

The Reasons for Low Uptake of New Antidiabetic Drugs with Cardiovascular Effects – a Family Doctor Perspective: Does Limited Applicability of Clinical Guidelines in Real-Life Practice Matter? A Narrative Review

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Review

The Reasons for Low Uptake of New Antidiabetic Drugs with Cardiovascular Effects—A Family Doctor Perspective: Does Limited Applicability of Clinical Guidelines in Real-Life Practice Matter? A Narrative Review

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Abstract: Chronic diseases, such as type 2 diabetes (T2D), are difficult to manage because they demand continuous therapeutic review and monitoring. Beyond achieving the target HbA1c, new guidelines for the therapy of T2D have been introduced with the new groups of antidiabetics (GLP-1ra and SGLT2-in). Despite new guidelines, clinical inertia, that can be caused by physicians, patients or healthcare system, results in T2D not being effectively managed. This opinion paper explores the shift in T2D treatment, challenging assumptions and evidence-based recommendations, particularly for family physicians, considering the patient's overall situation in decision-making. We looked for the possible reasons of clinical inertia and poor application of guidelines in the management of T2D. Guidelines for antidiabetic drugs should be more precise, providing case studies and clinical examples to define clinical contexts and contraindications. Knowledge communication can improve confidence and should include clear statements on areas of decision-making not supported by evidence. Precision medicine initiative in diabetes aims to identify subcategories of T2D patients (including frail patients) using clustering techniques from data science applications, focusing on CV and poor treatment outcomes. Clear, unconditional recommendations for personalized T2D management may encourage drug prescription, especially for family physicians dealing with diverse patient contexts and clinical settings.

Keywords: type 2 diabetes; therapeutic inertia; clinical guidelines; sodium-glucose cotransporter-2 inhibitors; glucagon-like peptide-1 receptor agonists; primary health care

1. Introduction

Managing chronic diseases is challenging, as they require continuous monitoring and evaluation of therapy. Guidelines for managing these diseases are rapidly changing, but due to clinical inertia, chronic diseases are often not well-controlled in clinical practice [1]. The term clinical inertia refers to healthcare professionals' inability to initiate or intensify therapy when desired therapeutic goals are

not achieved, and is considered a medical error with adverse effects on health-related outcomes and healthcare costs [2].

Type 2 diabetes (T2D) is a prevalent disease among the older population and is expected to increase due to the epidemic of obesity and global population aging [3]. Apart from well-known cardiovascular (CV) complications, T2D is also associated with a higher risk of other age-related conditions such as sarcopenia, malnutrition, falls, urinary incontinence, and cognitive impairment [4]. It is therefore among the most disabled illnesses. Multiple comorbidities and complicated care regimens affect the quality of life of these patients, while healthcare providers face challenges in delivering quality care [5]. Family physicians are under immense pressure in their role to provide comprehensive and patient-centered care [6]. Clinical inertia and low adherence to evidence-based recommendations are common issues in managing T2D [7,8].

Factors that contribute to clinical inertia can be attributed to doctors, patients, or the healthcare system, but they are often interconnected [2,9,10] (Table 1). In a narrow sense, clinical inertia refers to poor adherence to evidence-based recommendations for medication therapy, by healthcare providers, which is termed "therapeutic inertia" [10,11]. This distinction is important because it helps differentiate doctor-related causes of clinical inertia from patient non-adherence to pharmacological treatment [12].

Table 1. Factors influencing therapeutic/clinical inertia.

Physician-related factors:	Patient-related factors:	Healthcare-related factors:
Lack of knowledge about the illness	Refuse to accept having the illness	
Overlooking the seriousness of the symptoms	Non-existence of symptoms	
Not starting the treatment	Inadequate knowledge regarding the health	The absence of clinical guidelines
Inability to identify clinical outcomes	Considering that the illness is not severe	No database of morbidity or illness registries
Not adjusting the treatment until the intended result has been attained	Taking too many medications	No visit strategy (not scheduling appointments)
Inability to recognize and address comorbid condition	Financial limitation (cost of medications)	Absence of decision assistance and team-based care
Patient takes over the therapeutic discussion and decision	The negative effects of medications	Insufficient funds and time
	Aspects of lifestyle	Technical deficiency
Lack of knowledge about the illness	Ineffective patient-doctor communication (lack of trust)	
Reactive care as opposed to a proactive treatment strategy		

With the emergence of new groups of antidiabetic drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1ra) and sodium-glucose cotransporter-2 inhibitors (SGLT2-in), which have significant cardio- and renal-protective effects, the pharmacological treatment of T2D has begun to undergo revolutionary changes [13]. It appeared that the framework outlined in international

actionable documents to efficiently combat cardiovascular disease (CVD) in patients with T2D has come to be realized [14]. The integrated management of T2D and CVD would be of the utmost importance for public health, as both conditions were found to share common risk factors and pathophysiology pathways. This is especially significant since CVD is a leading cause of death worldwide [15,16]. Despite the proven efficacy of novel antidiabetic drugs in reducing CV morbidity and mortality in T2D patients, their prescription rates remain low in many countries and across clinical disciplines [17].

