.4.5 Discussion

In a sample of older people with T2D from a diabetes specialty care institution, the findings suggest that polypharmacy and PIMs can alter the glycemic targets of these patients. While only PIMs have found to have an impact on kidney function. Patients on polypharmacy found to have average age above 70 years, frequently females, had higher glycemic targets, a longer mean of FBG, longer duration of disease, more hypertensive with fewer diabetes complications, and using more insulin, sulfonylureas, GLP-1 receptor agonists, metformin in combination with DPP-4 inhibitors, and SGLT2 inhibitors than those not on polypharmacy. Similar results were found by Noale et al. Although, the study reported a higher prevalence of polypharmacy (57.1%) and a higher prevalence of diabetes complications (11).

These differences might be due to the different healthcare settings where the patients received their diabetes care. Naole et al reported that the data of older adults with T2D were collected from 57 primary care centers (11). While in our study, the data were collected from the administrative database of a diabetes specialty care institution, that is, the APDP.

McAlister et al, found that patients receiving care in diabetes specialty care institution were seen more often by primary care physician and by all doctors, were more likely to be treated with insulin and a combination of oral hypoglycaemic agents, and more likely to receive efficacious treatment to prevent atherosclerotic complications (12), and ensuring a better quality of care in terms of process measures (13).

The study has shown that potentially serious clinically relevant DDIs are less frequent when compared to that previously found in-home health care by Ibrahim et al, where the prevalence reached 38.8% (14). Nevertheless, it should be noted that the drug-interaction platform used was different, and therefore, the classification of interactions may not be equivalent, as well as the medicines regimens of older diabetic patients are monitored systematically and frequently in specialty care diabetes institutions than in home health care services.

The most common potentially serious clinically relevant DDIs interacting medicine pair was found between dexamethasone and fluoroquinolones which can increase the risk of tendon rupture. Persson et al found that in older adults with diabetes, the excess risk of any tendon rupture was much higher for concomitant fluoroquinolones and corticosteroids use versus corticosteroids alone (OR 21.2, 95%CI 11.3–31.2), and the risk of any tendon rupture was higher among concomitant corticosteroids use (OR 6.6, 95%CI 3.9–11.1) (15).

Fluoroquinolones might be avoided in individuals who have had previous serious side effects. They should be used with special caution in the elderly people greater than 60 years, corticosteroid therapy, kidney failure, obesity, hyperlipidemia, diabetes, and history of musculoskeletal disorders, because these patients are at a higher risk of tendon disorders, especially Achilles tendonitis. Since the use of a corticosteroid with fluoroquinolones increases this risk, the combined use of these medicines is recommended to be avoided (16,17).

The interaction between the calcium channel blockers and clopidogrel can be associated with a reduction of the clopidogrel efficacy through limiting the ability to inhibit platelet aggregation, which accounted for 13.6% of the most interacting medicine pairs identified in the study. There are controversies in the literature regarding this interaction, since some studies found a reduction in the effect of clopidogrel with this combination (18)(19), and other studies could not confirm any evidence of a reduction in the anti-platelet activity of clopidogrel (20)(21).

Another important potential DDI was found from a combination of clopidogrel and proton pump inhibitors, which can result in reduced clopidogrel effect and possible adverse cardiovascular events. A meta-analysis by Serbin et al found that concomitant use of this combination was significantly associated with an increase in the composite major adverse cardiac event (MACE) (HR 1.28; 95% CI 1.24–1.32), myocardial infarction (HR 1.51; 95% CI 1.40–1.62) and stroke (HR 1.46; 95% CI 1.15–1.86) (22). Whereas Pang et al found that patients using clopidogrel without PPIs were observed to be associated with less risk of MACE (RR 0.82, 95%CI 0.77–0.88), myocardial infarction recurrence (RR 0.72, 95%CI 0.57–0.90), stent thrombosis(RR 0.71,95%CI 0.56–0.92), Target vessel revascularization (RR 0.77, 95%CI 0.63–0.93) and stroke (RR 0.72, 95%CI 0.67–0.76). this effect mainly appears from the use of omeprazole or esomeprazole with clopidogrel (23).

The most common PIM reported in the study was the use of ACE inhibitors or ARBs in patients with hyperkalemia. Hyperkalemia is common in older adults with diabetes who have cardiorenal comorbidities and often limits the use of guideline-recommended ACE inhibitors and ARB's in the subgroups of patients who are expected to derive the greatest benefit, especially in those with chronic kidney disease (24). Bandak et al found that hyperkalemia within the first year of ACE inhibitors or ARBs treatment was relatively uncommon among people with eGFR>60 mL/min per 1.73 m^2 (25). Older age, lower eGFR, diabetes, heart failure, and use of ACE inhibitors or ARBs were all associated with higher hyperkalemia risk (26).

The increased odds of polypharmacy and PIMs are associated with alteration of HbA1c targets of ≤ 8.00% and ≤ 9.00% in the current study. Achieving strict glycemic targets in elderly people with T2D through polypharmacy can be associated with diminishing benefits and greater risks of harm and clinically meaningless. Timbie et al found that a significant proportion of people with diabetes will fail to achieve glycemic targets despite using high doses of multiple, conventional treatments (27). In the light of European and American clinical practice guidelines for the management of older adults with T2D (28,29), several randomized controlled trials (RCTs) (30–32), and observational data (33,34), the harms associated with HbA1c targets lower than 7.5% or higher than 9% are likely to outweigh the benefits for the majority of older adults age 65 years or more with T2D. Taken together, the current finding suggests that there might be an impact of both polypharmacy and PIMs on HbA1c targets but did not exceed the recommended limits.

The increased odds of PIMs are also associated with severe kidney function in the current study. Previous studies either found that polypharmacy was associated with severe kidney function (OR 2.8, 95%CI 1.4-5.7) as reported by Dorks et al (35), or did not find any association between PIMs and severe kidney disease as reported by Secora et al (5). Ueda et al found that

insulin therapy, serum albumin, mean blood pressure, and hemoglobin, were independent and significant factors of progression to renal failure (36). Whereas Kaewput et al found that the risk factors associated with progression to end-stage kidney disease were diabetes duration, systolic blood pressure, serum uric acid, albuminuria, and baseline eGFR.

In the current study, 16 patients were exposed to the use of non-steroidal anti-inflammatory drugs (NSAIDs), which identified in the study as one of the PIMs that might be associated with an increased risk of severe kidney disease. Physiologically, NSAIDs have been shown to inhibit cyclooxygenase function, reduce prostaglandin production, and change hemodynamics in the kidney, leading to acute kidney failure and glomerular filtration rate alteration (37). A greater risk of chronic kidney disease attributable to NSAIDs use was noted among people with T2D aged ≥ 65 years than for those aged < 65 years (38).

However, renal outcomes related to the use of NSAIDs, especially the progression to end-stage kidney disease, in population-based studies remain inconclusive (39). Previous results from observational studies have indicated that NSAIDs could further deteriorate already impaired renal function. it was shown that patients with chronic kidney disease who took non-selective NSAIDs, compared with those who did not, were 56% more likely to develop end-stage kidney disease (40). Besides, it has been documented that high-dose NSAID use in the elderly with chronic kidney disease was a significant risk factor that accelerated chronic kidney disease progression (41). By contrast, the harmful effects of NSAIDs on kidney function could not be confirmed in some epidemiological studies. Therefore, NSAIDs should be prescribed with caution, especially in older adults with T2D at high risk for kidney disease progression.

Some potential limitations exist in the current study. For example, in the interaction between fluoroquinolones and dexamethasone, we cannot confirm if the patients were on long-term dexamethasone for two main reasons: firstly, the administrative database of the APDP only show the last updated medications used for each patient. Secondly, based on our study design, we did not follow the patients prospectively, and then we can be sure about the duration of the use of dexamethasone. Ultimately, we can confirm that patients started dexamethasone after the diagnosis of T2D and while they are being treated at APDP. Although, we cannot confirm how long the patients were using dexamethasone.

The sample of the study is relatively small, and the data collected from one specialty care diabetes institution (the APDP), this can reduce the generalized directly on the national level. Several possible confounders that might impact the associations found in the study such as age, female gender, number of comorbidities, complications, BMI, and duration of diabetes for which we did adjust all. We defined polypharmacy as the use of five or more medicines. Using

other definitions (e.g., 10 or more medicines) might form a barrier against concluding the impact of polypharmacy on glycemic targets. Similarly, the DDIs can be classified as major, moderate, and minor according to the MICROMEDEX platform. The current definition has been chosen to identify the clinically important DDIs based on strong scientific evidence, that might influence on the other hand the impact on glycemic target or kidney function.

The study showed that polypharmacy is prevalent among elderly people with T2D in specialty care diabetes institution and underlines the importance of assessing the conditions leading to multiple prescriptions. The study found that the presence of polypharmacy can be associated with older adults' HbA1c targets. Most patients' HbA1c levels increase over time, older adults and their clinicians must decide whether to intensify or de-intensify therapy.

The risks of treatment to achieve HbA1c targets in older adults should be carefully weighed with the benefits at the individual level. Although, the net benefit of intensifying treatment with polypharmacy remains unclear. Currently, there are no RCTs assessed the benefit-harm of polypharmacy in older adults with T2D. The study has shown that potentially serious clinically relevant DDIs could be a cause of adverse events and outcomes. Although they are relatively low, it seems that DDIs identified can be associated with severe, life-threatening adverse consequences.

The study findings revealed that not only polypharmacy can be associated with glycemic targets, but also the presence of PIMs can pose the same risk. Clinicians should be frequently, and carefully review and update the list of medicines with special awareness to the medicines that can interfere with diabetes management, individualize their glycemic targets, and provide them with patient-centered care.

The study also adds another important finding, that is, the presence of PIMs can be associated with the risk of severe kidney function. While the use of HbA1c could be helpful to evaluate glycemic targets, attention to kidney function might also be monitored more frequently. Providers might also look for nephrotoxic medicines when reviewing their medicines lists.

