Implications of health and metabolic heterogeneities for glycaemic management in older patients with type 2 diabetes

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Aptissima omnino sunt, [...], arma senectutis artes exercitationesque uirtutum, quae in omni aetate cultae, cum diu multumque uixeris, mirificos ecferunt fructus, non solum quia numquam deserunt, ne extremo quidem tempore aetatis [...], uerum etiam quia conscientia bene actae uitae multorumque bene factorum recordatio iucundissima est.

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CICÉRON, *Caton l'Ancien, ou de la Vieillesse*, I, 3.

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LIST OF ABBREVIATIONS

AD	Anno Domini
ADA	American Diabetes Association
ADL	Activities of daily living
AIC	Akaike information criterion
ATC	Anatomical Therapeutic Chemical
ATC	Anatomical Therapeutic Chemical Classification System
BC	Before Christ
BCF	Beta Cell Function
BIC	Bayesian information criterion
BMI	Body Mass Index
CAD	Coronary artery disease
CCS	Cross sectional study
CFS	Clinical frailty scale
CI	Confidence interval
CPG	Clinical practice guidelines
CVD	Cerebrovascular disease
DbC	Diabetes centre
DC	Diabetes Canada
DDD	Defined daily dose
DPP4-I	Di-peptidyl peptidase-4 inhibitor
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
ES	Endocrine Society

GL	Glucose-lowering
GLP1a	Glucagon-like peptide 1 receptor agonist
GLT	Glucose-lowering therapy
GLT	Glucose-lowering therapy / treatment
GP	General Practitioner
HA	Hypoglycaemic agent
HbA1c	Glycated haemoglobin
HOMA2	Homeostasis Model Assessment 2
HOMA2%- βxS	Residual β-cell function (assessed using HOMA 2)
HOMA2%-S	Insulin sensitivity (assessed using HOMA 2)
HOMA2%-β	β-cell function (assessed using HOMA 2)
HR	Hazard ratio
iADL	Instrumental activities of daily living
Imp.	Impairment
IR	Incidence rate
IRR	Incidence rate ratio
LADA	Latent Autoimmune Diabetes in Adults
LE	Life expectancy
LL	Log likelihood
LOE	Level of evidence
LPA	Latent Profile Analysis
LTC	Long-term care
MMSE	Mini-mental state examination
NHGA	Non hypoglycaemic agent
OGTT	Oral glucose tolerance test
OHA	Oral Hypoglycaemic Agents

OR	Odds Ratio
Overttt	Overtreatment
PAD	Peripheral artery disease
PCS	Prospective cohort study
RCS	Retrospective cohort study
RCT	Randomised controlled trial
SGLT2i	Sodium glucose cotransporter 2 inhibitor
SOR	Strength of recommendation
SUH	Sulfonylureas
T2D	Type 2 diabetes
Underttt	Undertreatment
VIF	Variance inflation factor

GENERAL INTRODUCTION

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Historical background

Diabetes mellitus is among the earliest documented diseases. The first known written description of diabetes was included in the Ebers Papyrus from 1550 BC, in particular about polyuria [1]. The term “diabetes” was first used by Aretaeus of Cappadocia (130-200 AD) and stems from the ancient Greek (diabaínein - διαβα′ινειν), meaning “passing through” [2, 3], to which was added the Latin word "mellitus" meaning "honey" about 1400 years later, by Thomas Willis (1621-1675 AD) [4]. The modern history of diabetes is made of numerous scientific advances addressing the understanding and the management of the disease (the discovery of islets of Langerhans in 1869 or the role of insulin in the early 20th century).

Diabetes definition and typology

Diabetes mellitus is a heterogeneous group of chronic diseases, characterised by glucose dyshomeostasis resulting in a chronic hyperglycaemia [5]. The most recent classification includes type 2 diabetes (T2D), type 1 diabetes, gestational diabetes and specific types of diabetes including monogenic diabetes syndromes, drug- or chemical-induced diabetes and diseases of the exocrine pancreas. Type 2 diabetes is the predominant form of diabetes in adult patients, in particular those aged > 65 years (90% of all types of diabetes) [6].

Epidemiology of diabetes in an ageing population

In Europe, in 2019, T2D was diagnosed in 59 million of adult patients (8.9%; IC 95%: 7.0 – 12.0%) [6]. The prevalence increases with age, and reaches a peak around 80 years, due to the higher incidence of the disease in older age-groups. Almost half of patients with T2D are diagnosed between the ages of 53 and 72 years for men, and 54 and 76 years for women [7]. The prevalence of diagnosed type 2 diabetes in patients aged ≥ 65 years is estimated at 20.1% (IC 95%: 15.3 – 25.8%) [6, 8].

Mainly due to the demographic ageing of the population in Europe, a significant increase of this prevalence is expected in the next 25 years [6, 8]. Overall, the number of people aged ≥ 65 with T2D is projected to reach 38.79 million in 2030 (20.2%) and 46.3 million in 2045 (20.5%) [8].

This high prevalence of T2D in older people and its predicted progression in the coming years is placing an increasing burden on public health and health care systems. As compared

to people of same age and sex, those with T2D generate health expenditures 2.3 times higher than those without diabetes [9]. The overall direct healthcare costs per patient was estimated between €2793.3 and €4882.1 in Germany (diabetes-specific and diabetes-associated direct costs) [10, 11]. Diabetes-related healthcare costs per patient are not significantly different between younger and older patients [10]. However, due to the demographic ageing, the majority of total diabetes-related healthcare costs was spent for patients aged ≥ 65 years [11, 12].

Clinical presentation and diagnosis of type 2 diabetes in older people

The classic symptoms of T2D present in adult patients (polyuria and polydipsia), are often absent in older ones. The clinical presentation of T2D in older patients is usually insidious or asymptomatic. It may manifest as confusion, dehydration, urinary incontinence or complications of chronic hyperglycaemia [13].

The diagnosis of T2D in older people relies on the same criteria as in other adults, namely a fasting plasma glucose ≥126 mg/dL or a 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT) or an HbA1c measurement ≥6.5%, or else a random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycaemia [14].

Pathophysiology of type 2 diabetes in older people

It is caused by impaired pancreatic β-cell function (decreasing insulin secretion), exacerbated by insulin resistance (decreasing peripheral sensitivity to insulin action) (Fig. 1(a)) [15-17]. In addition to the strong polygenic predisposition, which contributes directly to β-cell dysfunction, insulin resistance and/or obesity, these mechanisms are promoted by several risk factors that are commonly associated with ageing.

In older people, insulin resistance is enhanced by lifestyle changes (decrease of physical activity and obesity), excess of adiposity in muscle, decrease of muscle mass and function (sarcopenia), chronic inflammation, hormonal dysregulation (age-related alterations in hypothalamic-pituitary-testicular, hypothalamic-pituitary-adrenal and insulin-like growth factor 1 axes) or mitochondrial dysfunction in brain and muscle [18-22]. In addition to age-related decline of β-cell mass, loss of adaptive response of β-cells to insulin resistance induced by age seems to play a major role in loss of insulin secretion, resulting in T2D [17, 23].

Complications of type 2 diabetes

Diabetes may be associated with acute or chronic complications. Chronic hyperglycaemia results in multiple complications affecting micro-vessels (microvascular complications), directly attributable to toxicity of hyperglycaemia. These include diabetic retinopathy, nephropathy and polyneuropathy [24]. The occurrence of these complications is dependent of the duration and severity of exposure to hyperglycaemia. Moreover, patients with T2D are at higher risk of cardiovascular diseases (also called "macrovascular complications" in the context of diabetes), such as ischaemic heart disease, peripheral artery disease, stroke and heart failure [25, 26].

The rates of these complications are different in older people than in younger ones. In older people aged 70-79 years with short duration of diabetes, coronary artery disease is the predominant complication (11.47/1000 person-years) followed by end-stage renal disease (2.6/1000 person-years), lower-limb amputation (1.28/1000 person-years) and acute hyperglycaemic events (0.82/1000 person-years) [26]. These incidence rates are higher in people of similar age with longer duration of diabetes, yet are prevalent to the same degree & distribution: coronary artery disease, end-stage renal disease, lower-limb amputation, and acute hyperglycaemic events (78.98, 7.64, 4.26 and 1.76/1000 person-years, respectively). Interestingly, for comparable known duration of diabetes, incidence rates of cardiovascular disease (macrovascular complications) increase with age, whereas the incidence rates of microvascular complications decrease with age [26, 27].

Finally, T2D is associated with a higher risk of death at all ages before 80 years, as compared to patients of similar ages without diabetes [28]. However, the relative risk of increased mortality are lower in older people with T2D than in younger ones, probably as a result of shorter life-expectancy due to age [29].