The new approach to treating T2D patients has undergone a shift that challenges some fundamental assumptions of clinical practice for T2D and the belief that following evidence-based recommendations can reduce clinical inertia. This conflict is particularly relevant for family physicians, which need to consider the patient's overall situation in their decision-making. In this opinion paper, we will explore some of these issues, with a particular focus on the family physician's perspective. This critical viewpoint refers primarily to the common guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), and their recent updates, as widely used among providers in European countries [18–20]. We will also illustrate some of our critiques using data collected through our research.

2. Hesitancy in delivering a new antidiabetic drug treatment strategy related to postulates of clinical inertia

To determine the extent of clinical inertia, three postulates are crucial: 1) the specific clinical outcomes that the treatment is intended to achieve, 2) the recommended therapy regimen that should be administered, and 3) the timeframe for timely intensification of therapy [2]. Regarding the first postulate, intermediate biomarkers, that measure the quality of care in T2D patients, like hemoglobin A1c (HbA1c), blood pressure, and low-density lipoprotein (LDL)-cholesterol have been preferred in most studies over end-point clinical outcomes, like general or cardiovascular mortality, or hospital admission rates, as the latter requires long-term prospective follow-up [8,11]. The laboratory marker, HbA1c, has been traditionally used as a standard to guide medication therapy in clinical guidelines and practice [13]. The development of novel anti-diabetic medications with cardiovascular advantages caused a change in treatment goals, with the main objective now being to reduce CV risk rather than just controlling glucose [18,20]. Healthcare providers might have faced an internal problem while making decisions regarding this switch. Even more so, the current ADA/EASD guidelines still recommend achieving optimal glycemic control, to minimize the risk of cardiac events in the long term [19,21]. Therefore, there is a need to meet the dual goal.

The question being considered is whether combining a classical hypoglycemic drug with a new-class drug, when optimal HbA1c is not achieved, is beneficial in the long run or the episodes of hypoglycemia, as evidence suggested, may rather cause harm, also regarding long-term health outcomes [22]. It might be a dilemma especially in older T2D patients with multiple health conditions, who are however the right candidates for new-class drugs [18,21]. On the other hand, does maintaining a suboptimal HbA1c diminish the positive CV effect of the new-class drug, in any manner, to avoid hypoglycemia? Two lines of concern that healthcare providers face are evident in this dilemma. The first one is fear of over-treating and resulting hypoglycaemia – a known reason for clinical inertia when managing T2D patients [23,24]. The second is the uncertainty associated with long-term outcomes, which is difficult to predict in individual patients, as multiple factors that characterize patients, and variations in treatment, can influence them [25]. Beyond the providers' hesitancy to intensify or change the therapy is not always indolence, but the fear of harming, or the difficulty of deciding conditions of uncertainty. The abovementioned is supported by studies demonstrating that therapeutic inertia increases with the prescription of more antidiabetic drugs over time and decreases when HbA1c levels rise [11].

Regarding the time from the problem detection to therapy intensification, the studies that were conducted before the advent of new antidiabetic drugs reported a long time delay despite the suboptimal glycaemic control [26,27]. How to know whether some of the GLP-1ra or SGLT2-in is delivered timely when there is more than one criterion to follow? Is early therapy intensification the

right choice in treating newly diagnosed, usually obese, T2D patients, and do they need to be treated with new antidiabetic drugs immediately or when clear signs of heart failure or renal function impairment become visible? How these choices fit into the national health strategy in terms of financial restraints is also crucial. However, the intensification of therapy for newly diagnosed T2D patients has always been a challenge [28]. The 2018 update of ADA/EASD guidelines provides an alternative prescribing policy for low-income countries, which is not based on evidence-based recommendations [18]. Sharing the results of cost-effectiveness studies on new antidiabetic drugs with national healthcare authorities could help overcome therapeutic inertia [29].

The primary healthcare system's ability to systemically screen T2D patients with low renal function—information that is crucial for evaluating T2D patients with chronic kidney disease (CKD)—remains an obstacle, particularly for family physicians. In particular, to obtain information on quantified heart failure (whether it is with preserved or reduced ejection fraction), an ultrasound examination is required, making it unreliable to assume that all T2D patients have this information. The recent trials, examining the structured model of care - that is the model with standardized elements of the care process, have shown benefits for quality of care, clinical outcomes, and cost-effectiveness [30,31].

Finally, considering that some patients may meet more than one set of indication criteria, how can the proportion of T2D patients who qualify for therapy with novel antidiabetic drugs be determined? (Figure 1).

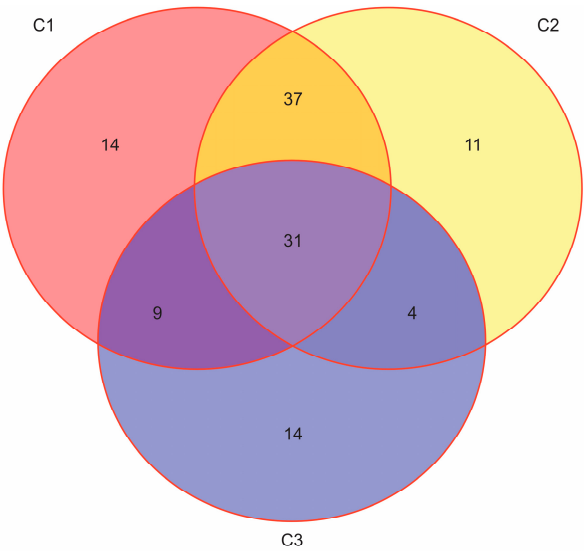


Figure 1. The overlap rates among the eligible patients for treatment with GLP-1ra or SGLT2inh. The results from our research (N=170, F: M = 95:75, age 50–89 years, median 66). The simplified criteria for prescribing GLP-1ra or SGLT2inh: C1: Atherosclerotic CVD (Coronary artery disease, or Periphery artery disease, or Cerebrovascular disease); C2: Age ≥55 years + chronic heart disease; C3: estimated glomerular filtration rate (eGFR) < 60 ml/min).