2.4.6 Conclusion

In a sample of older people with T2D from specialty care institution, the results have shown that polypharmacy, potentially serious clinically relevant DDIs, and PIMs are prevalent in this population as expected. The findings also suggest that the presence of polypharmacy and PIMs might put these patients at high-risk of glycemic targets alteration, and the impact on the deterioration of kidney function more likely to be from the use of PIMs. Considering these

findings, it appears crucial to ensure that iatrogenic risks remain minimal for this population who is already vulnerable to these outcomes and mainly rely on hastening to help and do no harm.

Declarations

Ethical approval ethical approval was obtained from the APDP ethics committee for health, official number (70/2019).

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Conflict of interest all authors declare that they have no conflict of interest

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CHAPTER 2.5

OVERTREATMENT AND UNDERTREATMENT IN A SAMPLE OF ELDERLY PEOPLE WITH DIABETES

2.5.1 Abstract

Background and objectives

In older adults with type 2 diabetes (T2D), overtreatment remains prevalent and undertreatment ignored. The main objective is to estimate the prevalence and examine factors associated with potential overtreatment and undertreatment.

Method

Observational study conducted within an administrative database of older adults with T2D who registered in 2018 at the Portuguese Diabetes Association. Participants were categorized either as potentially overtreated (HbA1c≤7.5%), appropriately on target (HbA1c≥7.5–≤9%), or potentially undertreated (HbA1c>9%).

Results

Of 444 participants, potential overtreatment, and undertreatment were found in 60.5% and 12.6% of the study population. Taking the patients on target as a comparator, the group of potentially overtreated showed to be more males (61.3% vs.52.2%), less-obese (34.1% vs.39.2), higher cardiovascular diseases (13.7% vs.11%), peripheral vascular diseases (16.7% vs.12.8%), diabetic foot (10% vs.4.5%), and severe kidney disease (5.2% vs.4.5%). Conversely, the potentially undertreated participants were more females (64.2% vs.47.7%), obese (49% vs.39.2%), had more dyslipidemia (69% vs.63.1%), peripheral vascular disease (14.2% vs.12.8%), diabetic foot (8.9% vs.4.5%), and infections (14.2% vs.11.9%).

The odds of potential overtreatment were mostly decreased by 59% of females, 73.5% in those with retinopathy, and 86.3% in insulin, 65.4% sulfonylureas, and 66.8% in SGLT2 inhibitors users. Contrariwise, an increase in the odds of potential undertreatment was more than 4.8times higher in insulin, and more than 3.1times higher in sulfonylureas users.

Conclusion

Potential overtreatment and undertreatment in older adults with T2D in routine clinical practice should guide the clinicians to balance the use of newer antidiabetic agents considering its safety profile regarding hypoglycemia**.**

Keywords: glucose-lowering medicines, glycemic control, hypoglycemia, specialty care, type 2 diabetes

2.5.2 Introduction

Globally, with the overall aging of the population, the prevalence of diabetes raises. According to the international diabetes federation (IDF) in 2019, it was estimated that the number of older adults aged between 65-99 years old with diabetes reached more than 135 million cases worldwide. This number expected to increase to more than 276 million cases achieving a prevalence of 19.6% by 2045, who majorly elderly diagnosed with type 2 diabetes (T2D) according to IDF (1). Older adults with T2D are a heterogenous, vulnerable, and frail population, at high-risk for microvascular and cardiovascular complications, geriatric syndromes (such as falls, dementia, and polypharmacy), hypoglycemia, or hyperglycemia than young adults (2) and historically excluded from traditional randomized clinical trials (RCTs) (3).

As a result, the literature is scarce regarding the benefits and risks associated with treatment intensification in the older T2D population (4). Despite the potential for harm, overtreatment remains common because of many health system factors including financial incentives, malpractice concerns, performance measures, practice behavior, and time limits (5). On the other hand, there is less attention to the undertreatment of older adults with T2D whom otherwise healthy, to achieve modest glycemic control. Consequently, clinical inertia can result in uncontrolled hyperglycemia in older T2D individuals that could potentially result in serious microvascular and macrovascular harm (6).

Besides, the definition of overtreatment and undertreatment is still debatable and unclear due to the differences in recent clinical diabetes practice guidelines, especially in the details of its recommendations for elderly people with diabetes categories and their glycaemic targets (2,7–9). Using a data of older adults with T2D from the Portuguese Diabetes Association (APDP), we aimed to investigate whether there is a shift toward the use of newer medicines, with low-risk of hypoglycemia according to the updated guideline recommendations (9–11), and to examine the characteristics and factors associated with individualized diabetes management focusing on potential overtreatment/undertreatment.

2.5.3 Methods

A cross-sectional study conducted using the administrative database of older adults with T2D of the Portuguese Diabetes Association (APDP). The APDP is the world's oldest diabetes association and a senior member of the IDF. Individuals were included if they are diagnosed with T2D, aged 65 years or more, and registered at APDP in 2018. 543 were identified according to the above-mentioned criteria. Of these, 99 individuals were excluded from the analysis as they just visited APDP for special consultation with no medical history and/or medicines records. Socio-demographic data, body mass index (BMI), diabetes duration, diabetes

complications, laboratory results including glycated hemoglobin (HbA1c), fasting blood glucose (FBG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), total cholesterol (TC), serum each of creatinine, sodium, and potassium, as well as the last blood pressure record (including both systolic (SBP) and diastolic blood pressure (DBP), medicines used for treatment of T2D and associated comorbidities were retrieved from the database of APDP.

Participants were considered hypertensive if they have blood pressure ≥ 140/90 mmHg or they were on anti-hypertensive medicines. For chronic kidney disease (CKD), we calculated the estimated glomerular filtration rate (eGFR) based on participant characteristics and serum creatinine using modification of diet in renal disease study equation (MDRD-GFR) (12). Polypharmacy was defined as the use of five or more medicines (13). According to the action to control cardiovascular risk in diabetes (ACCORD) trial (14) the review by Lipska and colleagues (15), and the recommendations from the European diabetes working party for older people with T2D clinical guideline (11), the majority of older people with T2D aged 65 years old or more, the harm from HbA1c target lower than 7.5% or higher than 9% are likely to outweigh the benefit. Therefore, the potential overtreatment defined as HbA1c target of (<7.5%), appropriately on target HbA1c between (≥7.5-≤9%), and potential undertreatment HbA1c target of (>9%), and were on treatment with glucose-lowering medicines in mono or combination therapy.

Statistical analysis

Participants were divided into categories of glycemic control: potentially overtreated (HbA1c <7.5%), appropriately on target (HbA1c ≥7.5-≤9%), and potentially undertreated (HbA1c>9%). We compared the demographic and clinical factors of these groups using t-test for categorical variables and Kruskal-Wallis test for continuous variables. P-value was set to be < 0.05. Multivariable binary logistic regression was used to explore factors associated with potential overtreatment and undertreatment compared to appropriately on target. Covariates in the model included age, sex, polypharmacy, gender, obesity (BMI≥ 30 K/m²), diabetes duration, comorbidities, macrovascular and microvascular complications, infections, estimated GFR, serum sodium, serum potassium, SBP, serum LDL, insulin use, and other glucose-lowering medicines. analyses were carried out using the SAS program (SAS Institute, Inc., Cary, NC).

2.5.4 Results

Of 444 older adults with T2D aged 65 years or older, 434 (97.7%) had documented the HbA1c test. Most of the study participants were males with a mean age of (72.9 ± 6.8). More than 35% were obese and almost 60% had more than 10 years of duration of diabetes with mean HbA1c (7.4 ± 1.5%). The study participants were diagnosed with other comorbid

conditions such as hypertension and chronic kidney disease (in more than 70% of the participants), and almost 50% have diagnosed with dyslipidemia. More than 20% of study participants have documented diabetes complications, mainly macrovascular complications, and retinopathy.

Polypharmacy was found in more than 40% of the study individuals. Approximately, 65% were using 1 or 2 of diabetes medicines and more than 25% were using 3 or more. 30.3% of the study participants treated with insulin, 25% with sulfonylureas, compared to 17.1% using of dipeptidyl peptidase-4 (DPP4) inhibitor, 13.7% using gliflozins, and 6.3% using glucagon-like peptide-1 (GLP-1) receptor agonist (Table 1). 269 (60.5%) participants were considered as potentially overtreated, 109 (24.5%) participants were appropriately on target, and 56 (12.6%) participants were potentially undertreated. Older adults with T2D who considered potentially overtreated were frequently males, with mean of age (72.9 ± 6.4) and 46.1% were pre-obese. The mean HbA1c was (6.5 ± 1.5%) and more than half had a longer duration of diabetes, associated with hypertension, dyslipidemia, and CKD especially severe stage (estimated GFR <30mL/min/1.73 m^2).

Table 1 General Characteristics of the Study participants

Characteristics	n (%) or Mean ± SD
N	**444**
Gender	
Male	**248 (55.8)**
Female	**196 (44.1)**
Age	**72.9 ± 6.8**
65-74	**144 (32.4)**
75-84	**288 (64.8)**
≥ 85	**12 (2.7)**
BMI	
Underweight (BMI < 18.5 kg/m²)	**1 (0.2)**
Normal (BMI 18.5 – 24.99 Kg/m²)	**73 (16.4)**
Pre-obese (BMI 25 – 29.99 Kg/m²)	**192 (43.2)**
Obese (BMI ≥ 30 K/m²)	**159 (35.8)**
	(NR=19)
Duration of Diabetes	
Less than one year	**0 (0)**
≥1-<3 years	**65 (14.6)**
≥3-<6 years	**60 (13.5)**
≥6-<10 years	**54 (12.1)**
≥10 years	**265 (59.6)**
HbA1c	**7.4 ± 1.5**
Potential overtreatment (HbA1c <7.5%)	**269 (60.5)**
Appropriately on target (HbA1c≥7.5-≤9%)	**109 (24.5)**
Potential undertreatment (HbA1c>9%)	**56 (12.6)**
	(NR=10)
FBG	**181.6 ± 70.7**
	(NR=8)
Medical History	