Relationship between type 2 diabetes, ageing and frailty

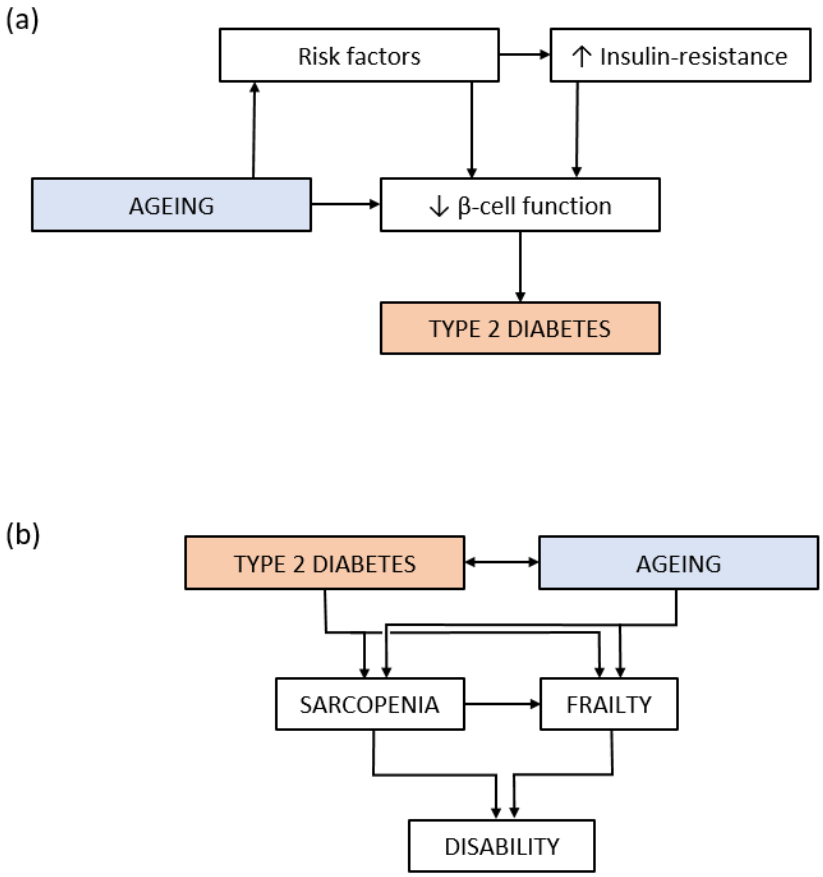
Besides influences of ageing on T2D pathophysiology (see paragraph PATHOPHYSIOLOGY OF T2D), diabetes also influences ageing and its consequences (fig. 1(b)). Overall, ageing and T2D are two acknowledged risk factors for functional decline and disability. Older people with T2D have indeed greater risk to develop functional decline or disability than people of similar age without diabetes, mobility disability, impairment in instrumental activities of daily living, and impairment in activities of daily living [30, 31]. Other classic geriatric syndromes are associated with T2D in older people, such as cognitive impairment,

falls, polypharmacy, depression, institutionalisation, malnutrition [32], and decreasing patient's quality of life [33].

Disability, functional impairment and subsequent geriatric syndromes are all components of frailty, a syndrome defined by a decrease of individual response to stressors and of physiological reserves [34, 35]. The Clinical Frailty Scale (or Frailty Index) proposed by Rockwood is among the commonest means used to define frailty [36]. Prevalence of frailty in overall older people varies between 7 and 30%, depending on populations' characteristics [37]. In older people with T2D, this prevalence increases, and the risk of frailty is higher as compared to people without diabetes [38].

A common cause of frailty is sarcopenia, defined by a loss of muscle mass and function [39]. As a consequence of insulin resistance, insulin deficiency and its catabolic effects, as well as changes in physical activity and nutrition, age-related loss of muscular mass and function, and micro-inflammation, diabetes and ageing all converge to promote sarcopenia [40, 41]. Thus, sarcopenia represents a crucial intermediate factor bridging T2D and frailty (Fig. 1(b)). Better understanding the relationships between diabetes, ageing, sarcopenia and frailty has become an emerging field of research over the last decade. Such links are increasingly acknowledged as a key mechanism in the pathophysiology of T2D in older people [42].

Fig. 1. **(a)** General pathophysiology of T2D in older-age people. **(b)** Relationship between ageing, T2D, sarcopenia and frailty.



Management of type 2 diabetes

T2D management has several dimensions: (i) controlling hyperglycaemia, (ii) reducing overall cardiovascular risk and (iii) managing and preventing glucose-related complications in target-organs [13]. Achieving these goals requires therapeutic control of several aspects of metabolism, including glycaemic control, anti-hypertensive management and lipid-lowering treatment. Glycaemic control is one of the most emblematic aspects of T2D treatment, and will be the sole dimension considered hereafter.

Table 1. Glucose-lowering drugs used for glycaemic control

GLUCOSE-LOWERING CLASS	PRINCIPAL MECHANISM	DISADVANTAGES	RISK OF HYPOGLYCAEMIA*
INSULIN	External substitution of insulin secretion	High risk of hypoglycaemia	High
SULFONYLUREAS (glipizide, glimepiride)	↑ insulin secretion from pancreatic β-cells	High risk of hypoglycaemia	High
METAGLINIDES (repaglinide)	↑ insulin secretion from pancreatic β-cells	High risk of hypoglycaemia	High
BIGUANIDES (metformin)	↓ hepatic glucose production	Gastro-intestinal intolerance & vitamin B12 deficiency, lactic acidosis, contra-indicated in eGFR<30ml/min	Negligible
DPP-4 INHIBITORS (sitagliptin, saxagliptin)	↑ insulin secretion (glucose-dependent)	Expensive	Negligible
GLP1 RECEPTOR AGONISTS (exenatide, liraglutide, semaglutide, dulaglutide)	↑ insulin secretion (glucose-dependent), ↑ satiety	Expensive, gastro-intestinal intolerance	Negligible
SGLT2 INHIBITORS (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin)	↓ glucose reabsorption by the kidney, ↑ urinary glucose and sodium excretion	Expensive, aggravates urinary incontinence and causes yeast infection of genitalia, volume depletion (risk of orthostatic hypotension) especially if concomitant use of diuretics	No
ALPHA-GLUCOSIDASE INHIBITORS (acarbose)	↓ Intestinal glucose absorption	Gastro-intestinal intolerance	No
THIAZOLIDINEDIONES (pioglitazone)	↑ insulin sensitivity	Fluid retention, small risk of bone fracture	No

DPP-4: Dipeptidyl peptidase 4, eGFR: estimated glomerular filtration rate (in ml/min/1.73m^2), SGLT2: sodium-glucose cotransporter 2, GLP1: glucagon-like peptide-1; * When used as monotherapy. Adapted from [43, 44].

Glycaemic control can be achieved through lifestyle changes (nutritional adaptation or physical exercise increase) with or without pharmacological glucose-lowering treatment.

Nine different drug classes are regularly used to control glycaemia, acting specifically to increase β-cell function (stimulating insulin production or replacing endogenous insulin, decreasing glucagon secretion), increase insulin sensitivity (decreasing hepatic gluconeogenesis, enhancing peripheral glucose uptake through insulin-mediated pathways), or other mechanisms (increasing glycosuria, promoting satiety, delaying intestinal glucose absorption, etc). Each drug class has advantages and disadvantages, including different risk of inducing hypoglycaemia (summarised in Table 1) [43, 45, 46]. Glucose-lowering therapies (GLT) are based on use of one drug among these drugs classes (i.e. monotherapy) or on a combination of two or more drugs of different classes (i.e. bitherapy or more).

The achievement of glycaemic control can be assessed and monitored using a variety of methods, the most widely used of which is the measurement of glycated haemoglobin (HbA1c). HbA1c is the fraction of haemoglobin to which a monosaccharide molecule is bound by a non-enzymatic process to that of total haemoglobin. Its standardised measurement, expressed as a percentage, reflects the average chronic exposure to blood glucose over the last 90-120 days (i.e. the lifespan of erythrocytes): the higher the glycaemia, the higher the HbA1c. However, HbA1c can be misinterpreted (under-estimated) in some conditions (haemolytic anaemia or acute blood loss) and it is a poor marker of glycaemic variability [47, 48].

The general principle of therapeutic monitoring is to adjust the anti-hyperglycaemic treatment (in the choice of doses and molecules) until the HbA1c target recommended for a given patient is reached, reflecting achievement of satisfying glycaemic control.

Hypoglycaemia

The paramount side-effect of glucose-lowering treatment is the risk of hypoglycaemic events. Three classes of GLTs are considered as putting patients at high-risk of hypoglycaemia: insulin, sulfonylureas and glinides (Table 1). Diagnosis of hypoglycaemia in older people is difficult, due to ageing. The physiological responses to hypoglycaemia (hormonal and behavioural adaptive mechanisms involving glucagon or adrenal response) are likely altered, such as awareness to hypoglycaemic events (due to the attenuation of autonomic response) [49, 50]. Hypoglycaemic events are therefore frequently silent due to the hypoglycaemic unawareness and this often delays diagnosis, turning minor events into major ones [51].

The precise incidence rate of hypoglycaemic events in older people is likely underestimated [52]. Nevertheless, it is widely recognised that older people are at higher risk of hypoglycaemia than younger people [53, 54]. Moreover, the incidence rate of hypoglycaemia is higher than that of any other complication of diabetes in people older than 70 years with diabetes of longer duration (>10 years).

Besides the obvious driving risk factor of taking GLTs at high risk of hypoglycaemia, some conditions increase risk of hypoglycaemia in older people, such as increasing age, extreme HbA1c values (particularly lower ones), glycaemic variability, polypharmacy, cognitive impairment, and frequent hospitalisation for frailty or multiple comorbidities [47, 55-60].

Hypoglycaemic events may have serious consequence for older people, especially frail patients, who are at higher risk of developing adverse consequences [61]. Hypoglycaemic episodes increase risk of cardiovascular events, transient ischaemic attack, cognitive impairment and dementia, falls with fracture, frailty, functional decline, disability and overall morbidity [62-66]. Of note, some previously cited conditions exert bidirectional adverse effects. There are both risk factors and adverse consequences of hypoglycaemia. In particular, frailty has a strong relationship with hypoglycaemia, in addition to the strong relationship with diabetes already described.