The clinical guidelines offer recommendations for delivering standardized and optimal care to patients based on scientific evidence. Adherence to guidelines by healthcare providers is considered the principal way to limit clinical inertia [10]. Despite the proven benefits, implementation rates remain below 50% historically across clinical disciplines [10,32]. Many attempts have been made to identify barriers that limit the implementation of clinical guidelines in daily medical practice [33,34]. It has been found that many guidelines manuals are too long and complicated, making it difficult to implement them effectively. Furthermore, they often fail to offer solutions for specific patient scenarios. Research on implementation strategies for guidelines needs to be intensified. Implementing guidelines should be part of a wider process of knowledge translation that results in the creation of protocols and workflows. Given the abundance of guidelines available, there is a

growing need for continuous quality assessment and improvement of the development process. In today's era of healthcare system digitalization, online tools such as websites, alerting systems, interactive platforms, and clinical decision support systems are being used to aid in the access and implementation of clinical guidelines. However, the effects on practice and clinical outcomes from these tools are still unknown.

In the diagnosis, treatment, and follow-up of chronic diseases, primary healthcare providers, mostly family physicians, play a central role [9]. They are even more concerned than specialist endocrinologists with decisions on when is the right time to change or intensify therapy in T2D patients because their decision-making is more complex and involves the care of the whole patient [35]. This may be particularly challenging in circumstances such as starting insulin therapy, introducing new medications in the treatment plan, or attempting to achieve glycemic control by combining two or more oral antidiabetic drugs, as it is usual in older patients with multiple comorbidities [36]. In such cases, family physicians tend to pass the responsibility of choosing the treatment to endocrinologists, trying to avoid any anxiety that may arise due to the side effects of intensifying the therapy or using medications that they have less experience with [37].

It can be challenging to implement clinical guidelines in primary care and family medicine due to the specific nature of the workflow, which involves a holistic approach to patient care, by considering patient preferences for treatment, their ability to take medications independently, and predicting their adherence to suggested treatment [25]. It is assumed that education on psychological factors that influence patient behavior in care uptake would reduce the providers' uncertainties during decision-making and should become a part of implementation strategies [38]. In addition, family physicians may have strong attitudes towards certain medications that they have experience with and that are well accepted by patients and may be hesitant to try new treatments, despite the evidence of their efficacy [37]. Based on that, it is important to research the psychological factors that may influence family doctors' attitudes towards their behavioural intentions and decisions for action, as well as on doctor-patient communication that can shape behavioral changes. This research should be an integral part of the process of clinical guidelines development [39].

Overall, clinical guidelines are generally not designed to suit the working style of primary care providers and family physicians [35,40]. In addition, there is a lack of competency-based workflow and effective communication models between different disciplines, which can also contribute to the non-adherence of family physicians to the guidelines [37]. Research performed thus far has identified several categories of barriers and enablers to the implementation of clinical guidelines in primary care [7,41,42]. Suboptimal inter-professional communication, non-transparent division of professional responsibilities, time constraints, limited applicability of the guidelines in real-life practice, lack of knowledge and skills of primary care providers (the lack of implementation strategies), poor motivation to use guidelines in everyday workouts, and inadequate reinforcement were among the most commonly reported barriers. The most frequently reported enablers were the presence of technical support, timely education, and training for both primary care providers and patients. It is widely assumed that conducting qualitative research among primary care providers and family physicians could be a valuable way of information gathering on guidelines gaps and barriers in implementation strategies that concern them specifically [42].

3. Trends in the ADA/EASD guidelines on T2D patient management strategy and the effect on new antidiabetic drug uptake

The recent updates of the ADA/EASD guidelines (2018, 2019, and 2022), and the position statements drawn from them, have brought several areas of improvement for managing T2D patients [18–20,43]. First, the requirement is emphasized for the systematic screening of T2D patients for CVD and increased CV risk and the treatment of these patients with antidiabetic drugs with proven CV efficacy. It marked the end of the long-standing paradigm that T2D is the risk equivalent of coronary artery disease (CAD) or, in other words that all patients diagnosed with T2D have the same risk for atherosclerotic CVD (ASCVD). The studies conducted in the past two decades have revealed that risk levels in T2D patients approach the CAD risk levels after a decade of T2D duration or in patients with

target organ damage (proteinuria, estimated glomerular filtration rate <30 mL/min/1.73 m², left ventricular hypertrophy or retinopathy) or in those with three or more CV risk factors [44]. This finding allowed the grading of CV risk in T2D patients in three categories, very high, high, and moderate levels. The target management, of those at high and very high CV risk, has become possible thanks to the results of CV outcome trials (CVOTs), that have become mandatory for all novel drugs used to treat T2D patients [45].