Hypertension	**321 (72.2)**
	(NR=8)
CKD	**311 (70)**
	(NR= 12)
Dyslipidaemia	**220 (49.5)**
	(NR=81)
Infections (unspecified)	**46 (10.3)**
	(NR=1)
Blood pressure measurement	
SBP, mm/Hg	**144 ± 20**
DBP, mm/Hg	**78.5 ± 11.4**
Lipid profile measurement	
TC	
< 200mg/dL	**287 (64.6)**
≥ 200mg/dL	**76 (17.1)**
LDL	
< 100mg/dL	**143 (32.2)**
≥ 100mg/dL	**219 (49.3)**
HDL	
> 40mg/dL for men, > 50mg/dL for women	**196 (44.1)**
< 40mg/dL for men, < 50mg/dL for women	**166 (37.3)**
TG	
< 150mg/dL	**171 (38.5)**
≥ 150mg/dL	**191 (43)**
CKD category	
1-(estimated GFR ≥ 90mL/min/1.73 m2)	**120 (27)**
2-(estimated GFR 60-89mL/min/1.73 m2)	**168 (37.8)**
3A-(estimated GFR 59-45mL/min/1.73 m2)	**82 (18.4)**
3B-(estimated GFR 44-30mL/min/1.73 m2)	**41 (9.2)**
4-(estimated GFR 15-29mL/min/1.73 m2)	**15 (3.3)**
5-(estimated GFR < 15mL/min/1.73 m2)	**6 (1.3)**
Electrolytes	
Sodium	
< 135 mEq/L	**16 (3.6)**
135-145 mEq/L	**411 (92.5)**
> 145 mEq/L	**1 (0.2)**
Potassium	
< 3.5 mEq/L	**6 (1.3)**
3.5-5 mEq/L	**364 (81.9)**
> 5 mEq/L	**58 (13)**
Diabetes Complications	
Yes	**100 (22.5)**
No	**344 (77.4)**
Cardiovascular diseases	**57 (12.8)**
Peripheral vascular disease	**69 (15.5)**
Neuropathy	**40 (9)**
Retinopathy	**48 (10.8)**
Nephropathy	**35 (7.8)**
Diabetic Foot	**37 (8.3)**
Polypharmacy	
Yes	**194 (43.6)**
No	**250 (56.3)**
Number of diabetes medicines	
0	**39 (8.7)**
1	**155 (34.9)**
2	**130 (29.2)**
3	**86 (19.3)**
≥ 4	**34 (7.6)**

Diabetes Medicines	
Insulin	**139 (30.3)**
Metformin	**174 (39.1)**
Sulfonylureas	**111 (25)**
GLP-1 ra	**28 (6.3)**
DPP-4 inhibitors	**76 (17.1)**
Metformin + DPP-4 inhibitors	**153 (34.4)**
SGLT2 inhibitors	**61 (13.7)**
Metformin + SGLT2 inhibitors	**23 (5.1)**
Others	**7 (1.5)**

BMI: body mass index, HbA1c: Glycated hemoglobin, FBG: fasting blood glucose, CKD: chronic kidney disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, GLP-1 ra: Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors: Sodium-glucose Cotransporter-2 inhibitors, NR: not reported.

Besides, more than 30% have macrovascular and more than 35% have microvascular complications. Polypharmacy was reported in more than 40% of them and they were treated with a mean of 1.5 ± 1.1 glucose-lowering medicines, mostly treated with metformin, metformin in combination with DPP-4 inhibitors and sulfonylureas. Older adults with T2D who were considered potentially undertreated were frequently females, with mean of age (71.9 ± 6.4) and 49% were obese. The mean HbA1c was 10.3 ± 1.5% and more than two-thirds had a longer duration of diabetes, have diagnosed with hypertension, dyslipidemia, and CKD. Besides, 23.2% have macrovascular and 30.3% have microvascular complications. Polypharmacy was reported in 42.8% of them and they were treated with a mean of (2.3 ± 1.1) diabetes medicines, mostly treated with insulin, metformin in combination with DPP-4 inhibitors, and sulfonylureas (Table 2).

Table 2 Participants Characteristics Stratified According to Individuals with a glycated haemoglobin target categorized as appropriately on target, potentially overtreated or undertreated

HbA1c achieved / Participant characteristics	Potentially overtreated (HbA1c <7.5%) (N=269) n (%) or Mean ± SD	Appropriately on target (HbA1c ≥7.5-≤9%) (N=109) n (%) or Mean ± SD	Potentially undertreated (HbA1c > 9%) (N=56) n (%) or Mean ± SD	P value
Gender				**P=0.0015**
Male	**165 (61.3)**	**57 (52.2)**	**20 (35.7)**	
Female	**104 (38.6)**	**52 (47.7)**	**36 (64.2)**	
Age	**72.9 ± 6.4**	**73 ± 6.3**	**71.9 ± 6.4**	**P=0.8822**
(65-74 years)	**174 (64.6)**	**67 (61.4)**	**38 (67.8)**	
(75-84 years)	**77 (28.6)**	**36 (33)**	**15 (26.7)**	
(≥ 85 years)	**18 (6.6)**	**6 (5.5)**	**3 (5.3)**	

BMI				**P=0.0200**
Underweight (BMI < 18.5 kg/m²)	**0 (0)**	**0 (0)**	**1 (1.8)**	
Normal (BMI 18.5 – 24.99 Kg/m²)	**51 (19.7)**	**19 (17.7)**	**3 (5.4)**	
Pre-obese (BMI 25 – 29.99 Kg/m²)	**119 (46.1)**	**46 (42.9)**	**24 (43.6)**	
Obese (BMI ≥ 30 K/m²)	**88 (34.1)**	**42 (39.2)**	**27 (49)**	
	(NR=11)	**(NR=2)**	**(NR=1)**	
HbA1c	**6.5 ± 1.5**	**8.1 ± 1.5**	**10.3 ± 1.5**	
FBG	**155.6 ± 70.7 (N.R =3)**	**200.1 ± 71**	**269.1 ± 71**	
Duration of Diabetes	**12.8 ± 10**	**17.2 ± 9.8**	**14.7 ± 9.9**	**P=0.0035**
≥1-<3 years	**52 (19.3)**	**4 (3.6)**	**5 (8.9)**	
≥3-<6 years	**39 (14.5)**	**14 (12.8)**	**6 (10.7)**	
≥6-<10 years	**32 (11.9)**	**14 (12.8)**	**8 (14.2)**	
≥10 years	**146 (54.2)**	**77 (70.6)**	**37 (66)**	
Hypertension				**P=0.4751**
Yes	**192 (71.9)**	**85 (77.9)**	**40 (72.7)**	
No	**75 (28)**	**24 (22)**	**15 (27.2)**	
	(NR=2)		**(NR=1)**	
Dyslipidemia				**P=0.2338**
Yes	**122 (57.2)**	**60 (63.1)**	**38 (69)**	
No	**91 (42.7)**	**35 (36.8)**	**17 (30.9)**	
	(NR=56)	**(NR=14)**	**(NR=1)**	
CKD				**P=0.5276**
Yes	**189 (70.7)**	**83 (76.1)**	**39 (69.6)**	
No	**78 (29.2)**	**26 (23.8)**	**17 (30.3)**	
	(NR=2)			
Severe stage kidney disease (estimated GFR <30mL/min/1.73 m2)	**14 (5.2)**	**5 (4.5)**	**2 (3.5)**	**P=0.8592**
	(NR=2)			
Infections (unspecified)				**P=0.2779**
Yes	**22 (8.2)**	**13 (11.9)**	**8 (14.2)**	
No	**246 (91.7)**	**96 (88)**	**48 (85.7)**	
	(NR=1)			

Macrovascular complications				
Cardiovascular diseases	**37 (13.7)**	**12 (11)**	**5 (8.9)**	**P=0.5312**
Peripheral vascular disease	**45 (16.7)**	**14 (12.8)**	**8 (14.2)**	**P=0.6182**
Microvascular complications				
Retinopathy	**27 (10)**	**16 (14.6)**	**3 (5.3)**	**P=0.1630**
Nephropathy	**22 (8.1)**	**9 (8.2)**	**4 (7.1)**	**P=0.9635**
Neuropathy	**25 (9.2)**	**10 (9.1)**	**5 (8.9)**	**P=0.9962**
Diabetic foot	**27 (10)**	**5 (4.5)**	**5 (8.9)**	**P=0.2268**
SBP, mm/Hg	**142.8 ± 20.3 (NR=4)**	**145 ± 19.3**	**146.4 ± 18.4 (NR=1)**	**P=0.3352**
DBP, mg/dl	**109.5 ± 31.3 (NR=56)**	**116.4 ± 33.1 (NR=14)**	**123.2 ± 38.7 (NR=1)**	**P=0.0421**
Sodium, mEq/L	**140.1 ± 2.5 (NR=6)**	**139.8 ± 2.3**	**138.2 ± 2.7**	**P<0.0001**
Potassium, mEq/L	**4.4 ± 0.4 (NR=6)**	**4.5 ± 0.4**	**4.6 ± 0.4**	**P=0.0053**
Polypharmacy				**P=0.1270**
Yes	**110 (40.8)**	**57 (52.2)**	**24 (42.8)**	
No	**159 (59.1)**	**52 (47.7)**	**32 (57.1)**	
Number of diabetes medicines	**1.5 ± 1.1**	**2.3 ± 1.1**	**2.3 ± 1.1**	
Insulin use	**41 (15.2)**	**53 (48.6)**	**41 (73.2)**	**P<0.0001**
Other diabetes medicines				
Metformin	**112 (41.6)**	**44 (40.3)**	**16 (28.5)**	**P=0.1883**
Sulfonylureas	**54 (20)**	**39 (35.7)**	**17 (30.3)**	**P=0.0042**
GLP-1 r a	**14 (5.2)**	**9 (8.2)**	**4 (7.1)**	**P=0.5137**
DPP-4 inhibitors	**49 (18.2)**	**17 (15.6)**	**9 (16)**	**P=0.8033**
DPP-4 inhibitors/Metformin	**87 (32.3)**	**45 (41.2)**	**19 (33.9)**	**P=0.2522**
SGLT2 inhibitors	**26 (9.6)**	**25 (22.9)**	**9 (16)**	**P=0.0028**
SGLT2 inhibitors/Metformin	**17 (6.3)**	**4 (3.6)**	**2 (3.5)**	**P=0.4800**

BMI: body mass index, HbA1c: Glycated hemoglobin, FBG: fasting blood glucose, CKD: chronic kidney disease, SBP: systolic blood pressure, LDL: low-density lipoprotein, GLP-1 ra: Glucagon-like peptide-1 receptor agonists, DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors: Sodium-glucose Cotransporter-2 inhibitors, NR: not reported.