Finally, hypoglycaemia in older people increases the risk of mortality. Over the last years, several major studies (ACCORD, Kaiser Permanente Northern America, UKPDS, Veteran Affairs study), have demonstrated the association between intensive glycaemic control and/or hypoglycaemia with poor outcomes in older people (and particularly mortality) [67-70].

Heterogeneity of health requires individualised management

The older population with T2D is widely heterogeneous in terms of global health status characteristics (comorbidities, functional and cognitive status), susceptibility to hypoglycaemic events, and remaining life expectancy [71-73].

This last decade, in addition to the results of major studies on the risks of intensive glycaemic management of older people (see paragraph HYPOGLYCAEMIA), the recognition of inter-individual clinical heterogeneity has initiated a major paradigm shift in therapeutic management of T2D in older people [74-76]. The former "one-size-fits-all" strategy (aiming at proposing a GLT of sufficient intensity to reach HbA1c < 7%) has been overtaken by an

"individualised" strategy. This individualisation aims at tailoring the therapeutic management of T2D to the patient's characteristics, addressing his/her specific needs.

In older people with T2D, there are major supporting facts justifying individualisation of diabetes management. Thus, older patients with T2D have (i) different long-terms benefits of intensive glycaemic control, (ii) different sensitivity to short-term risks of intensive glycaemic control (i.e. hypoglycaemia), and (iii) different abilities in self-management of their condition.

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AIMS AND THESIS OUTLINE

Aim of the thesis

This thesis aimed at addressing the implications of health and metabolic heterogeneities for glycaemic management in older patients with type 2 diabetes (T2D).

In this regard, the three specific objectives of this thesis are:

(1) Reviewing the current recommendations for individualised glycaemic management from recent Clinical Practice Guidelines on the management of T2D in older people.

(2) Describing the diabetes (glycaemic) overtreatment in terms of frequency, risk factors and one-year mortality, in older patients with T2D.

(3) Investigating the metabolic heterogeneity in older people with T2D.

Outline of the thesis

This thesis is structured into three sections, each one answering one of the objectives (Figure 1). Each of the six chapters of this thesis relates to one of our articles (published or in preparation).

SECTION I. Current recommendations for individualised glycaemic management in older patients with type 2 diabetes

This section is composed of two chapters (1 and 2) focusing on the current recommendations released by recent major clinical practice guidelines on the management of glycaemic control in older patients.

CHAPTER 1 is a systematic review of the current recommendations on individualisation of glycaemic management provided by the CPGs on diabetes treatment in older patients released by major Western scientific societies. Our review compares three CPGs as regards

to their methodological quality, as well as their recommendations on individualisation of glycaemic management (content, level of evidence, strength of recommendation).

CHAPTER 2 is a cross-sectional study comparing the appropriateness glycaemic control in geriatric patients according to the three CPGs included in our systematic review (see above).

SECTION II. Diabetes overtreatment in older patients with type 2 diabetes

This section consists in three chapters (3, 4 and 5) assessing the adherence to recommendations for individualised glycaemic management in older patients with T2D in poor, intermediate and good health status. The focus of this section is the inappropriate glycaemic control, with a particular emphasis on the glycaemic control overtreatment. In this thesis, glucose-lowering treatment overtreatment (CHAPTER 3) and diabetes overtreatment (CHAPTERS 4 and 5) were both used to refer to the glycaemic control overtreatment.

CHAPTER 3 reports a cohort study of 318 geriatric inpatients with T2D (from the geriatric ward St-Luc university hospital) which analysed the prevalence of inappropriate glycaemic control (diabetes overtreatment and undertreatment) according to the guidelines recommendations, and factors associated with one-year mortality.

CHAPTER 4 aims to provide an external validation of the results obtained in CHAPTER 3, using data from a recent European multicentre cluster randomised controlled trial, and including 490 older patients aged ≥ 70 years, with multimorbidity, polypharmacy and T2D. Specifically, this study assesses the poor outcomes at one year (mortality, hospitalisation and functional decline) associated with diabetes overtreatment.

CHAPTER 5 focuses on the definition of diabetes overtreatment. It aims at critically reviewing the definitions of diabetes overtreatment used in recent research studies of older patients with type 2 diabetes.

SECTION III. Metabolic heterogeneity among older patients with T2D

This section aims at investigating the metabolic heterogeneity among older patients with T2D. It consists in a single chapter (CHAPTER 6).

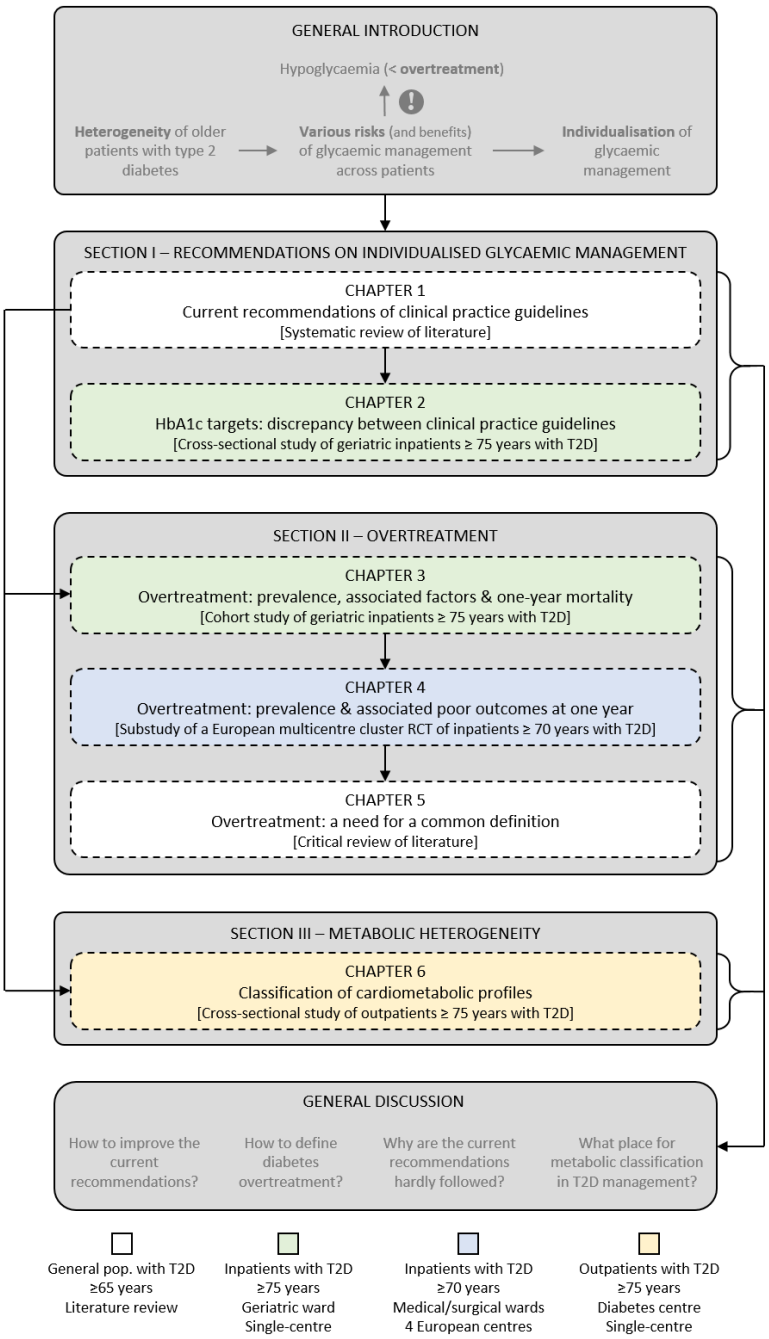
CHAPTER 6 is a cross-sectional study on the heterogeneity of cardiometabolic features of patients aged ≥ 75 years with type 2 diabetes and to classify them into relevant cardiometabolic profiles using mixture models as Latent Profile Analysis (LPA).

GENERAL DISCUSSION

The GENERAL DISCUSSION first provides a summary of the main findings of this thesis. It then focuses on four points of interest related to the results of each section, namely (i) how to improve the current recommendations; (ii) how to define diabetes overtreatment; (iii) why are the current recommendations hardly followed; (iv) what could be the place of the patient's metabolic profile in the individualised management of glycaemic control.

The overall strengths and limitations of the thesis, and its perspectives are finally reported.

Fig. 1. Graphical outline of the thesis



T2D: Type 2 diabetes; RCT: Randomised controlled trial

Data sources

Three different data sources were used in this thesis (Table 1).

Table 1. General description of the different database used throughout the thesis

Database	Thesis chapters	Patients (number)	Setting	Age (at inclusion)	Age, median
Geriatric ward	CHAPTER 2 CHAPTER 3	N = 318	Inpatients (geriatrics), Brussels	≥ 75 years	84 years
OPERAM Project	CHAPTER 4	N = 490	Inpatients (medical and surgical) Bern, Brussels, Cork, Utrecht	≥ 70 years	78 years
Diabetes centre	CHAPTER 6	N = 147	Outpatients (diabetes centre) Brussels	≥ 75 years	80 years

Geriatric ward (U23, St-Luc university hospital, Brussels)

This database consists of retrospectively-collected data from 318 patients hospitalised in one geriatric ward (25 beds in the unit of care) of our university hospital in Brussels (Belgium) between 2008 and 2015. Inclusion criteria were: having a T2D, being treated by a glucose-lowering therapy (GLT) before hospital admission, and having an HbA1c measured during hospital stay. This databased of 318 geriatric patients was used in CHAPTER 2 and CHAPTER 3.