Up to date, significant CV benefits have been proven for several GLP-1ra and SGLT2-in drugs, and they are advised as a preferred treatment choice for patients with T2D and established ASCVD or those at increased risk for ASCVD, independently of the glucose control level and the background use of metformin (the first-line medication). The therapy with SGLT2-in takes precedence over GLP-1ra for T2D patients with chronic heart failure (CHF) and chronic kidney disease (CKD) [21,45]. In addition, increased CV risk can be ameliorated through the potent effect of these drugs, in particular, GLP-1ra and emerging insulin secretion stimulating drugs tirzepatide, on body weight reduction [46,47].

Nevertheless, the uptake rates of GLP-1ra and SGLT2-in drugs remain low. The potential barriers in their prescribing, that refer to the gaps in the guidelines, include safety concerns, lack of clarity about when is the right time, and to whom, exactly, the therapy with either of these drugs should be initiated, as well as the lack of understanding of the treatment effects such as glycaemic, cardiac, and renal outcomes, including possible side-effects, concerning the specific sociodemographic, clinical, and laboratory characteristics of patients to whom these drugs are to be prescribed (48 - 50). For example, differences in patient socioeconomic status may be important for the uptake of SGLT2-in, if the costs are a concern [48]. A lesser glycaemic response can be expected for SGLT2-in in case of lower renal function and for GLP1-ra in case of patient reduced insulin secretion ability [49]. The knowledge is still insufficient on the full range of health effects of new antidiabetic drugs, in particular, SGLT2-in, and safety issues cannot be predicted with sufficient confidence [51–53]. An introduction of these drugs into the existent therapeutic scheme, in particular of older patients with multiple comorbidities and polypharmacy, may potentially cause interactions with other treatments or disease-related conditions, which may cause concerns among providers and family physicians about indications for these medications' therapy [49,54–56] (Table 2).

Table 2. Possible side effects and heterogeneous treatment effects for SGLT2-in and GLP-1ra.

Heterogeneous treatment effects	Possible side effects
Higher baseline HbA1c values are associated with greater glycaemic response.	Concerns regarding the start of SGLT2-in in patients with CVD or kidney illness, as well as the necessity of close observation of diabetic ketoacidosis (DKA) in cases of COVID-19 or other acute conditions requiring hospitalization.
GLP-1ra: there is no proof that renal function affects the response to glucose; SGLT2-in: lessened glycaemic response in patients with diminished kidney function.	There is a higher risk of genital and urinary tract infections , which can be attributed to prolonged and increased glycosuria.
There isn't any reliable proof that body mass index significantly modifies the glycaemic response.	Raised concerns about gliflozin-induced cancers (bladder and breast cancer), even though causality cannot be established. More research is required.
GLP-1ra: less glycaemic response is linked to longer duration of diabetes ; SGLT2-in: the length of diabetes does not consistently affect glycaemic response.	Gliflozins cannot rule out drug-induced liver damage . Due to SGLT1 transporters' reduced inhibition there may be a lower risk of severe hypoglycemia when using gliflozins.
GLP-1ra: no proof that aging affects glycaemic response; SGLT2-in: some research indicates that an older age may be linked to a lower glycaemic response.	Hypovolemic events are frequent with gliflozins and DKA can appear infrequently and be more challenging to diagnose. Gliflozins-associated fracture risk is likely influenced by a number of variables that require additional research. Symptoms of glucose-galactose malabsorption were uncommon in clinical trials.
No reliable proof that gender or ethnicity significantly modifies the glycaemic response.	

SGLT2-in: no indication of variation in the reaction to treatment for patients with obstructive sleep apnea or for insulin secretion and insulin; GLP-1ra: studies indicate that lower fasting C-peptide and lower urine C-peptide-to-creatinine ratio, are linked to a reduced glycaemic response.	Renal function needs to be regularly monitored due to a possible reduction in GFR. Elderly patient and with renal impairment should use much more caution. There is a link to a greater rise in the less atherogenic significant LDL-C subfraction. The ratio of LDL-C to HDL-C remains nearly unaltered because of a concurrent rise in HDL-C.
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The question that needs to be clarified is how much variations between drugs, trial designs, or patient characteristics may influence the differences in the treatment effects of these drugs. In trial designs significant differences between CVOTs have been detected. Post-hoc analyses, with patient re-grouping into different CV risk categories, have been suggested as a solution to overcome these disparities [50]. In addition, the structure of patients included in CVOTs does not match the characteristics of T2D patients in real-life conditions, which could undermine the providers` confidence in recommendations provided by the guidelines [57]. Recognizing this problem, the CVOT Summit 2022 has issued a Report with recommendations to analyze the real-world data (that are routinely collected in practices), to complement the results of CVOTs, by providing more specific information on treatment options, patient risks, and safety issues related to these medications, which could help the decision-making process [58]. For example, an insight into the safety of SGLT2-in in specific patient groups such as elderly individuals has been obtained this way [59].

The general expert view is that the guidelines should be more precise in terms of how to use these drugs in specific situations, by providing case studies and clinical examples, to more specifically define clinical contexts in which to initiate their use or for which contraindications may exist [48]. Similarly, family physicians assume that their confidence can be improved by strategies such as appropriate knowledge communication with them. They also assume that the guidelines should contain clear statements about which areas of decision-making are not sufficiently supported by evidence, and for which subgroup of patients the harm-benefit ratio when using new antidiabetic drugs is not well understood [42,60].