In the adjusted multivariable logistic regression, female gender, FBG, retinopathy, use of insulin, sulfonylureas, and sodium-glucose co-transporter-2 (SGLT2) inhibitors were statistically significant associated with decline in the potential overtreatment. Conversely, the use of insulin, and sulfonylureas were significantly associated with greater odds of potential undertreatment, and diabetes duration was significantly associated with lower odds of potential undertreatment (Table 3).

Table 3 Variables Associated with Potential Overtreatment/Undertreatment

Variables	Potential overtreatment		Potential undertreatment	
	Odd Ratio (OR)	95% confidence interval (CI)	Odd Ratio (OR)	95% confidence interval (CI)
Polypharmacy	1.273	0.645 to 2.512	0.718	0.257 to 2.005
Age group (75-84 years) vs age group (65-74 years)	1.008	0.487 to 2.084	0.380	0.128 to 1.133
Age group (≥ 85 years) vs age group (65-74 years)	2.946	0.491 to 17.663	1.045	0.094 to 11.673
Gender Female vs Male	0.410	0.213 to 0.789	2.690	0.989 to 7.315
Diabetes Duration	0.988	0.956 to 1.021	0.935	0.887 to 0.986
Obesity	0.852	0.426 to 1.705	2.017	0.762 to 5.341
Estimated GFR	0.997	0.990 to 1.004	1.007	0.997 to 1.018
Macrovascular complications				
Cardiovascular disease	1.129	0.357 to 3.574	0.308	0.032 to 3.005
Peripheral vascular disease	1.860	0.473 to 7.314	1.472	0.124 to 17.497
Microvascular complications				
Retinopathy	0.265	0.075 to 0.937	0.144	0.014 to 1.459
Nephropathy	1.954	0.443 to 8.622	2.313	0.208 to 25.760
Neuropathy	0.484	0.090 to 2.590	0.071	0.005 to 1.086
Diabetic foot	4.116	0.531 to 31.907		
Glucose lowering medicines				
Insulin use	0.137	0.063 to 0.298	4.878	1.602 to 14.855
Metformin	0.742	0.381 to 1.444	0.447	0.158 to 1.261
Sulfonylureas	0.346	0.165 to 0.724	3.176	1.056 to 9.548
DPP-4 inhibitors	1.261	0.500 to 3.178	0.833	0.202 to 3.430
Metformin + DPP-4 inhibitors	1.130	0.553 to 2.310	0.594	0.200 to 1.760
SGLT2 inhibitors	0.332	0.145 to 0.762	0.417	0.122 to 1.422

Metformin + SGLT2 inhibitors **GLP-1 agonists**	**1.277** **0.897**	**0.297 to 5.486** **0.251 to 3.200**	**0.104** **0.340**	**0.005 to 2.388** **0.063 to 1.849**
Systolic blood pressure (SBP)	**1.009**	**0.993 to 1.025**	**1.008**	**0.984 to 1.032**
Low-density lipoprotein (LDL)	**0.991**	**0.981 to 1.001**	**1.005**	**0.993 to 1.018**
Serum sodium	**3.879**	**0.391 to 38.461**	**5.745**	**0.350 to 94.230**
Serum potassium	**0.685**	**0.268 to 1.751**	**3.415**	**0.983 to 11.860**
Infections (unspecified)	**0.484**	**0.164 to 1.425**	**2.084**	**0.528 to 8.220**

2.5.5 Discussion

In the present study, a low prevalence of use of newer medicines with low-risk of hypoglycemia was found among the treatment of elderly people with T2D. These results appear opposite to the guideline recommendations and place those individuals as high-risk of hypoglycemia and other adverse outcomes (7,8,11). Hypoglycemia is a common adverse effect, especially with sulfonylureas that have the highest rates of serious hypoglycemia. Although, differences in hypoglycemic rates are varied among different types of sulfonylureas (16).

Similarly, using claims data from more than one and a half million people with T2D from 2006 to 2013 in the united states of America, there was a slight increase in the use of GLP-1 receptor agonist (2-3.4% age 65-74 years; 0.4-1% age ≥75 years), a greater increase in DPP-4 inhibitors (0.4-14.1% age 65-74 years; 0.1-10.8% age ≥75 years), and insulin (16.4-23.6% age 65-74 years; 17.2-20.4% age ≥75 years), and a slight decline in sulfonylureas (39.4-33.9% age 65-74 years; 37.9-32.9% age ≥75 years) as well as in other medicines including SGLT2- inhibitors (2.6-1.8% age 64-74 years; 2-1.7% age ≥75 years). Rates of severe hypoglycemia were highest among the elderly people with T2D (17).

The study has shown that more than 60% were potentially received tight glycemic control and more than 12% were potentially undertreated. Contrary to the expectations, the use of insulin and sulfonylureas were associated with less likelihood of potentially tight glycemic control and more likely to be associated with potential undertreatment (18,19). Shah et al addressed that less than one-half of diabetes individuals with high HbA1c levels had treatment intensification. Diabetes specialists were found to be more aggressive with insulin therapy than primary care physicians (20).

The results showed that SGLT2 inhibitors were used more in the potentially overtreated group, which can be associated with less hypoglycemia to those elderly people with T2D. A Recent meta-analysis confirms that, efficacy profile of gliflozins is unchanged by age, and the hazard ratio (HR) for major cardiovascular events (MACE) was (HR 0.87, 95%CI 0.81–0.94) in elderly T2D people taking a statin and (HR 0.88, 95%CI 0.77–1.01) for elderly T2D people not taking a statin (21). The study also shown that a potential non-statistically significant association between polypharmacy and potential overtreatment. McCracken and colleagues also found an association between polypharmacy and overtreatment (Relative risk (RR) 4.0, 95%CI 0.97 to 16.41) that approached the statistical significance (p=0.054) (22). This potential association could serve as a clinical indicator for tighter glycemic and overall management.

In addition, the study found that neuropathy was less associated with those who received potentially tight glycemic control. The VA Cooperative Study on T2D (VA CSDM) found that, no effect of glycemic intensification on the prevalence of neuropathy (23). Diabetes duration was found less associated with potential undertreatment. A non-significant association was previously reported with either overtreatment or undertreatment with diabetes duration (24). Clinicians frequently converge their management of risk factors on gaining specific targets of HbA1c, and other important outcomes such as blood pressure and lipid profile. This may be suitable for young adults with T2D, but older adults could not achieve the same benefits, especially when it takes a long time to provide its influence on outcomes and could result in the prompt potential for harm.

On the other hand, the opposing concept that clashes when clinicians consider management for T2D, which is the undertreatment of healthy older adults can result in clinical inertia. Many older adults with T2D can experience years of blood glucose levels above recommended targets and, consequently, higher microvascular and macrovascular risk.

Some potential limitations exist in the current study. Firstly, the study have cross-sectional design, which limits us to distinguish the harms from potential overtreatment/undertreatment and may limit the generalizability of the results. Secondly, there are several factors were not reported in the APDP administrative database (such as hypoglycemia episodes, hospitalization, death records) as these data are not intended primarily for research more than it is for administrative purposes. Which can be considered as one of the disadvantages of real-world data. Thirdly, the study may associate with a relatively small sample size, that could reduce the generalizability of results.

Our data show that there is a critical need to revise the management of older adults with T2D. Firstly, the clinical practice guideline developers should clearly define the concept of overtreatment and undertreatment of older adults. The definition should not be based solely on the HbA1c level but also involve the presence of comorbidities, complications, life expectancy, electrolyte balance, the risk for hypoglycemia or hyperglycemia, polypharmacy, and treatment costs. Secondly, our results suggest the need for more real-world observational studies due to the exclusion of older, and especially frail older adults from most traditional RCTs of diabetes interventions which left us with large scarcity in our knowledge of how best to address T2D management in the elderly group with the highest prevalence rates.

Lipska and colleagues suggested evidence-informed steps that could help clinicians to make individualized treatment. These steps included assessments of potential benefits and harms of intensive glycemic control. The need for treatment, duration of diabetes, cognitive impairment, and estimated life expectancy can be used to determine the likelihood of harms associated with treatment. In addition to patient preferences that should play a major role in determining the appropriate glycemic target as well as reducing polypharmacy (15).

Thirdly, even with the lack of certainty that found in some factors, acknowledging the presence potential overtreatment and undertreatment from routine clinical practice could help the clinicians to re-evaluate therapy that may cause more harm than benefit among those elderly people with T2D with advanced and/or multiple comorbidities, which may lower their risk of hypoglycemia or hyperglycemia. Fourthly, although the concept of overtreatment and undertreatment still not well defined, our assumed criteria are based on important key references, including results from a clinical trial, clinical practice guidelines recommendations, and critical review on the management of older adults with T2D. Finally, the use of an administrative database has several key advantages for measuring benefit-risk in real-world clinical practice; it can be implemented speedily and less costly compared than experimental studies providing health outcomes on a large special population such as the elderly vulnerable individuals that usually are not included so frequently in clinical trials (25).

2.5.6 Conclusion

Our key findings show that potential overtreatment and undertreatment have a higher prevalence among elderly T2D people that mostly in severe condition and currently under the care of a very specialized unit for diabetes care. Therefore, most of these patients at higher risk for hypoglycemia and hyperglycemia that can result in poor health outcomes. Insofar, the need for ensuring better access to diabetes care, linking glycemic targets to patients' goals and preferences, minimizing short-term and long-term complications, reducing polypharmacy, and

improving quality of life still are aims of the utmost importance in the management of diabetes patients. In addition, more real-world studies in the safety and effectiveness of current therapies are required to move from reliance on surrogate markers toward mortality outcomes identifying medicines that achieve the aims of diabetes care.

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CHAPTER THREE

GENERAL DISCUSSION AND CONCLUSIONS

The knowledge gap between the randomized controlled trials (RCTs) and the clinical practice guidelines regarding the definition and the impact of polypharmacy and overtreatment on patients' health-related outcomes can impose safety challenges in medication practices. In recent decades, the risks are increasing due to higher polypharmacy, drug-drug interactions, inadequate prescribing, leading causes for safety severe and moderate outcomes.