OPERAM database

This is a subset of the data of the OPERAM project (a European multicentre cluster randomised controlled trial (Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) [1]) in patients aged ≥ 70 years with multimorbidity (≥ 3 conditions) and polypharmacy (≥ 5 different drugs/day) admitted to a university hospital in four countries (Switzerland (Bern), Netherlands (Utrecht), Belgium (Louvain) and Republic of Ireland (Cork)). The subset used in CHAPTER 4 includes the 490 diabetic with GLT before hospital admission and concomitant measurement of HbA1c. Patients were included regardless of their inclusion site or group (intervention or control) in the OPERAM

trial. Patients were excluded if they were admitted to palliative care within 24 hours after hospital admission.

Diabetes centre (Diabetes centre St-Luc university hospital, Brussels)

The third database comprised data prospectively collected in outpatients followed at the diabetes clinic of our university hospital (Prof Michel P. Hermans, St-Luc Brussels, Belgium). All patients were aged ≥ 75 years (N = 147). This database was used in CHAPTER 6.

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SECTION I - Current recommendations for individualised glycaemic management in older patients with type 2 diabetes

Chapter 1. Individualisation of glycaemic management in older people with type 2 diabetes: a systematic review of Clinical Practice Guidelines Recommendations

Chapter 2. Large discrepancy in glycaemic control appropriateness in geriatric patients with type 2 diabetes according to major clinical practice guidelines

Chapter 1. Individualisation of glycaemic management in older people with type 2 diabetes: a systematic review of Clinical Practice Guidelines Recommendations

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ABSTRACT

BACKGROUND. Recommendations for individualised glycaemic management in older people with type 2 diabetes (T2D) have recently been provided in clinical practice guidelines (CPGs) issued by major scientific societies. The aim of this systematic review is to compare the content of these recommendations concerning health assessment, targets for glycaemic control, lifestyle management and glucose-lowering therapy across CPGs.

METHODS. The CPGs on T2D management in people aged ≥ 65 years published in English after 2015 by major scientific societies were systematically reviewed in accordance with the PRISMA statement. The quality of the CPGs included was assessed using the AGREE-II tool. The recommendations for individualised glycaemic management were extracted, and their level of evidence (LOE) and strength of recommendation (SOR) recorded.

RESULTS. Three CPGs of high methodological quality were included, namely those from the American Diabetes Association 2020, the Endocrine Society 2019 and the Diabetes Canada Expert Committee 2018. They made 27 recommendations addressing individualised glycaemic management, a minority of which (40%) had a high LOE. Comparison of the 27 recommendations identified some discrepancies between CPGs, e.g. the individualised values of HbA1c targets. The 13 strong recommendations addressed 10 clinical messages, five of which are recommended in all three CPGs, i.e. assess health status, screen for cognitive impairment, avoid hypoglycaemia, prioritise drugs with low hypoglycaemic effects and simplify complex drug regimens.

CONCLUSIONS. While there is a consensus on avoiding hypoglycaemia in older patients with T2D, significant discrepancies regarding individualised HbA1c targets exist between CPGs.

KEY POINTS

- Individualisation of glycaemic management is a crucial issue for older people with type 2 diabetes.
- This systematic review found three CPGs about individualised glycaemic management in older patients and compared their content about health assessment, targets for glycaemic control, lifestyle management and glucose-lowering therapy.
- All three clinical practice guidelines included are of high methodological quality but provide a low level of evidence.
- There is a consensus among clinical practice guidelines on avoiding hypoglycaemia in older patients.
- There are divergences between clinical practice guidelines regarding targets for glycaemic control.

INTRODUCTION

Type 2 diabetes (T2D) in older people is a major public health concern, since T2D is one of the commonest and most frequently occurring chronic diseases in the older population. The global prevalence of T2D in patients aged 65-99 years is estimated at 19.3% (20.1% in Europe and 27.0% in North America) [1]. Moreover, with the demographic increase in the older population, epidemiological projections predict a significant increase in the number of older patients with T2D [1]. The therapeutic management of T2D in older people is therefore a significant issue for healthcare professionals.

The management of T2D in older people, particularly glycaemic management, is challenging for several reasons. The therapeutic needs of older people with T2D vary considerably, due to their wide heterogeneity in terms of health status, functional status and life expectancy [2]. The potential benefits of intensive treatment with glucose-lowering therapy (GLT) vary greatly between patients, as does their susceptibility to GLT adverse effects (such as hypoglycaemic events), which are particularly harmful for older people and costly to the healthcare system [3-5]. The intensity of glycaemic management and particularly of GLT prescribing should be individualised in each patient in order to prevent hypoglycaemia [6-8].

In recent years, individualisation of glycaemic management in older patients with T2D has become the gold standard of practice and practical recommendations have been made in clinical practice guidelines (CPGs) set out by major scientific societies.

This systematic review aims to compare the recommendations provided in CPGs for glycaemic management in older patients in terms of availability, quality and content regarding four key aspects, namely patient health assessment, individualisation of targets for glycaemic control, lifestyle management and GLT management.

METHODS

The protocol for this systematic review [9] was prospectively registered in the PROSPERO register (CRD42020203785) in August 2020. The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statements [10] (checklist available in Appendix 1).

SEARCH STRATEGY AND SELECTION CRITERIA

Literature searches were performed in three major databases (MEDLINE, EMBASE and CINAHL) and on specific websites providing repositories of clinical practice guidelines (Appendix 2) up to 18 August 2020, using synonyms of the keywords "older adults", "diabetes" and "guideline". Search equations and resulting records are detailed in Appendix 2. Once the literature search was completed, duplicates were removed.

The inclusion criteria were: 1) clinical practice guidelines (as defined below) addressing the management or treatment of diabetes in people aged ≥ 65 years (specifically mentioned by the CPG), 2) supported by scientific societies in Europe or North America and 3) published in English after 2015 (limiting the search to the most recent updated recommendations). Clinical practice guidelines were defined as "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options", according to the Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines [11]. Articles reviewing available evidence but not explicitly citing specific recommendations were therefore not considered to be CPGs. Inclusion was limited to CPGs from scientific societies in Europe and North America to ensure that the demographic, genetic and epidemiological context in which recommendations were made was comparable across CPGs.

Two reviewers independently screened the references following a two-step strategy. Firstly, titles and abstracts were screened based on the inclusion criteria. Secondly, after exclusion of non-relevant records, the full texts were analysed to determine the eligibility of the remaining records. Disagreements between the two reviewers were discussed under the

supervision of a third reviewer, who made a decision on any conflicts remaining after each step.

QUALITY ASSESSMENT OF THE CLINICAL PRACTICE GUIDELINES

The methodological quality of the CPGs included was assessed using the AGREE-II tool (Appraisal of Guidelines for Research and Evaluation II, version updated in 2017) [12], which consists of 23 items divided into six quality domains targeting different areas of the methodological quality of CPGs: scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence. Each item was scored on a grading scale from 1 (strongly disagree) to 7 (strongly agree). Four reviewers first completed the AGREE-II training tool and then independently applied the AGREE-II tool to all three CPGs included. Their scores for each domain were added together. The quality score for each domain is the percentage of its maximum possible score ([Obtained score – Minimum possible score] / [Maximum possible score – Minimum possible score]) [12]. Following the methodology of other studies using the AGREE-II tool [13], CPG quality was considered high when it scored ≥ 60% in three or more domains, including "rigour of development".

EXTRACTION AND SYNTHESIS OF THE RECOMMENDATIONS

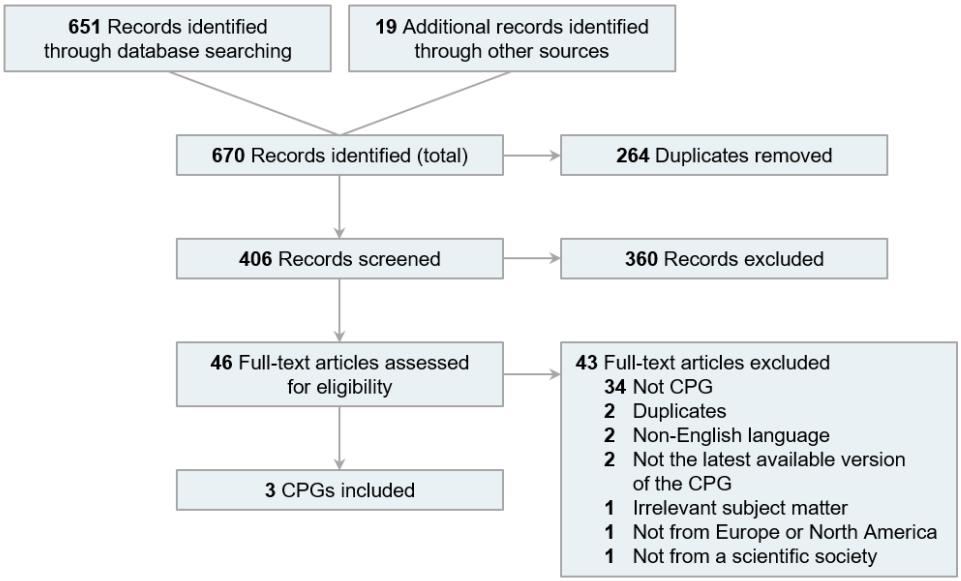
Recommendations formally identified as such in the CPGs and related to four aspects were extracted: patient health assessment, individualisation of targets for glycaemic control, lifestyle management and GLT management (without going into detail on the use of glucose-lowering drug classes or individual drugs). These four aspects were selected due to their relevant impact on individualisation of glycaemic management in older patients with T2D. The level of evidence (LOE) and strength of recommendation (SOR) were extracted for the recommendations. A standardised grading scale was designed in order to deal with the differences between grading scales used in the different CPGs selected (detailed in Appendix 3). Data were extracted and synthesised by two reviewers.