Many of these gaps, which can lead to difficulties in making decisions about individualized therapy for T2D patients, are the result of a lack of study data. Nevertheless, in the development of the recent updates to the ADA/EASD guidelines for the management of T2D patients, there is a clear intent to promote a patient-centered approach that could help healthcare providers, particularly family physicians, alleviate concerns in decision-making and ultimately reduce clinical inertia [18–20]. According to these updated guidelines, the choice of antidiabetic drugs should be made with the patient in mind. Consideration should be given to comorbidities, but also to the risk of hypoglycemia, the impact on weight, the treatment cos, the side effects, and the patient's preferences. In addition, the 2022 ADA/EASD guidelines focus on the social determinants of health and healthcare systems and provide the necessary evidence for counseling patients on non-pharmacological treatment and behaviour change, including physical activity, sleep hygiene, weight management, and nutrition [19]. While the ADA/EASD guidelines still do not explain the need for systematic assessment of mental health and well-being in T2D patients, the openness for continued knowledge development and implementation into practice is clearly outlined.

4. T2D patient complexity and endeavor towards precision medicine

The possibilities of medication treatment of T2D patients are expanding, and advances in technology support such as continuous or intermittent scanning of glucose levels, mobile health, digital support, and visualization systems are leading to improvement in the management of these patients [18–20]. On the other hand, the requirements for a high standard of care, which include patient-centered and personalized approaches, may be constrained by still insufficient understanding of patient complexity. The complexity means a great variability among patients in clinical characteristics, comorbidity patterns, organ damage degrees, and the potential for negative health outcomes, and is in particular characteristic of elderly patients (65+), who in turn involve a

major part of T2D patients [4,61]. This group experiences T2D alongside aging and accumulation of comorbidities and geriatric syndromes such as sarcopenia, malnutrition, cognitive impairment, and frailty, which can alter the pathophysiology of T2D, treatment effects, and outcomes [4].

In particular, older T2D patients with frailty are more prone to hypoglycaemia and its adverse consequences, including falls, fractures, hospitalization, CV events, and mortality. Consideration should be given to simplification, switching, or de-escalation of the therapeutic regimen in these patients [62,63]. However, if insufficiently treated, hyperglycemia can lead to acute complications such as dehydration, poor wound healing, and hyperglycaemic hyperosmolar coma, which should be avoided [63]. There is a delicate balance between over-treating and suboptimal treating, which requires an individualized treatment approach, by carefully planning both pharmacological and non-pharmacological treatments [64]. Sometimes, it is not clear how much under-prescription of the guideline-recommended therapy to frail patients, and how much the frailty status per se, contributes to poor outcomes [65].

Frailty is considered a state of failure of homeostasis in multiple organs and systems and is manifested by non-specific symptoms and signs such as muscle mass reduction, slow walking, low activity, and a feeling of exhaustion that are progressive in number and severity with aging and the presence of comorbidities [66]. Experts agree that an assessment of frailty should become a part of older T2D patients' examination so that glycaemic targets and therapeutic choices can be modified accordingly [63]. Nevertheless, knowledge is still insufficient to allow the formal guidelines development to help healthcare providers in their decisions of how to precisely manage these patients. One of the reasons may be the complex interplay between T2D, CVD, CKD, sarcopenia, and frailty (Figure 2). These conditions share common pathophysiology pathways and can potentiate the development of each other [64,67,68].

Frailty is associated with incident T2D in an older population and increased risk of comorbidities and poor outcomes; and vice versa, T2D predicts transition to higher frailty levels, while vascular complications of T2D and associated malnutrition accelerate functional decline associated with frailty [64].

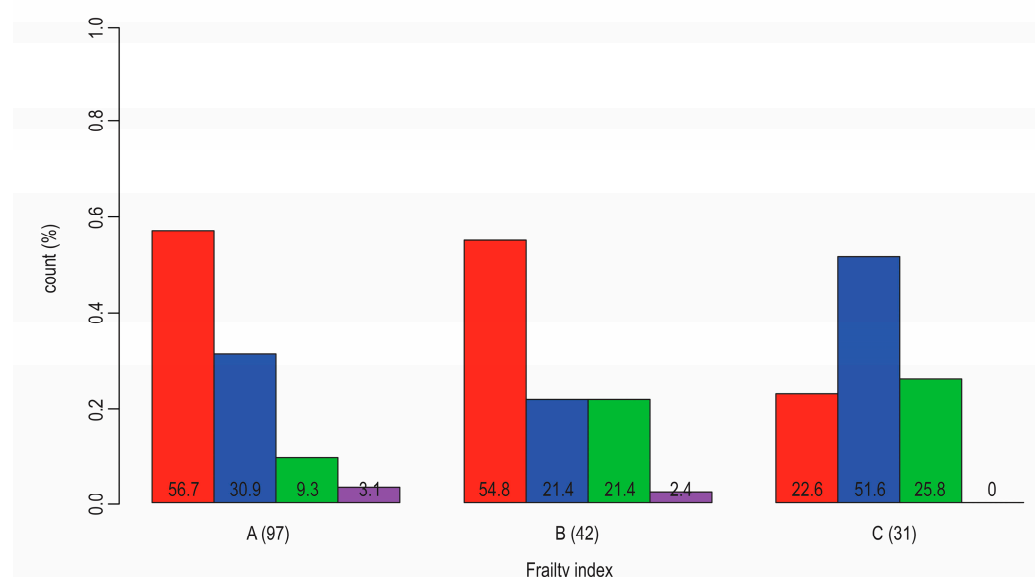


Figure 2. Distribution of patients with T2D and diagnosed with CVD (red: no CAD or CHD; blue: both CAD and CHD; green: only CHD; red: only CAD) according to frailty status (A: nonfrail, B: pre-frail, C: frail); Fisher Test p-value (0.003). The results from our research (N=170, F: M = 95:75, age 50–89 years, median 66).