In *Chapter 2.2*, a systematic review and meta-analysis was conducted to investigate the impact of polypharmacy on different health outcomes using observational studies from routine clinical practice in older adults with T2D. Previous reviews by Fraval *et al* (1), Mathur *et al* (2), Lipska *et al* (3), and Dardano *et al* (4) were not systematic reviews and did not focus specifically on the concept of polypharmacy and concluded only that the presence of polypharmacy could be associated with a greater risk of hypoglycemia.

Systematic reviews and meta-analysis aim to identify, evaluate, and summarize the findings of all relevant individual studies over a health-related issue, thus being considered the best source of evidence-making, and more accessible to decision-makers (5). A systematic review and meta-analysis of observational studies is used when RCTs evidence is considered inexistent; RCTs may be considered infeasible or unethical, not reporting long-term or less common serious outcomes (particularly harms), or not reflecting use in real-world settings in terms of populations included, especially the elderly population (6).

The findings of the current study have shown that there is a recent investigation regarding polypharmacy in older adults with T2D, as they reflect data published between 2012 and 2018. Within the same time frame, clinical practice guidelines started mentioning polypharmacy as one of the major geriatric syndromes, as stated in the Standards of Medical Care in Diabetes 2012 (7). Accordingly, it can be considered a contributing factor to medicine-related adverse events and hypoglycemia, as mentioned in the International Diabetes Federation (IDF) guideline for older adults with T2D (8).

The findings have shown that the prevalence of polypharmacy reached more than 90% in older adults with T2D, defining the concept in numerical value mostly as using five or more medicines. Similarly, a global systematic review by Jokanovic *et al* of 44 studies assessing medication use in older adults aged ≥ 65 years in long-term care facilities found a 38.1–91.2% prevalence of polypharmacy where it was defined as ≥ 5 medications (9). In Europe, a cross-sectional analysis by Midãoa *et al* found that the prevalence of polypharmacy using the same definition threshold was 34.2% (10).

The word polypharmacy is derived from the ancient Greek "*polús*" meaning "many", and "*pharmakeía*" meaning "the use of drugs"(11). Despite the increasing prevalence of polypharmacy, the term continues to lack of clear universal consensus clinical definition, being mostly described in practice as the number of medicines exceeding a simple numeric threshold. The King's Fund report and the Scottish government's polypharmacy model of care group advocated that the definition of polypharmacy can be based on the appropriateness of medicines used, being classified as either appropriate or problematic (12,13). The World Health Organization (WHO), on the other hand, advanced that the term 'polypharmacy' naturally implies whether it is appropriate to prescribe several medications or not, although it is often assumed to be the same as being inappropriate (14).

The use of a numerical definition for polypharmacy might be more convenient than the qualitative term, as it is more straightforward to implement in clinical database systems and readily applicable to epidemiological studies. In addition, some researchers suggest that the use of five or more medicines as a definition of polypharmacy can be used to estimate the medication-related adverse effects for frailty, disability, mortality, and falls in the older population intending to reduce medicines-related harm (15).

To the best of our knowledge this, systematic review and meta-analysis is the first to address the association between polypharmacy and mortality, myocardial infarction (MI), stroke, and hospitalization in elderly people with T2D. The result of the random effect model in meta-analysis has shown that Polypharmacy was associated with 62% risk of all-cause mortality. The meta-analysis includes two cohort observational studies which have shown no sign of heterogeneity, with low risk of bias.

The systematic review and meta-analysis by Leelakanok *et al* addressing the association between polypharmacy and risk of death in general older adults supports the findings present in this thesis. The former study uses both discrete (having odds of 8% increase in risk of death) and categorical definitions of polypharmacy, where using 1-4 medicines, 5 medicines, and 6-9 medicines were significantly associated with greater odds of death (24%, 31%, and 59%, respectively). Excessive polypharmacy (10 or more medicines) was also associated with greater odds of death (96%). Although a higher level of heterogeneity (I^2= 91.5%) was found in the study, it could be due to different sample sizes and designs of the studies included in the meta-analysis (16).

While mortality hazards naturally increase with advancing age, the factors associated with this risk in older people with T2D become more complex, and include diabetes-related tissue damage and complications, polypharmacy, comorbidity, mental and physical frailty. Forbes *et al* found that the mortality gap between older people with and without T2D remains persistent, with excess mortality being 10% greater than in the general population, especially in older people with longer duration of T2D (17). Polypharmacy is a significant problem in the elderly with T2D where people need to take multiple hypoglycemic therapies, antihypertensives, and lipid-lowering therapies, conveying additional mortality hazards in older age (18). The number of prescribed medicines is high in people with T2D, and higher for older individuals with T2D than for those with Type 1 diabetes (T1D) (19).

Simultaneously, there are several lessons learned from previous large RCTs, namely the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (20), especially from the post-hoc analyses of the ACCORD study by Riddle *et al* (21). The well-known epidemiological relationship between glucose levels and greater risk of mortality has been confirmed in ACCORD with (+66% per 1% HbA1c) in the intensified strategy arm, to weak (+14% per 1% HbA1c) in the standard strategy arm. The inappropriate intensification led to polypharmacy: 42% of participants in the intensive therapy group were receiving 3 or more classes of oral agents, either alone (17%) or in combination with insulin (25%); in the standard group, such combinations were used in 19% of the participants (21). This use of multiple combinations of glucose-lowering medications in ways that are not used in standard care could have played a role in increasing mortality.

The systematic review and meta-analysis have shown that older adults with T2D on polypharmacy stand at the odds of 96% of having risk of MI. A retrospective cohort study by Zullo *et al* of 4,787 nursing home residents aged ≥ 65 years between 2007-2010 examined the effect of using more guideline-recommended medicines after MI in the frailest and oldest segment of the U.S. population. It found that prescribing 3 or 4 secondary prevention medicines to predominantly frail, older adults was associated with a 26% relative decrease in mortality compared with individuals who received 1 medication after acute MI. Although, the use of polypharmacy for secondary prevention was associated with a 30% relative increase in functional decline after excluding antiplatelet medicines from the exposure (22). It should be noted, however, that guidelines' recommendations for secondary prevention of cardiovascular diseases are conflicting. Therefore, these medications should be interrupted with caution, especially in elderly, frail people with T2D.

The systematic review and meta-analysis found that older adults with T2D on polypharmacy might be at a 33% higher risk of having a stroke. The question of whether a similar trend may be representative of the relationship between observed increases in older adults with T2D and risk of stroke deserves further investigation. It is worth advancing that a systematic review by Gallagher *et al* could not find an association between polypharmacy and risk of stroke in elderly people with atrial fibrillation (AF)(23). According to the American Diabetes Association (ADA) guideline, however, older individuals with T2D have higher rates of stroke than those without diabetes (24), although the guideline did not declare any risk factors that could be contributing to stroke in elderly people with T2D, or any specific recommendations to avoid (24). Moreover, an analysis of a 1,424,378, nationally representative sample of people in Scotland, showed that multimorbidity (18% have diabetes) and polypharmacy were more common in elderly people with a diagnosis of stroke, but no association was examined between polypharmacy and risk of stroke (25).

Alternatively, a very recent retrospective analysis by Mentias *et al* was conducted between 2015 and 2017 to evaluate patients with newly diagnosis of AF who initiated an oral anticoagulant (*i.e.* apixaban 5 mg twice daily, rivaroxaban 20 mg once daily, or warfarin) within 90 days of diagnosis, in which polypharmacy was categorized from low (≤3), to moderate (4-8), or high (≥9); it subsequently found that among individuals with high polypharmacy there may be a 2.3 times higher stroke risk with apixaban compared with warfarin, and 1.38 times stroke risk with rivaroxaban. However, differences were of borderline significance (26).

The systematic review and meta-analysis found that there is 72% greater odds of hospitalization in older adults with T2D on polypharmacy. Older adults are more likely to require hospitalization than younger adults, and those with diabetes are at very high risk of requiring hospitalization. The clinical practice guidelines provide a framework to clinicians for the management of older adults with T2D (24), yet these guidelines provide evidence-based orientation for inpatient treatment of adults who are not critically ill, not being based on either age or comorbidities (24,27).

Due to the lack of evidence on the subject, a recent cohort study by Anderson *et al* was conducted with 16,178 older adults with diabetes hospitalized in the veterans' health administration national health system and, found that 1 in 10 patients were discharged with intensified diabetes medications resulting in polypharmacy. Nearly 50% of patients receiving treatment intensification had already reached outpatient blood glucose goals or had limited life expectancy. The median number of medications for this cohort was 9, and one-fourth of patients was on 12 or more medicines (28). Hospitalization is common in people with T2D: nearly 1 in 4 diabetes-related hospital admissions were due to hypoglycemia. While the overall

rate of hypoglycemia-associated admission was low, the age-specific rate was nearly 2.5 times higher in older adults (29), especially in those using both insulin and sulfonylurea as the most likely to experience a hypoglycemia-related hospitalization (30).

No association between polypharmacy and glycemic control in older adults with T2D was found in the systemic review and meta-analysis. The review by Lipska *et al* (3), mentioned that diabetes polypharmacy (not overall therapy) can be associated with diminished benefits and greater risks of harm. The first glucose-lowering medication which often starts at higher HbA1c levels, compared with the levels when the second agent starts, decreases HbA1c more than subsequent medications. Starting a second or third medication for glycemic control leads to smaller reductions in HbA1c, as opposed to starting that same medication as monotherapy (3).

The systematic review also could not find an association between fall or fall risk and polypharmacy in older adults with T2D. However, many studies in the general older population have found this association. A systematic review by Ming *et al* found that polypharmacy (using four or more medicines) caused 1.5–2 times higher possibility of recurrent falls in older adults (31). Dahlawani *et al* found that using ≥ 4 medicines meant the rate of falls was 18% higher in people with polypharmacy compared with people without, whereas when using ≥10 medicines, polypharmacy was associated with a 50% higher rate of falls (32). Additionally, Woollcott *et al*, showed that the use of antidepressants and benzodiazepines is prevalent in older adults with T2D and demonstrated a significant association with falls (33).