RESULTS

Figure 1 details the PRISMA flow diagram. Overall, 670 records were identified during the literature searches through database searching (n= 651, i.e. 206 from MEDLINE, 320 from EMBASE and 125 from CINHAL), as well as specific databases of CPGs (n=19). Of the 406 references remaining after removal of duplicates, 360 were excluded during screening. The full texts of the remaining 46 records were reviewed for eligibility and 43 of them were excluded (34 were not CPGs; see Figure 1 for the other reasons). Three CPGs were included

in this systematic review. These were issued by the American Diabetes Association in 2020 (ADA20) [14], the Endocrine Society in 2019 (ES19) [15] and Diabetes Canada in 2018 (DC18) [16].

Figure 1. PRISMA Flow diagram (CPG: Clinical Practice Guideline)



GENERAL CHARACTERISTICS OF THE CPGs

Table 1 shows the general characteristics of ADA20, ES19 and DC18. All three CPGs were endorsed by international or North American (USA, Canada) scientific societies in the areas of endocrinology or diabetology, while ES19 was also endorsed by two European scientific societies: one in the field of endocrinology and the other in gerontology. ADA20 is the annual update of this CPG, ES19 was the first edition of this CPG and DC18 is the second edition, published five years after the first one. Regarding the definition of older age, ADA20 and ES19 were dedicated to patients aged ≥ 65 years, while DC18 mainly addressed patients aged ≥ 70 years and considered not to be in excellent general health, functionally independent or with ≥ 10 years of healthy life expectancy.

Table 1. General characteristics of the clinical practice guidelines

CPG	Scientific society	Year	Region	Patient's age	Previous version
ADA20 [14]	American Diabetes Association	2020	USA	≥ 65 years	Yes (2019)
ES19 [15]	Endocrine Society *	2019	USA, Europe	≥ 65 years	No
DC18 [16]	Diabetes Canada	2018	Canada	≥ 70 years	Yes (2013)

CPG: Clinical Practice Guideline; ADA20: American Diabetes Association 2020; ES19: Endocrine Society 2019; DC18: Diabetes Canada 2018. * Co-sponsoring societies: European Society of Endocrinology, Gerontological Society of America, Obesity Society.

QUALITY ASSESSMENT OF THE CPGs

According to the rating by the reviewers using the AGREE-II tool, all three CPGs were of high quality (three or more domains with scores ≥ 60%, including the rigour of development domain) (Table 2). All three CPGs had high scores (≥ 75%) in three domains, i.e. scope and purpose, clarity of presentation and editorial independence. The CPGs had lower scores in the stakeholder and applicability domains.

Table 2. Quality appraisal of the three CPGs according to the six domains in the AGREE-II tool

CPGs	Domain (%)					
	Scope and purpose	Stake-holder	Rigour of develop-ment	Clarity of presen-tation	Applica-bility	Editorial indepen-dence
ADA20 [14]	79.2	61.1	71.9	87.5	67.7	87.5
ES19 [15]	88.9	68.1	60.9	84.7	49.0	75.0
DC18 [16]	76.4	55.6	86.5	77.8	47.9	89.6

Legend: Based on independent assessments by four raters, scores for each AGREE-II domain are shown as a percentage of the maximum score (see Methods section). ADA20: American Diabetes Association 2020; ES19: Endocrine Society 2019; DC18: Diabetes Canada 2018.

CHARACTERISTICS OF THE RECOMMENDATIONS

All three CPGs made 27 recommendations on the four aspects of individualised glycaemic management in older patients with diabetes. Only two of these recommendations (7%) had a high level of evidence (LOE A = well-performed RCTs or very strong evidence from

unbiased observational studies), while nine (33%) had a moderate level of evidence (LOE B: RCTs with some limitations or strong evidence from unbiased observational studies (well-conducted cohort studies or case-control studies)). The LOE was low or poor (LOE C or D: RCTs with major flaws, observational studies with bias, case report, non-systematic clinical observations or expert consensus) for the other 16 recommendations (60%). The LOE was generally higher for recommendations relating to aspects of lifestyle management and glucose-lowering therapy than for those relating to aspects of health assessment or individualised targets. Half of the recommendations (n=13) were strong (SOR = 1, "we recommend"), while the other half were weak (SOR = 2, "we suggest"). The majority of recommendations concerning lifestyle and GLT management were strong (Appendix 4).

SUMMARY AND COMPARISON OF THE RECOMMENDATIONS

Patient health assessment

Assessment of the patient encompassing the medical, psychological, functional and social domains and screening for specific geriatric syndromes are strongly recommended by ADA20. All three CPGs suggest that this patient health assessment should be performed in order to determine the patient's individualised glycaemic targets. Based on the patient health assessment, all three CPGs suggest classifying patients using a three-tier health status classification (Table 3).

ADA20 uses functional status, cognitive status and comorbidities according to the study by Blaum et al. (2010) [17] and the review by Kirkman et al. (2012) [18]. ES19 uses the same assessment criteria. However, DC18 uses the Canadian Clinical Frailty scale developed by Moorhouse and Rockwood [19] to classify patients into functionally independent, functionally dependent or frail/demented patients.

None of the three CPGs provides recommendations on the frequency of health assessment, while ADA20 acknowledges that patients may move between health status categories over the years.

Cognitive assessment is addressed in all three CPGs. ADA20 recommends screening for cognitive impairment "in order to prevent difficulties in diabetes self-management and diminution of quality of life" and ES19 suggests performing periodic cognitive screening to identify undiagnosed cognitive impairment. A nutritional assessment in all older patients with T2D is strongly recommended by ES19.

Table 3. Comparison of tiered patient health classification systems and individualisation of targets for glycaemic control (HbA1c target ranges) between the three CPGs

American Diabetes Association (2020) [14]			
Health category	HEALTHY	COMPLEX / INTERMEDIATE	VERY COMPLEX / POOR HEALTH
Criteria	No ADL impairment or Intact cognitive status or 0-2 chronic illnesses [a]	≥ 2 IADL impairment or Mild to moderate cognitive impairment or ≥ 3 chronic illnesses [a]	≥ 2 ADL impairment or Moderate to severe cognitive impairment or End-stage illnesses [b] or LTC
Targets	HbA1c: < 7.5% Glycaemia: Fasting: 90-130 mg/dl Bedtime: 90-150 mg/dl	HbA1c: < 8.0% Glycaemia: Fasting: 90-150 mg/dl Bedtime: 100-180 mg/dl	HbA1c: < 8.5% Glycaemia: Fasting: 100-180 mg/dl Bedtime: 110-200 mg/dl
Endocrine Society (2019) [15]			
Health category	GOOD HEALTH	INTERMEDIATE HEALTH	POOR HEALTH
Criteria	≤1 IADL impairment and no ADL impairment Intact cognitive status 0-2 chronic illnesses [a]	≥ 2 IADL impairment Mild cognitive impairment or early dementia ≥ 3 chronic illnesses [a]	≥ 2 ADL impairment Moderate to severe dementia End-stage illnesses [b] LTC
Targets in low-risk [c]	HbA1c: < 7.5% Glycaemia: Fasting: 90-130 mg/dl Bedtime: 90-150 mg/dl	HbA1c: < 8.0% Glycaemia: Fasting: 90-150 mg/dl Bedtime: 100-180 mg/dl	HbA1c: < 8.5% Glycaemia: Fasting: 100-180 mg/dl Bedtime: 110-200 mg/dl
Targets in high-risk [d]	HbA1c: ≥ 7.0 % and < 7.5% Glycaemia: Fasting: 90-150 mg/dl Bedtime: 100-180mg/dl	HbA1c: ≥ 7.5 % and < 8.0% Glycaemia: Fasting: 100-150 mg/dl Bedtime: 150-180 mg/dl	HbA1c: ≥ 8.0 % and < 8.5% Glycaemia: Fasting: 100-180 mg/dl Bedtime: 150-250 mg/dl
Diabetes Canada (2018) [16]			
Health category	FUNCTIONALLY INDEPENDENT	FUNCTIONALLY DEPENDENT	FRAIL AND/OR WITH DEMENTIA
Criteria	Clinical frailty index 1-3	Clinical frailty index 4-5	Clinical frailty index 6-8
Targets in low-risk [e]	≤ 7.0%	< 8.0%	< 8.5%
Targets in high-risk [f]	≤ 7.0%	7.1 - 8.0%	7.1 - 8.5%

Legend: [a] Chronic illnesses may include: arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage ≥ 3 chronic kidney disease, myocardial infarction, stroke. [b] End-stage chronic illnesses: stage 3–4 congestive heart failure, oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer. [c] Low risk of hypoglycaemia (absence of insulin, sulfonylureas or glinides in ES19). [d] High risk of hypoglycaemia (presence of insulin, sulfonylureas or glinides in ES19). [e] Low risk of hypoglycaemia (absence of insulin or sulfonylureas in DC18). [f] High risk of hypoglycaemia (presence of insulin or sulfonylureas in DC18). LTC = long-term care; IADL = instrumental activities of daily living; ADL = activities of daily living. Adapted according to [14-16].