Frailty contributes to the heterogeneity of patients with T2D. At least two frailty phenotypes exist in older T2D patients. One is associated with obesity and high insulin resistance (sarcopenic obese phenotype) and another is associated with weight loss, the body's shrinking, and low insulin

resistance (anorexic malnourished phenotype) [69]. The growing evidence indicates that the clinical expression of frailty is sex-dependent, which means that women are more prone to frailty and frailty-related physical disability than men, while men experience frailty at older ages than women [70,71] (Figure 3). Contrary to what is the case in the general population, women with T2D are more prone than men with T2D to CVD, but preferably for a non-atherosclerotic type of CAD and CHD [72,73].

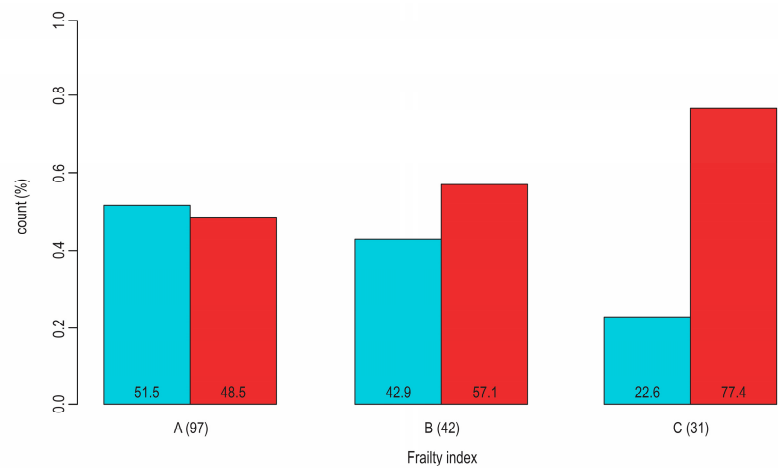


Figure 3. Sex-dependent distribution (blue: men, red: women) of patients with T2D according to their frailty status (A: nonfrail, B: pre-frail, C: frail); Pearson Chi-Square (p-value = 0.02). The results from our research (N=170, F: M = 95:75, age 50–89 years, median 66).

In summary, the relationship between T2D and frailty is complex, and many questions are still unanswered, which makes the treatment of older T2D patients challenging. This can also be applied to the treatment of these patients with new antidiabetic drugs, GLP-1ra and SGLT2-in (Table 3).

Table 3. A list of studies indicating the effect of older age and/or frailty on treatment effects with GLP-1ra and SGLT-2-in in patients with T2D.

Study (design)	Findings summary
Lin TK, et al., 2023. (population-based longitudinal cohort study) [74]	SGLT2-in use was associated with a non-significantly decreased risk of ACS. No difference in the SGLT2-in subtype was observed in subgroup analyses. The results indicated an increased risk for the incidence of ACS in male and older (> 70 years) patients.
Leong DP, et al., 2023. (population-based longitudinal cohort study) [75]	Frailty confers substantial incremental prognostic information to prognostic variables for predicting death and hospitalization in heart failure patients. The relationship between frailty and these outcomes is consistent across countries at all income levels.
Kutz A, et al, 2023. (1:1 propensity score-matched cohort studies) [76]	SGLT2-in and GLP-1ra safely improved CV outcomes and all-cause mortality, with the largest absolute benefits among frail people.
Young KG, et al., 2023. (a systematic review)	Current evidence on treatment effect heterogeneity for SGLT2-in and GLP-1ra

[49]	therapies is limited, likely reflecting the methodological limitations of published studies. Robust and appropriately powered studies are required to understand T2D treatment effect heterogeneity.
Strain WD, Griffiths J, 2021. (a systematic review and meta-analysis) [77]	GLP-1ra and SGLT2-in reduced MACE outcomes in older adults who were eligible to participate in clinical trials. Whereas this is reassuring for the biologically robust, it should not be extrapolated to frail older adults without further investigation.
Karagiannis T, et al., 2021. (a systematic review and meta-analysis) [78]	In older adults (≥65) with T2D, GLP-1ra reduced MACE and its components. SGLT2-in reduced MACE, heart failure, and renal outcomes.
Vart P, et al., 2023. (a randomized controlled trial) [79]	The relative benefit of dapagliflozin in patients with chronic kidney disease (with/without T2D) for all outcomes was consistent across all frailty categories, with no difference in associated safety.

ACS: acute coronary syndrome; MACE: major cardiovascular event; T2D: type 2 diabetes; CV: cardiovascular; HF: heart failure.