Despite not being presented as a primary outcome, the systematic review also reported that the presence of severe hypoglycemia led to an increase in the risk of emergency visits due to the interaction between sulfonylureas (glyburide and glipizide) and co-trimoxazole antibiotic found mainly in older adults with T2D on polypharmacy. Sulfonylureas are used in the management of T2D and a known adverse effect of sulfonylureas is hypoglycaemia, with a reported rate of 1.23 hospitalizations per 100 patients per year (34). Further, the use of long-acting sulfonylurea glyburide is known to be associated with 90% a greater hypoglycaemic risk than glipizide (35). Ultimately, hypoglycaemia can result in significant morbidity, including deterioration in cognitive function, higher risk of dementia, strokes, and death (36), especially in older adults with T2D. Nevertheless, this sulfonylurea is still being widely prescribed by clinicians to this population.

Although the systematic review and meta-analysis examined the association between polypharmacy and critical outcomes, there are other important outcomes which either could not be addressed due to the lack of studies, namely kidney function or quality of life that usually address the association with disease not the treatment (37), or did not show an

association with polypharmacy, such as glycemic control. Additionally, there is not only a lack of studies reporting serious or severe drug-drug interactions which can be considered clinically significant, but also a lack of knowledge about what are the main potentially inappropriate medicines that can impact the management of older adults with T2D.

C*hapter 2.3 presents* a cross-sectional study conducted using data taken from older adults with T2D from a nationwide, pharmacy-based intensive monitoring study of glucose-lowering medicines in Portugal that took place between 2014-2015. The study's main aim was to investigate whether the presence of polypharmacy, potentially serious clinically relevant DDIs, and potentially inappropriate medicines (PIMs) can be associated with the low quality of life of older adults with T2D.

The study found that older adults with T2D on polypharmacy are associated with 80% greater odds of having a lower quality of life than those not on polypharmacy. Laiteerapong *et al* found that geriatric syndromes were associated with lower physical health-related quality of life (HRQL), and only hypoglycemia was associated with lower mental HRQL. No association between quality of life and polypharmacy was tested (38). In the general older population, a study by Schenker *et al* evaluated associations between polypharmacy, symptom burden, and quality of life. It found that higher polypharmacy (use of ≥ 14 medicines) was associated with lower quality of life. Adjusting for symptom burden weakened the association between polypharmacy and quality of life without a significant interaction, suggesting that worse quality of life associated with polypharmacy may be related to medication-associated symptoms (39).

The study has shown that those on potentially inappropriate medicines (PIMs) were associated with 57% greater odds of having a lower quality of life than those not on PIMs. Older adults with T2D frequently seek more health advice and worry more about their health, as its management is more complex than that of the general older population; this can lead to multiple prescribers' visits, from the GPs to the endocrinologists, which in turn can result in more prescriptions. Part of these medicines are inappropriate to use for their age and treatment of their current health problems which will ultimately increase the risk of harm from these medicines towards hospitalization and lower quality of life.

In the general older population, literature on the impact of PIMs on the quality of life agrees with our findings. In a prospective cohort study, which linked pharmacy dispensing data by Wallace *et al,* of 904 older adults aged 70 years or more between 2010-2012, found that the presence of PIMs was associated with adverse drug events, poorer health-related quality of life, and ≥ 1 accident, and emergency visit (40). Additionally, Harrison *et al,* also found that the increasing numbers of PIMs were also associated with lower EuroQol Five Dimensions

Questionnaire scores and Dementia Quality of Life Questionnaire-Self-Report-Utility scores (41). The PIMs most often used in the study (benzodiazepines and long-acting sulfonylureas) have all been associated with negative consequences, such as impaired cognition, increased risk fall and fractures, which can lead to more hospitalization or re-hospitalization and a decline in quality of life.

There might be an association between potentially serious clinically relevant drug-drug interactions (DDIs) and the low quality of life index score, but it does not reach the statistical significance level, which is obviously due to low prevalence of these interactions in the older adults with T2D in the study. The association may be indirect; these interactions are more possibly results of polypharmacy and are potentially associated with a high risk of adverse drug reactions and life-threatening complications leading to hospitalizations, morbidity, and reduced quality of life.

These potentially serious clinically relevant DDIs are mostly related to cardiovascular medicines. Such interactions can be associated with an increased risk of thrombotic events, hypotension or renal failure, myopathy, and risk of digoxin toxicity. No potential hypoglycemic risk was identified from these interactions in the study, which can be due to the original study focusing on specific type hypoglycemic agents, that is, the newer medicines (glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors). These agents are less associated with risk of hypoglycemia and have a less known interaction profile than old very well-known hypoglycemic medicines such insulin and sulfonylureas.

Although the study provides that polypharmacy, DDIs and PIMs might have an impact on the quality of life of older adults with T2D, these data are baseline and results may differ if the impact of these risk factors would be measured prospectively. The sample size of this population is relatively small. However, even if data were collected from a nationwide study, it could not be considered representative of all of the older adults with T2D on national and international levels, as the data used only included patients using certain types of glucose-lowering medicines. The relevant identified DDIs and PIMs are both potential, and their real-life impact needs further studies. In addition, the data did not include any laboratory findings, which limits our analysis. Furthermore, due to the nature of the study design, we are not sure whether the prescribed medicines for both T2D and other chronic and comorbid conditions were indeed consumed, nor if other herbal medicines or supplements were consumed by the patients.

C*hapter 2.4 presents* a cross-sectional study conducted with data of older adults with T2D who registered in 2018 through the administrative database of the Portuguese Diabetes Association (APDP). Administrative data sets provide a readily available source of real-world health care data on a large population of underrepresented patients in RCT such the elderly population (42). The study's main aim is to examine whether the presence of polypharmacy and potentially serious clinically relevant DDIs or PIMs can have an impact on glycemic control and kidney function.

The study findings suggest that older adults with T2D on polypharmacy are associated with twice the odds of having HbA1c ≤ 8%. The ADA clinical practice guideline recommended that "older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as HbA1c <7.5%), while those with multiple coexisting chronic illnesses, cognitive impairment or functional dependence should have less stringent glycemic goals (such as HbA1c <8–8.5%)" (24).

On the other hand, the European Diabetes Working Party for Older People stated that a range of HbA1c between 7–7.5% is suggested for older patients with T2D without major comorbidities, and 7.6–8.5% for frail patients (dependent, multisystem disease, home care residency including those with dementia), where the hypoglycemia risk may be high and the likelihood of benefit relatively low (43). Furthermore, the majority of adults older than 65 years, the harms associated with a haemoglobin HbA1c target lower than 7.5% or higher than 9% are likely to outweigh the benefits, based on several RCTs and observational studies (3)(44). Taken together, there might be an impact of polypharmacy on glycemic control, but it did not cross the recommended targets.

Conversely, the presence of polypharmacy can be associated with a harmful impact on glycemic control in older adults with T2D. Although it is not significant, the study found that polypharmacy might be associated with the likelihood of having a higher glycemic target (HbA1c > 9%), meaning that using multiple medicines may not be necessarily helpful in achieving therapeutic targets. Rational medication prescription dictates that the fewest medications be used to achieve the therapeutic goals as determined by clinician and patient.

In the UK Prospective Diabetes Study (UKPDS) Group, Turner *et al* concluded that the progressive deterioration of diabetes control was such that after 3 years, approximately 50% of patients could attain this goal with monotherapy, and after 9 years this declined to approximately 25% (45). Moreover, the meta-analysis by Bloomgarden *et al* showed that for patients with baseline HbA1c levels between 9% to 9.9%, oral agents decreased HbA1c levels by 1%. For patients with baseline HbA1c levels between 8% to 8.9%, oral agents decreased HbA1c

levels by only 0.6%; and for patients with baseline HbA1c levels between 6% to 6.9%, the average reduction was only 0.2% (46). Timbie *et al* adds that a significant proportion of people with diabetes will fail to achieve targets despite using high doses of multiple, conventional treatments, which raises concerns about the polypharmacy burden needed for tight risk factor control (47).

The study also found that the presence of PIMs was associated with 2.5 times greater odds of having HbA1c ≤ 9%. Several potentially inappropriate medicines used by older adults with T2D may interfere with glycemic control. Recent reports suggest that newer antipsychotic medications may also contribute to clinically significant hyperglycemia through inducing glucose regulatory dysfunction. Hyperglycemia and diabetic ketoacidosis can result in the increase of HbA1c levels, with multiple reports for clozapine and olanzapine, and more limited reports of significant hyperglycemia for quetiapine and risperidone (48–51). Fluoroquinolones are the only class of antibiotics consistently associated with the development of hyperglycemia (52). Other medicines that can cause hyperglycemia include thiazide diuretics, statins, and corticosteroids (53).

Older adults with T2D in the study who associated with at least one PIM are at 5.5-fold greater odds of having severe kidney function. Diabetic kidney disease is the leading cause of chronic kidney disease resulting in end-stage renal disease and premature death in older adults with diabetes (54). Elderly people with severe kidney function, especially those on hemodialysis, were prescribed PIMs more often than previously reported for the general elderly population (55).

The most identified kidney-based PIMs in the study which might be associated with risk severe kidney disease is the use of non-steroidal anti-inflammatory drugs (NSAIDs) for those with a creatinine clearance below 30mL/min/1.73m². NSAIDs are the most widely used drugs among the elderly people, the benefit-risk balance of individual NSAIDs is chiefly driven by their gastrointestinal, cardiovascular, and kidney safety profile. The clinical practice guidelines (56) for the management of older adults with T2D has for many years recommended the use of aspirin for primary and secondary prevention of cardiovascular diseases, as the death of diabetic patients over the age of 65 years is 68% attributable to coronary heart disease (CHD) and 16% to strokes (57). However, the side effects and potential toxicities of long-term NSAID use have raised concerns, including the increased risk of kidney toxicity.

NSAIDs have been identified as nephrotoxic agents with both acute and chronic effects on kidney function. While the short-term biological effects of sodium retention, edema, and acute renal failure with NSAIDs are well documented, limited scientific data are reporting the safety of these drugs on kidney function when NSAIDs are taken chronically or when they are taken by patients with pre-existing kidney disease. Existing data regarding long-term NSAID exposure is inconsistent. It was shown that patients with chronic kidney disease who took non-selective NSAIDs compared with those who did not were 56% more likely to develop end-stage kidney disease and require dialysis. Further, it has been documented that high dose NSAID use in the elderly with chronic kidney disease was a significant risk factor that accelerated chronic kidney disease progression (58,59).