Individualisation of targets for glycaemic control

The targets for glycaemic control are expressed in each CPG as different HbA1c target ranges (Table 3). ES19 and DC18 suggest HbA1c target ranges according to both health status and use of drugs that may cause hypoglycaemia (e.g. insulin, sulfonylureas and glinides), while ADA20 does so according to health status only. The ranges of HbA1c targets are slightly different between CPGs, with DC18 having the most stringent HbA1c target overall (i.e. the lowest values). More importantly, lower boundaries for the HbA1c target ranges are proposed by ES19 and DC18 for patients using glucose-lowering agents with a high risk of hypoglycaemia, but not by ADA20 (Table 3).

They all share a common recommendation on avoiding hypoglycaemia, especially in frail patients. Only ADA20 suggests avoiding hyperglycaemia that results in symptoms despite relaxed glycaemic targets.

Due to limitations of HbA1c interpretation in older patients (in particular, the inability of HbA1c to detect hypoglycaemic events), ADA20 and ES19 also express targets in terms of glycaemic ranges for fasting and bedtime periods.

Lifestyle management

ES19 recommends lifestyle modifications as the first-line treatment in older ambulatory patients with T2D, and strongly recommends the management of malnutrition in all older patients with T2D. Optimisation of nutrition, including protein intake for all older patients, is strongly recommended by ADA20, while ES19 suggests it for frail patients. DC18 suggests the use of regular diets instead of restrictive nutritional formulas (i.e. “diabetic diets”).

On physical exercise, ADA20 and DC18 both recommend that older patients with diabetes should take regular exercise, including aerobic activities and/or resistance training if these activities can be safely performed.

Management of glucose-lowering therapy

Frequent fingerstick glucose monitoring and/or continuous glucose monitoring is recommended in ES19 for older people with diabetes who are treated with insulin. ADA20 and DC18 do not provide recommendations on blood glucose monitoring.

All three CPGs recommend prioritising the use of glucose-lowering drugs with low risk of hypoglycaemia. In addition, ADA20 recommends de-intensifying of regimens in patients taking non-insulin GLT by either lowering the dose or discontinuing some medications, while respecting the individualised HbA1c target. ADA20 provides an algorithm to simplify complex insulin therapy regimens, as well as a table illustrating situations where simplification of the regimen may be required and where GLT de-intensification or deprescription may be necessary.

CLINICAL MESSAGES

Based on the 13 strong recommendations, 10 clinical messages were identified (Table 4), covering all four aspects of individualised glycaemic management. Five clinical messages were supported by recommendations in all three CPGs (including at least one strong recommendation), i.e. “assess the patient’s health status”, “screen for geriatric syndromes”, “avoid hypoglycaemia”, “prioritise GLT with low risk of hypoglycaemia” and “aim for simplification of complex GLT” (Table 4).

Table 4. Clinical messages provided by the strong recommendations in the three CPGs

Clinical messages	ADA20	ES19	DC18
Assess health status (tiered classification) to determine glycaemic control targets	● (12.1)	○	○
Screen for geriatric syndromes and cognitive impairment	● (12.2)	○	○
Assess nutritional status to detect malnutrition		● (4.4)	
Consider lifestyle modifications as first-line treatment		● (4.3)	
Verify optimal nutrition and protein intake, avoid malnutrition	● (12.10)	● (4.4)	
Maintain physical exercise when safe and possible	○		● (7)
Avoid hypoglycaemia	○	● (4.1)	○
Prioritise glucose-lowering drugs with low risk of hypoglycaemia	● (12.11)	● (4.1)	○
Monitor blood glucose when insulin is prescribed		● (4.2)	
Aim for simplification/reduction of intensity of complex glucose-lowering drug regimens	● (12.13)	● (6.2)	○

Legend: ADA20: American Diabetes Association 2020; ES19: Endocrine Society 2019; DC18: Diabetes Canada 2018. ● : Clinical message given in a strong recommendation. The reference number of the corresponding recommendation is indicated in brackets. ○: Clinical message given in a weak recommendation in this CPG. The strength of recommendation was defined as follows: DC18: grade A-B; ES19: grade 1; ADA20: since grade was not provided, the wording “we recommend” was considered a strong recommendation, and "we suggest" a weak recommendation (see Methods and Table S3).

DISCUSSION

This systematic review found three CPGs for T2D management in older people meeting the inclusion criteria. The CPGs were of high methodological quality, based on the appraisal using the AGREE-II tool. They address all four selected aspects concerning the individualised approach to glycaemic management, making 27 recommendations, the majority of which have a low/poor LOE. The main discrepancies between CPGs were in the area of individualised targets for glycaemic control.

The number of CPGs included in this study was limited despite the extensive systematic research. This finding is mainly related to the inclusion criteria, i.e. 1) a formal CPG [11],

2) focusing on older people (aged ≥ 65 years) with T2D and 3) published recently (> 2015) by major scientific societies. The number of CPGs on this topic is very low in view of the burden of T2D in older patients on public health.

The use of the AGREE-II tool provided an overall view of the methodological quality of the three CPGs by scanning different important domains and highlighting strengths and weaknesses of each one. According to the AGREE-II tool, all three CPGs obtained comparable scores, indicating high quality. However, these results should be interpreted with caution since the scores are somewhat subjective, despite the involvement of four independent reviewers, as recommended in the AGREE-II guidelines [12], and despite the fact that AGREE-II is a validated and frequently used tool for quality appraisal of CPGs [20].

The recommendation forming the first step in each of the three CPGs deals with the patient health assessment and individualisation of targets for glycaemic control. This is very relevant because it determines most aspects of the individualised approach to glycaemic management in older patients, e.g. the choice of GLT classes or intensity.

In this review, comparing the content of related recommendations between CPGs showed similarities and discrepancies in the definition of HbA1c target values according to the patient's health status. Firstly, the criteria used to classify patients into the three health status tiers are very similar. ADA20 and ES19 use a classification based on the Blaum et al. study [17], while DC18 uses a classification based on the Canadian Clinical Frailty scale [19]. These two classification systems are driven by functional criteria, as well as criteria related to cognitive status and numbers of comorbidities, to which ADA20 and ES19 add criteria related to the place of residence. ADA20 and ES19 classifications have already been used in previous ADA guidelines since 2014 [21] and in other guidelines before 2015 [18]. The slight differences observed between these two classification systems should not significantly affect the classification of patients. Further studies should determine whether or not this difference modifies the patient's classification. Secondly, the values provided for HbA1c target ranges differ considerably between CPGs, since ES19 and DC18 define a minimum HbA1c value when hypoglycaemic drugs are prescribed (i.e. insulin, sulfonylureas and glinides), while ADA20 does not provide a lower limit for HbA1c. The absence of a minimum HbA1c value in the target range may lead to a significant risk of hypoglycaemia in patients on hypoglycaemic drugs with a low HbA1c [22, 23]. Thirdly, the HbA1c target ranges proposed in the three CPGs are slightly different. Nevertheless, it is not possible to determine, based on the knowledge currently available, whether these differences can have an impact on outcomes that matter for the older patient (functional

status, quality of life or mortality). Further studies should be conducted to answer this question and guide physicians in choosing which recommendation to follow.

The extracted recommendations often had a low level of scientific evidence, which does not mean that they are inaccurate. There is a great need for additional evidence from studies involving older people, and particularly patients with frail status, to improve the quality of these recommendations [24].

The 13 strong recommendations address 10 clinical messages. These clinical messages are aimed at carefully assessing patients' health and managing their treatment safely and appropriately for their profile (avoiding malnutrition and hypoglycaemic events and simplifying GLT). It should be noted that the strongest recommendations regarding GLT management in older patients primarily suggest protective glycaemic management rather than an intensive attitude.

The strengths of this systematic review include its methodological rigour and the extensive literature search. Guidance on designing rigorous systematic reviews of CPGs were followed [13] and the PRISMA statements were used to improve the reporting of this systematic review [10]. To our knowledge, this is the first systematic review performed on clinical practice guidelines for older patients with diabetes. This review also contributes to the dissemination of guidelines recommending the individualisation of glycaemic management in older patients with T2D, which remain largely unknown or at least insufficiently implemented. The review does have a limited scope, however, defined by its inclusion criteria. For the sake of clarity, only recommendations related to the selected topics of interest were extracted from the CPGs.

Some perspectives should be considered in the light of these results. There is a great need for studies in older patients with diabetes, including those with poorer health status or higher frailty, to remedy the lack of evidence in this important area. It would also be useful to compare the implementation of these recommendations in older patients with diabetes, in order to describe the effects of differences between CPGs on several outcomes that matter to older patients.

CONCLUSIONS

This systematic review appraised and compared the recommendations on individualised glycaemic management made in three major clinical practice guidelines. These high-quality clinical practice guidelines provide precise recommendations, which may be strong or weak, covering relevant aspects of individualising glycaemic management in older patients.

Ten clinical messages extracted from the strong recommendations were identified. The main messages concerned assessing the patient's health, avoiding hypoglycaemia, prioritising glucose-lowering drugs with a low risk of hypoglycaemia and simplifying complex glucose-lowering treatment. The clinical practice guidelines differ, however, in the definition of a minimum value for HbA1c target ranges. Further studies in the area of individualised glycaemic management are needed to strengthen the evidence base for recommendations in future editions of these guidelines.