Although the common conclusion of the studies performed so far is that SGLT2-in and GLP-1ra improve CV outcomes in older (≥65) and frail patients, concerns remain when narrowly defined patient subgroups are used for analysis such as older men and those older than 70 years [74]. In addition, frailty may change the harm-benefit balance of these drugs. One of the main concerns about their use in older or frail patients, in particular regarding GLP-1ra, is the effect of these drugs on weight loss, which in these patients could be counterproductive. For SGLT2-in, it is also important to take care of the presence of urinary incontinence, a disorder often associated with frailty, since the use of SGLT2-in may lead to worsening of this disorder, or cause serious infections in these patients [55]. In addition, the reduced hypoglycaemic effect of SGLT2-in in patients with low renal function may potentially increase the risk of diabetic ketoacidosis [55,63].

Following increased awareness of the heterogeneity of T2D patients and the requirement for individualized treatment, an initiative has been launched for precision medicine in diabetes [80,81]. Studies that assess the feasibility of using clustering techniques from data science application areas are underway, wanting to identify subcategories of patients with T2D that can be discriminated against in terms of CV and other poor outcomes and responses to treatment. Our research group has contributed to these efforts [82–84]. Regarding treatment, precision medicine looks at variations in drug effectiveness in specific patient subgroups and seeks markers (especially genetic markers) that can predict adverse drug events [80]. However, many challenges still need to be overcome before it will be possible to implement precision medicine in the management of T2D patients [71].

5. Discussion

Taken together, the evidence is still limited on how different patient features, including age, sex, body mass and shape, comorbidity patterns, frailty status, and the level of renal function decline, may impact differences in how individuals respond to GLP-1ra and SGLT2-in. This is partly due to the traditionally inadequate characterization of participants in clinical trials, who are not systematically assessed for comorbidities, functional status, and frailty. Clinical inertia is known to be exacerbated by ambiguous guidelines and pathways. On the other hand, being aware of the broader patient context, and how it may predict responses to certain treatments, will allow for better-informed decisions for personalized management of patients with T2D.

According to the above discussion, the heterogeneity of older patients with T2D and an insufficient understanding of factors that influence treatment outcomes in older patients with T2D, might be a key barrier to individualized patient care and a reason for poor adherence of healthcare providers and family physicians to guidelines. For healthcare professionals to safely prescribe antidiabetic medications and make decisions about when to escalate or de-escalate treatment, the guidelines should be designed to assist the treatment of older adults with type 2 diabetes. This would be especially important for family physicians, who usually do not feel confident to radically change therapy by themselves. The international authorities emphasize the necessity of comprehensive patient assessment, which would allow the multilayered and holistic approach to managing these patients [80]. Data indicating comorbidities, co-medications, functional disabilities, mental health disorders, doctor-patient communication, patient health literacy, issues such as a willingness to change or a preference for a certain type of therapy, and the patient's need for support, are all things to take into account. Many of these factors have an impact on medication uptake rates, and ultimately on the patient response to treatment and the outcomes.

Evidence from epidemiologic research indicates that the time perspective of disease progression is critical to consider for hyperglycemia management, treatment regimen planning, and the prediction of CV events in T2D patients [85]. Variables such as T2D duration, patient age, and age at T2D diagnosis showed prognostically meaningful, considering that the diagnosis earlier in the life course, younger age, but longer T2D duration, carry out higher CV risk [104]. The fact that CKD, which usually accompanies T2D, is regarded as an independent CV risk factor, is also an important issue to take care of [86,87]. The variables specifically significant for the prognosis of T2D patients are age at T2D onset, eGFR, and HbA1c. These variables were aligned with the latest classification system for CV event risk estimation (SCORE2), which comprises classical CV risk factors such as age, sex, smoking, systolic blood pressure, total and HDL-cholesterol, and re-calibrated into a new system, SCORE-2 Diabetes, used for estimating the ten-year risk of CV events in T2D patients of European countries [21,88].

By allowing T2D patients to be included in CV risk assessments as those who are most at risk for CVD, the model mentioned provides important advancements in the prevention of CVD [89]. Many CV risk prediction models applicable to patients with T2D have been developed so far, but they could not accurately predict individuals who will probably experience CVD [90,91]. The applicability of SCORE-2 Diabetes has yet to be proved, concerning the accuracy of the prediction and the adequacy of the risk factors that have been included in the model [92]. In-depth evaluation of T2D patients is still necessary to precisely identify individuals with subclinical CVD who are at very high CV risk and are, therefore, also candidates for introducing therapy with new antidiabetic drugs [18,93]. Once cardiac biomarkers are approved for routine usage, routine testing using them will be a more straightforward method of accurately screening these patients [93,94].

The classical CV risk factors (which make up the SCORE2 model) do not perform well as CV risk predictors in this group, while some new variables like pharmacologic treatments, cognitive decline, and frailty have been proven to be better predictors. This makes the SCORE-2 Diabetes model particularly uncertain when it comes to predicting CV risk in elderly T2D patients. [95,96]. There are also uncertainties related to the effect of sex on CV outcomes in T2D patients and on the expression of frailty phenotypes, which may have implications on responses to treatment [72,97,98].