Additionally, there might be other factors playing a role along with NSAIDs in the acceleration of kidney failure. Older people with T2D who have hypertension and/or are taking anti-hypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors/ angiotensin II receptor blockers (ARBs), were in a high-risk chronic kidney disease group, and had more chronic kidney disease-related risk factors. Besides, it has been noted that poor glycaemic control in older people with T2D is one of the key risk factors leading to the development and progression of chronic kidney disease (60,61).

Older adults with T2D and chronic kidney disease might suffer from drug-disease interactions more than drug-drug interactions. Dumbreck *et al* found that drug-disease interactions were common in chronic kidney disease, which occurred with T2D. These authors concluded that guideline developers should always explicitly decide whether chronic kidney disease is common enough in the real-world population, with the disease under consideration, to require comment or modification of recommendations. Prevalence of comorbidity with chronic kidney disease was about 4% in patients with depression, 14% in patients with T2D, and 23% in patients with heart failure. Ultimately, it might be better that guideline developers consider chronic kidney disease with heart failure and possibly T2D (62).

Despite the associations found between polypharmacy and its potential adverse reaction with glycemic control and kidney function, the data of older adults with T2D used in the study were the last updated data, and there is variability in the date of the last update among the included patients. For example, the HbA1c of a patient might be lastly updated 6 months before data collection, and new HbA1c might show different results. The same applies for the medicines, as many of these patients have their medicines list updated three or four months before data collection, which might also show different findings if a change occurs or the patient stops taking the prescribed medicines. The data used in the study was only according to those registered in 2018, and the results might be different if other patients from previous

years were included. Data regarding the chronic conditions and diabetes-related complications as well as laboratory data are incomplete for all patients, which also limits our analysis. Besides, the medicines recorded are only those related to T2D and to chronic and acute associated conditions; no OTC or herbal and/or supplements were recorded, nor was any dosage form, concentration, or frequency of administration, underestimating the prevalence of the potential serious clinically relevant DDI in the study. Although the data are collected from the most specialized diabetes institution in Portugal, it is not possible to generalize the results to the older adults with T2D on the national level, as these data are only collected from a single diabetes institution. Additionally, the results from the analysis of DDIs and PIMs are merely potential, and we do not know if it can have the same impact in real-life.

While the descriptive characteristics between the older adults with T2D in the previous two studies in the thesis did not show a *major* difference, the prevalence of polypharmacy (43.6% *vs*.72%), potentially serious clinically relevant DDIs (8.7% *vs*.10.5%), and PIMs (24.2% *vs*.36.1%) is lower in the study conducted within the APDP database, despite using the same study design, polypharmacy definition and the same explicit criteria for identifying PIMs and Micromedex drug-interaction platforms for DDIs.

The data of older adults with T2D in the previous study (Chapter 2.3) derived from a nationwide, pharmacy-based intensive monitoring (MOMI) study in Portugal of a T2D population whose only incident or prevalence of specific glucose-lowering medicines was with the GLP-1 receptor agonists, DPP-4 inhibitors and SGLT2 inhibitors. The data of the sample of this study (Chapter 2.4) derived from the most specialized diabetes institution in Portugal (APDP), which makes this study more representative for the purposes of this study, as it is capturing a population of T2D with different use of glucose-lowering medicines. In addition to medicines for T2D and other chronic conditions, the original MOMI database also captured over-the-counter medicines (OTC), supplements, and herbal medicines. Oppositely, the APDP database includes only T2D and other chronic and acute conditions medications. This is taken as having impacted the increase in the prevalence of polypharmacy, DDIs, and PIMs.

Chapter 2.5 analyses the concepts of overtreatment and undertreatment by conducting a cross-sectional study using the data of the older adults with T2D from the administrative database of APDP. Participants were categorized according to their HbA1c level from potentially overtreated (HbA1c≤7.5%), to appropriately on target (HbA1c≥7.5–≤9%) or potentially undertreated (HbA1c>9%). The reason behind choosing these glycemic targets is that several RCTs (65–67), observational studies (68,69), and the recommendation from clinical practice guidelines suggest that the harms associated with an HbA1c target lower than 7.5% or higher than 9% are likely to outweigh the benefits. With the current availability of hypoglycemic

agents with low risk of hypoglycemia, one could argue that the proposed glycemic target might be lower than that which has been suggested. If medicines with low treatment burden and hypoglycemia risk are the only required, a lower HbA1c target may be appropriate for older adults with T2D, considering life expectancy, other chronic conditions and/or diabetes related complications (70,71).

The results of the study have shown that the prevalence of potential overtreatment was identified in more than 60% of study participants. Comparing to older adults with T2D who are considered potentially on target, the group of potentially overtreated participants has shown to be more males, less obese, who have higher prevalence of macrovascular complications, neuropathy, and diabetic foot, and those associated with a higher prevalence of severe chronic kidney disease. These results suggest that attempts to achieve an intensive glycemic target below 7.5% will lead to net harm in most older adults with T2D, whereas the cardiovascular and microvascular benefits are uncertain for the majority of older adults with T2D, and the marginal benefits of decreasing HbA1c lower than 7.5% seems to be small (72).

On the other hand, our (the APDP) study identified more than 12% of the study participants as potentially undertreated, shown to be more females, obese, with a higher prevalence of dyslipidemia, peripheral vascular disease, infections, and diabetic foot, and using more insulin compared to potentially on-target participants. There is uncertainty behind the proper glycemic targets for this group of older adults with T2D. Nevertheless, there is a general consensus that HbA1c values higher than 9% should be avoided because they can lead to immediate symptoms, which might include polyuria, possibly occurring at blood glucose levels above the renal threshold (>180–200 mg/dL), which might lead to dehydration. In addition, hyperglycemia may cause fatigue, increased risk for infection, and/or cognitive impairment (73).

An important reason behind the undertreatment of older adults with T2D may be clinical inertia, which can be defined as the failure to start or intensify glycemic therapy when it is clinically indicated and inhibits the achievement of a proper glycemic target. Delayed treatment of older adults with T2D does not appear to be specific of primary care comparatively to specialty care despite some differences found (74). Given the complexity of T2D management in older adults, it is impossible to determine the extent to which apparent clinical inertia may reflect routine clinical practice in a reasonable or at least understandable manner. One possible explanation for this is that the clinical inertia is more related to clinician behavior, especially when dealing with those elderly patients who are asymptomatic despite elevated HbA1c level, and because of the fear of adverse consequences of treatment intensification such as hypoglycemia, potentially reduced quality of life, and perceived reduced adherence to treatment.

Additionally, current practice guidelines would likely favor initiating or intensifying pharmacotherapy. A variety of factors could nevertheless delay this decision, including the clinician's knowledge of attitudes towards evidence-based guidelines, clinical judgment and experience, ability to implement an appropriate decision in a given clinical and organizational context, and awareness of the patients' behaviors, and preferences. Another important issue is the absence of a universally accepted measure to quantify clinical inertia. Moreover, the clinical practice guidelines recommend a step-wise intensification following the loss of glycemic control. It remains unclear how this should be implemented in older adults, who are heterogeneous and may suffer from multiple comorbidities, complications, and/or chronic conditions, nor is it clear whether the intensification can carry more benefits than harm in those patients.

The study has found that the odds of potential overtreatment decreased by 59% in the case of females, by 73.5% in those with retinopathy, by 86.3% in those on insulin, by 65.4% of those on sulfonylureas, and by 66.8% on SGLT2 inhibitors. The increase in the odds of potential undertreatment was more than 4.8 times higher in insulin users and more than 3.1 times higher in sulfonylureas users. These results are different from those found in the literature, where insulin and sulfonylureas are main risk factors of overtreatment in older adults with T2D (75,76). There are several factors which might explain this difference: firstly, the glycemic target (HbA1c) which is used in this study is different from that reported in the literature (<7.5% *vs*. <7%); secondly, it is also possible to say that there is an influence of the healthcare setting. These elderly patients with T2D are being treated in diabetes specialty care institutions, where specialists may have more experience and comfort with glucose-lowering medications and hence may be more aggressive with their use when glycemic control is inadequate. Finally, specialists may give closer focus to diabetes issues during patient visits and offer improved access to nonphysician providers and patient education resources. Being continuously monitored by the same physician in a diabetes specialty care institution seems to ensure a better quality of care in terms of process measures. Specialists were less prone to clinical inertia than primary care practitioners, perhaps because specialists can focus closely on diabetes and on its related conditions during consultations (74).

The care of undertreated older adults with T2D by non-specialist teams might be suboptimal and random (8). The reasons for this are unclear but incorporate lack of knowledge and fear of inducing hypoglycemia. Additionally, these undertreated older adults with T2D might not receive proper treatment regimens with other agents such as metformin, DDP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists that leave them exposed to long periods of hyperglycemia, leading to inadequate glycemic control, and contributing to diabetes

complications. Insulin therapy offers the most potent antihyperglycemic effect of all diabetes agents and has a unique ability to induce diabetes remission when used to normalize glycemia.

As the data used in this study (chapter 2.5) is analogous to the previous one (Chapter 2.4), similar constraints were observed. Additionally, the administrative database in the APDP does not report other important outcomes such as hypoglycemic episodes, hospitalization, emergency rooms' visits, as well as frailty risk, and death records for the older adults with T2D, which limits further analysis for potentially overtreated and undertreated older adults with T2D. Finally, as there is no internationally agreed definition for either overtreatment or undertreatment.