Individualised glycaemic management is a challenge in older patients, due to the consequences of hypoglycaemic events in these patients. A good knowledge and critical appraisal of the recommendations in the major clinical practice guidelines should help clinicians make a wise choice of the safest and most appropriate treatment for older patients with type 2 diabetes.

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APPENDICES

Appendix 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 (PICO not applicable)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-8 Table 1, Table 3, Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2. Search equation and details of records (performed the 18/08/2020)

1. MEDLINE: 206 results

Search	Restriction item	Query	Results (n)
#7		#5 AND #6	206
#6	Published ≥2015 in English	"2015/01/01"[Date - Publication] : "3000"[Date - Publication] AND english[Language]	6,533,926
#5	-	#3 AND #4	521
#4	CPG	"guideline*" OR "recommend*" OR "statement*" OR "guidance*" OR "consensus"	1,344,885
#3	-	#1 AND #2	4,609
#2	Older age	old[Title] OR older*[Title] OR elder*[Title] OR geriatric*[Title] OR oldest[Title]	342,853
#1	Diabetes	diabetes[Title]	228,408

2. EMBASE: 320 results

Search	Restriction item	Query	Results (n)
#6	Published ≥2015 in English	#3 AND #4 AND [english]/lim AND [2015-2020]/py	320
#5	-	#3 AND #4	791
#4	CPG	guideline* OR recommend* OR statement* OR guidance* OR consensus	1,950,227
#3	-	#1 AND #2	6,617
#2	Older age	older:ti OR old:ti OR geriatric*:ti OR oldest:ti OR older*:ti OR elder*:ti	454,898
#1	Diabetes	diabetes:ti	326,889

3. CINHAL: 125 results

Search	Restriction item	Query	Results (n)
#6	Published ≥2015 in English	#3 AND #4 AND [english]/lim AND [2015-2020]/py	125
#5	-	#3 AND #4	311
#4	CPG	guideline* OR recommend* OR statement* OR guidance* OR consensus	476,271
#3	-	#1 AND #2	2,901
#2	Older age	TI Older* OR Old OR Geriatric* OR Oldest OR Elder*	161,358
#1	Diabetes	TI Diabetes	99,847

4. OTHER SOURCES: 19 results

- American Academy of Family Physicians: Clinical Practice Guidelines (https://www.aafp.org/family-physician/patient-care/clinical-recommendations/clinical-practice-guidelines/clinical-practice-guidelines.html): no result
- Cochrane Library (https://www.cochranelibrary.com/): 14 results

- CPG InfoBase from (Evidence-base Canadian clinical practice guidelines; https://joulecma.ca/cpg/homepage#_ga=2.45516327.2020913388.1609771427-24162178.1609771427): 2 results
- EPC reports (Evidence-based Practice Centers), Agency for Healthcare Research and Quality (https://www.ahrq.gov/research/findings/evidence-based-reports/search.html): no result
- Guideline Central® (https://www.guidelinecentral.com/summaries/): no result
- Guidelines International Network (https://g-i-n.net/): 3 results
- NICE (National Institute for Health and Care Excellence) guidance (https://www.nice.org.uk/guidance): no result
- SIGN (Scottish Intercollegiate Guidelines Network; https://www.sign.ac.uk/): no result
- U.S. Preventive Services Task Force (https://www.uspreventiveservicestaskforce.org/uspstf/): no result
- Veterans Affairs Clinical Practice Guidelines (https://www.healthquality.va.gov/): no result

Appendix 3. Common grading system used to define recommendations' level of evidence and strength of recommendations.

Common grading system		Translation into grading systems used in CPGs		
		ADA20	ES19	DC18
	LEVEL OF EVIDENCE			
A	High quality of evidence (Well performed RCTs or very strong evidence from unbiased observational studies)	A	●●●●	1
B	Moderate quality of evidence (RCTs with some limitations or strong evidence from unbiased observational studies (well conducted cohort studies or case-control studies))	B	●●●○	2
C	Low quality of evidence (RCTs with major flaws, observational studies with bias, case series or case report)	C	●●○○	3
D	Poor quality of evidence (Very indirect evidence from observational studies, unsystematic clinical observations or expert consensus)	E	●○○○	4
	STRENGTH OF RECOMMENDATION			
1	Strong recommendation ("We recommend…")	*	1	A-B
2	Weak recommendation ("We suggest …")	*	2	C-D
NG	Ungraded recommendation	N/A	NG	NG

RCT: Randomised clinical trial. * SOR of recommendations provided by ADA20 were assessed by authors interpreting the formulation of the recommendation. For example, recommendations written in imperative form or containing the words "we recommend" were considered as strong recommendations. Recommendations written in a conditional form or containing the words "we suggest" were considered as weak recommendations.

Appendix 4. Level of evidence (LOE) and Strength of recommendations (SOR) for recommendations extracted from the three CPGs

Number of recommendations by level of evidence (LOE)				Topics of recommendations	Number of recommendations by strength of recommendations (SOR)		
A	B	C	D		1	2	NG
	3	3	2	Health assessment	3	5	1
	1	3	4	Targets for glycaemic control	3	5	
2	2	1	2	Lifestyle management	4	3	
	3	1		Glucose-lowering therapy	3	1	
2 (7%)	9 (33%)	8 (30%)	8 (30%)	Total (n=27)	13 (48%)	13 (48%)	1 (4%)

Strength of recommendation (SOR): 1 = strong recommendation, 2 = weak recommendation, NG = ungraded. Level of evidence (LOE): A = high quality evidence; B = moderate quality evidence; C = low quality evidence; D = poor quality evidence

Chapter 2. Large discrepancy in glycaemic control appropriateness in geriatric patients with type 2 diabetes according to major clinical practice guidelines

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ABSTRACT

PURPOSE. In geriatric patients with type 2 diabetes (T2D), appropriate glycaemic control is crucial to avoid overtreatment and hypoglycaemia. This study compared glycaemic control appropriateness across three major clinical practice guidelines (CPGs).

METHODS. Retrospective study of geriatric older inpatients with T2D and glucose-lowering treatment before admission. Patients were classified as appropriately treated, overtreated or undertreated using CPGs from Diabetes Canada 2018 (DC18), the Endocrine Society 2019 (ES19) and the American Diabetes Association 2021 (ADA21).

RESULTS. Of the 318 geriatric patients (median age 84 years, 54% women, 66% in poor health), 46%, 25% and 82% were appropriately treated, while 38%, 57% and 0% were overtreated, based on DC18, ES19 and ADA21, respectively.

CONCLUSION. Large discrepancy of glycaemic control appropriateness was detected across these CPGs and concerned mainly overtreatment. This finding relates to the absence in ADA21 of a lower HbA1c value, which may be an obstacle to the prevention of hypoglycaemia.

KEY SUMMARY POINTS

Aim: This study compared glycaemic control appropriateness across three major clinical practice guidelines

Findings: Large discrepancy exists in glucose-lowering appropriateness classification between clinical practice guidelines, particularly in overtreatment detection.

Message: This finding relates to the absence in ADA21 of a lower HbA1c value, which may be an obstacle to the prevention of hypoglycaemia.

INTRODUCTION

In older patients with type 2 diabetes (T2D), hypoglycaemic events are associated with adverse outcomes, such as functional impairment, deterioration of health status or death [1, 2], which are even more damaging for older patients who are frail or in poor health [3].

Hypoglycaemic events are induced by too tight glycaemic control using glucose-lowering drugs at high risk of hypoglycaemia, namely insulins, sulfonylureas or glinides (i.e. overtreatment) [2, 4, 5].

While avoiding overtreatment is therefore crucial, reaching appropriate glycaemic control is a challenge for geriatric people with T2D. Due to the wide heterogeneity of health status existing in this population, the treatment objectives should be individualised according to some patient's characteristics (such as their comorbidities, functional or cognitive status, or residual life expectancy) [6, 7].

Despite a lack of strong scientific evidence in this field [8], some major clinical practice guidelines (CPGs) provided these last years recommendations on the individualised management of glycaemic control in older people [9]. This study aimed at comparing glycaemic control appropriateness in geriatric patients with type 2 diabetes according to major these CPGs

METHODS

STUDY DESIGN AND PARTICIPANTS

This retrospective study includes consecutive patients aged ≥75 years hospitalised in a geriatric ward (Brussels, Belgium) between 2008 and 2015 [10], with type 2 diabetes, glucose-lowering treatment (GLT) before hospital admission, and HbA1c measured during

the hospital stay. A patient was included only once. Type 2 diabetes was defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [11].