6. Future directions

Precision medicine hoped to improve the health of individuals or specific population subgroups by identifying biomarkers (genetic, epigenetic, or biochemical) for early detection of important diseases which, in turn, would guide interventions [99]. The success of this approach has been shown partially. One of the primary causes is the potential for exceedingly complex disease etiology, particularly in the case of prevalent non-communicable diseases. In chronic complex diseases, genetic associations have a small effect size on the expression of phenotypes, in contrast to the more robust contribution of behavioral and social factors [80]. Moreover, these diseases develop as a part of the aging process, by sharing common pathophysiological pathways with aging and with each other,

showing a tendency to cluster together [100]. Knowing the clinical, biological, and sociodemographic characteristics that are consistently linked to variations in clinical outcomes is essential for treating patients with chronic complicated diseases on an individual basis [49].

Today, there is an emerging trend in using large-scale person-generated health data from electronic health records, smartphones, and wearables, to characterize different patient subgroups, and to improve the health and well-being of particular patient subgroups through strategies customized to their specific characteristics [101]. Based on our own experience, we recommend the implementation of Artificial Intelligence (AI) and data-driven research methods in primary care and family medicine, to become a part of the routine healthcare workflows [102]. As an answer to doubts about the accuracy and repeatability of the results of these methods, it is worth mentioning that the techniques in the field of AI applications that already exist can guarantee the generalizability of findings or can consider the patient effect heterogeneity. It might diminish uncertainties associated with patient complexity, and support family physicians in more individualized decisions, especially in areas where guidelines cannot provide clear recommendations. The search for simple-to-obtain biomarkers of CVD or frailty that can be used in population-based studies could also help harness uncertainty.

In addition to CVOTs, further research efforts should focus on preparing real-life studies, aimed at addressing complex issues such as different comorbidity patterns. Priority should also be given to advancing translational and implementation sciences, which should obligatorily include qualitative research including primary care providers and family physicians. This will hopefully help remove obstacles to the practical application of the guidelines in practice and tailored recommendations.

To summarize, the unresolved issue of how to manage the heterogeneity of patients with T2D and to define subgroups with different levels of CV risk is the main barrier to individualized treatment and the reason for low uptake of GLP-1ra and SGLT2-in drugs, despite accumulating evidence on their CV benefits and decreasing costs. The shortcomings of the guidelines primarily reflect the methodological limitations of the current evidence base. Intensification of research, with the introduction of new research methods and approaches is necessary to fill the current research gaps and allow the translation of new evidence into the guidelines` recommendations and clinical practice. This ultimately involves the discovery of new biomarkers for CVD and frailty.

We summarized priorities for future work that should fill the gaps in the current evidence-based recommendations, as identified by this review, including strategies that refer to designing future research, the process of the guidelines development, and knowledge implementation strategies (Table 4).

Table 4. Future directions for overcoming T2D patient heterogeneity and increasing uptake of GLP-1ra and SGLT2-in drugs.

Research	Guidelines development	Knowledge implementation
More comprehensive patient profiling for CVOTs	Clear division of areas where there is no support by evidence	Continuous knowledge translation
Real-world data-driven research	Case report, Examples dealing with real-life experience	Educational training modules for healthcare providers, health policy officials, and patients
Patient clustering based on multiple descriptors (including comorbidity patterns)	Monitoring for the side effects of the treatment regimens The effects of comorbidity and frailty on treatment outcomes	Learning on case reports Audit analysis of real-world data with the support of information technology
Research intensification on the treatment effects of non-pharmacological	Evidence provided by cluster-analyses	

interventions, in particular including psychological factors	Clear recommendations on when to intensify and when to de-escalate therapy	Implementation of care protocols and workflows Empowerment of family doctors in life science knowledge
New biomarkers exploration	Clear statements on when to start with the cardio-protective therapy in the course of the disease	The establishment of the platform for data collection and curation from electronic health records, smartphones, and wearables;
Integrated models of care	The effects on outcomes of non-pharmacological interventions, in particular, concerning psychological factors	Data selection for data-driven modeling
Qualitative research – assessing family doctors` attitudes	Problem-solving approach	The results of data modeling become visible in the workplace by using AI visual techniques
Translation research intensification	Guidelines adaptation for use in primary care	

7. Conclusions

Current evidence on treatment effect heterogeneity for GLP1-ra and SGLT2-in therapies is limited, reflecting the methodological limitations of the underlying research. The introduction of new research methods and approaches is necessary to fill the current research gaps and allow for an understanding of treatment effect heterogeneity in T2D patients. The translation of new evidence into the guidelines` recommendations and clinical practice needs to involve different methods and more active approaches. Clear and unconditional recommendations for individualized management of patients with T2D may encourage the prescription of these drugs by the providers, which is especially crucial for family physicians who deal with a wide range of specific patient contexts daily, as well as various clinical and social settings.

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Abbreviations

T2D	type 2 diabetes
CV	cardiovascular
GLP-1ra	glucagon-like peptide 1 receptor agonists
SGLT-2in	sodium-glucose cotransporter-2 inhibitors
CVD	cardiovascular disease
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes
HbA1c	hemoglobin A1c
LDL	low-density lipoprotein
CAD	coronary artery disease
ASCVD	atherosclerotic cardiovascular disease
CVOT's	cardiovascular outcome trials
CHF	chronic hearth failure
CKD	chronic kidney disease
AI	Artificial Intelligence
DKA	diabetic ketoacidosis

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