Conclusions and Implication for Practice

Through the use of different healthcare databases from routine clinical practice, this thesis contributed to the examination of the impact of polypharmacy and overtreatment on older adults with T2D where the knowledge gap of these two important issues in the population is narrow in both RCTs and clinical practice guidelines. Several studies were conducted, and the most relevant findings as well as its implications to practice are as follows:

- The global overview of polypharmacy in older adults with T2D has shown that polypharmacy can be associated with 62%, 96%, 33%, and 72% odds of mortality, MI, stroke, and hospitalization respectively, compared to those not on polypharmacy. These data show the clinical importance for distinguishing the potential harms of multiple medicines and asserts the need for further investigations to confirm whether polypharmacy can be considered as a marker for prescribing appropriateness.
- The analysis of pharmacy-based data revealed that polypharmacy, potentially serious clinically relevant drug-drug interactions, and potentially inappropriate medicines have shown to be associated with more 80%, 34% and 57% odds of lower health-related quality of life in older adults with T2D, respectively. In spite of providing evidence that supports the need for greater adherence to recommendations for appropriate medication use, these findings further advance that efforts to maximize the quality of life of older adults with T2D should be considered as high a priority as preventing diabetes complications, namely through managing and screening for geriatric syndromes and avoiding hypoglycemia.
- The analysis of APDP administrative-based data has shown that polypharmacy and potentially inappropriate medicines can be associated with 2 to 2.5-fold greater odds of alteration of glycemic control, and that potentially inappropriate medicines can also be

associated with 5.5-fold greater odds of severe kidney function in older adults with T2D. These patients are vulnerable and frail with CKD. Management of these patients is often complex and lacking specific evidence-based treatment guidelines. Reducing these risk factors might be associated with good glycemic control and reducing the progression of kidney function. However, further larger RCTs involving older adults with T2D are needed to better understand the impact on glycemic control and kidney function in the future.

- In a specialized diabetes care institution, that is the APDP, more than 60% of older adults with T2D have found to be potentially overtreated, whereas 12% were found potentially undertreated. The former patients showed to be more males, pre-obese, have higher macrovascular, neuropathy, and diabetic foot, and associated with a higher prevalence of severe chronic kidney disease; the latter were more females, obese, have a higher prevalence of dyslipidemia, peripheral vascular disease, infections, and diabetic foot, and use more insulin compared to those appropriately on target. Personalized treatment in older people with T2D is still not common practice. A substantial number of older people are overtreated, and a lesser number is undertreated with probable harmful consequences. Major clinical guidelines for the treatment of older adults with T2D still recommend therapy with a primary objective of reaching set glycemic targets. Although guidelines promote individualized glycemic targets for patients based on their comorbidities, hypoglycemia, and capacity to carry out the treatment plan, a more profound shift is needed. Treatment should be selected to target specific complications and inherent risks and not solely HbA1c. Patients at high risk of cardiovascular disease may benefit from treatment with drugs that lower this risk. Setting an individualized glycemic target without accounting for the types and number of drugs needed to achieve it is no longer congruent. If these results have taught us anything, it is that there is no single recipe for glycemic management in older adults with T2D. To promote personalized care and overcome overuse, it is essential to incorporate the best available evidence (balancing harms and benefits) with the clinician's judgment (individualizing the evidence based on a patient's risk profile, prognosis, and context), as well as the patient's preferences and values (via shared decision making).

Future Perspectives

To optimize polypharmacy and/or overtreatment and undertreatment, a clear internationally agreed definition is required. This will give researchers, policymakers, and guideline developers a better understanding and a more concrete vision towards proposing a management plan. Clinical practice guidelines should also undergo a paradigm shift from the focus on single disease management toward multimorbidity and a patient's individualized treatment, with more attention to the data generated from real-world clinical practice. A comprehensive geriatric assessment tailoring therapy to the patient's individual needs should be placed in the frame of everyday practice since it takes into consideration the high heterogeneity in elderly T2D population. Several drug-drug interaction platforms are now available. However, most of these platforms produce theoretical interactions rather than practical, which are sometimes opposite to guidelines recommendations and may therefore be associated with low quality of evidence with the frequent omission of a method of administration or dosage form.

It is desirable to use more than one platform and compare the results. The quality of evidence for these interactions should be assessed carefully. More studies from routine clinical practice are needed; relying only on spontaneous reporting to identify patterns of drug-drug interactions is not enough. Active pharmacovigilance is required. The presence of explicit criteria like STOPP can help healthcare providers and alert them to potential inappropriate medicines use, helping to improve prescribing. More studies are needed to conduct a benefit-risk assessment regarding deprescribing medications in routine clinical practice, with special care required in prescribing and monitoring pharmacologic therapies in older adults with T2D.

Overtreatment and undertreatment in elderly people with T2D seems a common clinical practice despite the recommendations toward deintensification. However, limited studies suggest that the benefits of deintensification outweigh the harms. Data from recent RCTs showed that cardiovascular, kidney, and mortality outcomes may be improved with the use of specific emerging glucose-lowering medicines independently of their glycemic effects. Clinicians should be aware that hypoglycemic agents are mostly released after RCTs, thus a multimorbid elderly patient with T2D is still underrepresented. Therefore, patient-centered outcomes need a paradigm shift from the focus on glycemic control as the main quality indicator, towards providing more adequate diabetes care, linking glycemic targets to patients' preferences, reducing complications and burden of polypharmacy, and improving their quality of life. Furthermore, avoiding the harm from polypharmacy and overtreatment/undertreatment as

well as maximizing the benefits requires a system that regularly monitors and updates patient information. The data generation process must, therefore, be established in daily clinical practice to produce continual improvement in care, a learning healthcare system that generates and applies the best evidence for the collaborative healthcare choices of each patient and clinician; one which drives the process of discovery as a natural outgrowth of patient care, and ensures innovation, quality, safety, and value in the health care being provided.

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APPENDICES

apdp
Associação Protectora
dos Diabéticos de Portugal

Exmo. Sr.
Prof. Dr. João Filipe Raposo
Director Clínico da A.P.D.P

Ofício N.° 70/2019

Lisboa, 20 de Março de 2019

ASSUNTO: ***Polypharmacy in elderly diabetes type 2 patients at Portuguese Diabetes Association (APDP), Cross sectional analytical study.***

Cumpre-me informar V. Exa. que a Comissão de Ética para a Saúde da APDP,na sua reunião de 20 de Março de 2019 emitiu, por unanimidade, **PARECER FAVORÁVEL** à realização do ensaio clínico supracitado.

Com os melhores cumprimentos
A Comissão de Ética para a Saúde

Casimiro Menezes
Presidente

Instituição Particular de Solidariedade Social
Fundado em 13 de Maio de 1926 - Pessoa Colectiva nº 500 851 875
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Despacho para ser afixado em local público
e divulgado na página da internet da ULisboa

NPG/PD/12/2020

Por meu despacho de 22 de dezembro, proferido no uso de competências cometidas nos termos do Despacho n.º 4636/2019, do Diário da República, 2.ª série, n.º 87, de 7 de maio são nomeados para fazerem parte do júri das provas de doutoramento, no ramo de Farmácia, especialidade de Farmacoepidemiologia, da Faculdade de Farmácia da Universidade de Lisboa, requeridas pelo Mestre Labib Abdulrasool Abdulrasak Al-Musawe:

Presidente: Doutor António José Leitão das Neves Almeida, Professor Catedrático e Presidente do Conselho Científico da Faculdade de Farmácia da Universidade de Lisboa, Presidente do júri por delegação de competências;

Vogais:

-Doutora Paula Maria Façanha Cruz Fresco, Professora Associada, Faculdade de Farmácia da Universidade do Porto

-Doutor Carlos Miguel Costa Alves, Professor Auxiliar, Faculdade de Farmácia da Universidade de Coimbra

-Doutor Bruno Miguel Nogueira Sepodes. Professor Associado com Agregação, Faculdade de Farmácia da Universidade de Lisboa

- Doutora Carla Alexandra de Matos Torre, Professora Auxiliar Convidada, Faculdade de Farmácia da Universidade de Lisboa, Orientadora

Faculdade de Farmácia da Universidade de Lisboa, 22 de dezembro de 2020

A Diretora,

(Professora Doutora Maria Beatriz da Silva Lima)

Faculdade de Farmácia da Universidade de Lisboa
Av. Professor Gama Pinto 1649-003 Lisboa · PORTUGAL
Tel. (+351) 217 946 400 · · Fax (+351) 217 946 470 ·
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EDITAL

Doutor António José Leitão das Neves Almeida, Professor Catedrático e Presidente do Conselho Científico da Faculdade de Farmácia da Universidade de Lisboa, Presidente do júri, por delegação de competências, das Provas de Doutoramento no ramo de Farmácia, especialidade de Farmacoepidemiologia, da mesma Faculdade, requeridas pelo Mestre Labib Abdulrasool Abdulrasak Al-Musawe faz saber que:

1 – O júri das referidas provas é constituído pelos seguintes vogais:

- Doutora Paula Maria Façanha Cruz Fresco,
- Professora Associada, Faculdade de Farmácia da Universidade do Porto;
- Doutor Carlos Miguel Costa Alves,
  Professor Auxiliar, Faculdade de Farmácia da Universidade de Coimbra;
- Doutor Bruno Miguel Nogueira Sepodes,
  Professor Associado com Agregação, Faculdade de Farmácia da Universidade de Lisboa;
- Doutora Carla Alexandra de Matos Torre, Professora Auxiliar Convidada, Faculdade de Farmácia da Universidade de Lisboa, Orientadora, Orientadora.

2 – A tese apresentada tem por título "*"Patterns of polypharmacy and potential overtreatment in elderly people with type 2 diabetes mellitus using real-world data"*";

3 – O ato público de defesa da tese realiza-se no dia 1 de fevereiro de 2021, pelas 10h30, nos termos do artigo 5.º da lei 1-A/2020, de 18 de março, por vídeo conferência à qual se pode aceder através do Link:

https://videoconf-colibri.zoom.us/j/83890139572?pwd=bDN5Wlc1ZEZFUDc4ejhseStVSjI4QT09

4 – A duração total não deve exceder as 2 horas e 30 minutos, dispondo o candidato de tempo igual ao das intervenções dos membros do júri;

5 – Concluídas as provas, o júri reúne para proceder à apreciação e respetiva qualificação, por votação nominal fundamentada, cujo resultado constará da ata.

Faculdade de Farmácia da Universidade de Lisboa, 13 de janeiro de 2021.

O Presidente de Júri,

Assinado com Assinatura Digital Qualificada por:
ANTÓNIO JOSÉ LEITÃO DAS NEVES ALMEIDA
Presidente do Conselho Científico
Faculdade de Farmácia da Universidade de Lisboa
Cartão de Cidadão
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(Professor Doutor António Almeida)