DATA COLLECTION AND DEFINITION OF VARIABLES

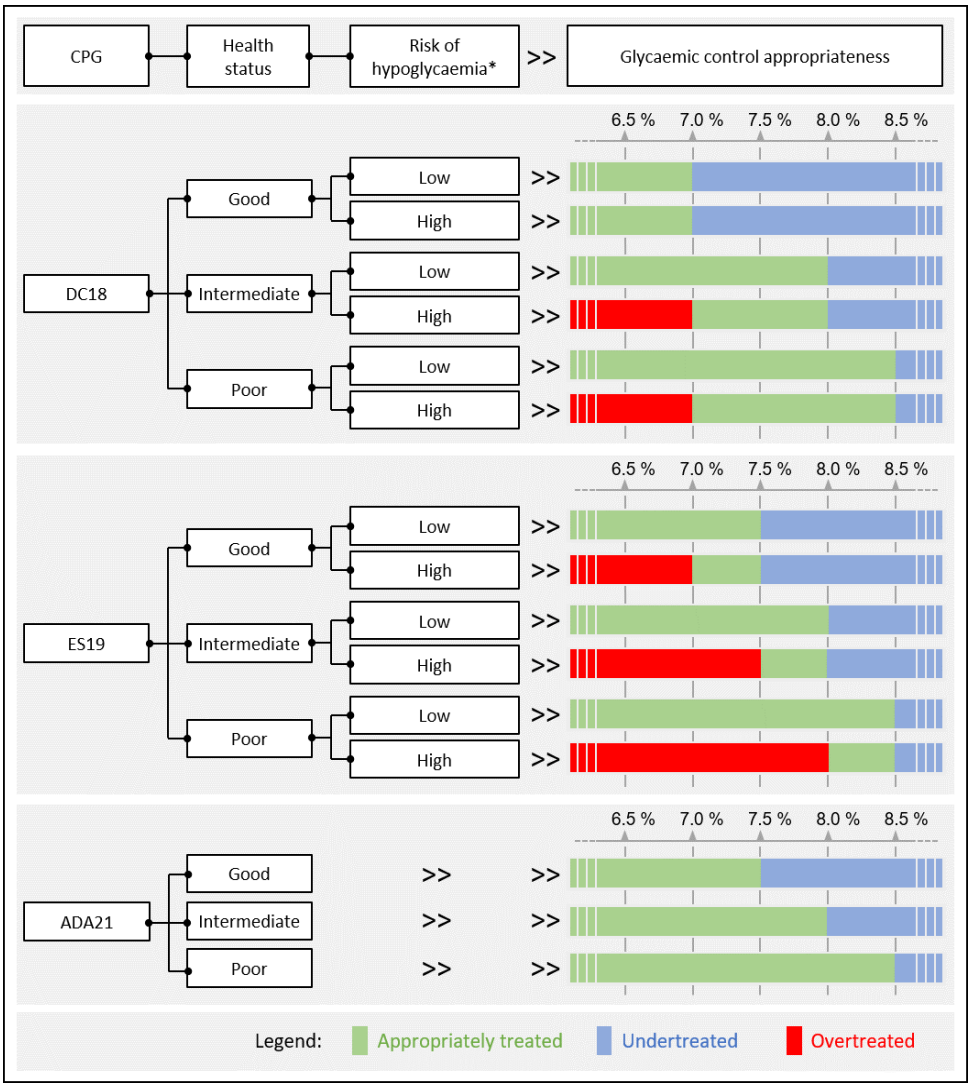
Socio-demographic, biomedical, geriatric and medication data were collected from patients' medical records at hospital admission. Geriatric features included functional impairment (≥2 impairments in 5 basic activities of daily living including eating, bathing, toileting, transferring and dressing) [12], severe polypharmacy (≥10 drugs/day), cognitive impairment (dementia or Mini-Mental State Examination <24/30), recent falls (≥2 falls within last year), malnutrition (diagnosed by a fulltime dietician after taking an anamnesis about patient's appetite loss, weight loss, eating habits as their evolution over time), and residency in a nursing home. HbA1c was expressed in % (NGSP nomenclature. Concerning GLT, agents with a high risk of hypoglycaemia (i.e. insulin, sulfonylureas and glinides) were distinguished from agents with a low risk of hypoglycaemia (i.e. biguanides, GLP1-receptor agonists, DPP4-inhibitors, thiazolidinediones and alpha-glucosidase inhibitors).

CPGs AND GLYCAEMIC CONTROL APPROPRIATENESS

Three major recent CPGs about diabetes management on older patients were used: Diabetes Canada 2018 (DC18) [13], the Endocrine Society 2019 (ES19) [12] and the American Diabetes Association 2021 (ADA21) [14]. These three CPGs recommend that glycaemic control management should be individualised according to patient's health status. Each CPG categorises global health status in three tiers (good, intermediate or poor) using different criteria related to the number of comorbidities, functional and cognitive status or place of residency [9].

For each health status tier, CPGs suggest the most appropriate HbA1c target range. Based on this interval, patients were classified in three groups of glycaemic control appropriateness: appropriately treated (patient's HbA1c in-target), overtreated (patient's HbA1c below the target range) and undertreated (patient's HbA1c above the target range) (Figure). Each CPG has its own HbA1c target ranges suggestion as shown in the Figure.

Figure. Classification of patient's glycaemic control appropriateness based on health status and risk of hypoglycaemia, according to three clinical practice guidelines.



Legend: CPG: Clinical Practice Guideline; DC18: Diabetes Canada 2018 [13]; ES19: Endocrine Society 2019 [12]; ADA21: American Diabetes Association 2021 [14]; * The risk of hypoglycaemia is high for patients taking glucose-lowering treatment with a high risk of hypoglycaemia (i.e. insulin, sulfonylurea or glinide) and low for other patients.

DATA ANALYSIS

Continuous variables were presented as medians [P25;P75]. Categorical variables were expressed as number (n) and percentages (%).

The degree of concordance among the CPGs (i.e. the raters) on patients' health status or on glycaemic control appropriateness was assessed using inter-rater reliability methods of Kappa coefficient. Cohen's kappa coefficient was used for assessment between two CPGs, while Fleiss's kappa coefficient was used for assessment between three CPGs. The level of concordance between CPGs was interpreted according to McHugh's recommendations: None ($\kappa \leq 20\%$), Minimal ($21\% \leq \kappa \leq 40\%$), Weak ($41\% \leq \kappa \leq 60\%$), Moderate ($61\% \leq \kappa \leq 80\%$), Strong ($81\% \leq \kappa \leq 90\%$) and Almost perfect ($\kappa \geq 91\%$).

Statistical analyses were performed using R studio software (R x 64 version 3.4.1). A p-value <0.05 was considered as statistically significant.

ETHICAL CONSIDERATION

This study was approved by the Institutional Review Board Committee (Commission d'Ethique Hospitalo-Facultaire, Cliniques universitaires Saint-Luc, Brussels, Belgium, IRB agreement nb. IRB00001530).

RESULTS

PATIENTS' CHARACTERISTICS

General characteristics of the 318 included geriatric patients (median age: 84 years; 54.1% female) are presented in the Table 1. The majority of the patients had functional impairment (63.2%) and cognitive impairment (57.5%). HbA1c was lower than 6.1% in a quarter of the patients (median = 6.9%). One-fourth of the patients were prescribed GLT bi- or tri-therapy. At least one hypoglycaemic agent was prescribed in 79.6% (Table 1), including insulin (29.9%), sulfonylureas (34.9%) and glinides (18.2%).

Table 1. Patients' general characteristics (N=318)

	All patients (N = 318) N (%) or Median [P25 ; P75]
Age, in years	84 [80 ; 88]
Female	146 (45.9)
Geriatric features	
Functional impairment [a]	201 (63.2)
Severe polypharmacy [b]	139 (43.7)
Cognitive impairment [c]	183 (57.5)
Recent falls [d]	169 (53.1)
Malnutrition [e]	96 (30.2)
Nursing home residency	71 (22.3)
Diabetes comorbidities	
Arterial hypertension	251 (78.9)
GFR < 30 ml/min	51 (16.8)
Ischaemic heart disease	136 (42.8)
HbA1c, in %	6.9 [6.1 ; 7.8]
< 6%	51 (16.0)
≥ 6% and < 7 %	119 (37.4)
≥ 7 % and < 8 %	80 (25.2)
≥ 8 %	68 (21.4)
Use of GLT classes	
Metformin	131 (41.2)
Other non-hypoglycaemic agents [f]	9 (2.8)
Hypoglycaemic agents [g]	253 (79.6)
GLT bi- or tri-therapy	78 (24.5)

GLT: Glucose-lowering therapy; [a] ≥2 impairments in 5 basic activities of daily living; [b] ≥ 10 drugs/day; [c] dementia or MMSE < 24/30; [d] ≥ 2 falls within last year; [e] diagnosed by a fulltime dietician; [f] Other non-hypoglycaemic agents included DPP4-inhibitors, GLP1-agonists, thiazolidinediones and alpha-glucosidase inhibitors; [g] Hypoglycaemic agents included insulin, sulfonylureas and glinides.

HEALTH STATUS DEFINITION BETWEEN CPGS

Overall, each CPG defined one-third of the patients as being in intermediate health status, while two-third of them being in poor health status (Table 2). As ES19 and ADA21 use identical criteria to define patients' health status, no difference between them was observed. A strong concordance was observed between health status definition by DC18 and ES19/ADA21 (Cohen's $\kappa = 0.86$). The change of health status tier between DC18 and ES19/ADA21 occurred respectively for 12 patients from intermediate to poor health status and for 9 patients from good to intermediate health status.

GLYCAEMIC CONTROL APPROPRIATENESS BETWEEN CPGS

DC18, ES19 and ADA21 classified respectively 45.6%, 24.8% and 82.1% of the patients as appropriately treated, 16.7%, 17.9% and 17.9% of the patients as undertreated, and 37.7%, 57.2% and 0% of the patients as overtreated (Table 2). The concordance of glycaemic control appropriateness classification between the three CPGs was minimal (κ=0.36).

The majority of patients considered as undertreated by ADA21 were also considered as undertreated by the other CPGs (93% of 57 patients). Of the 182 patients considered as overtreated by ES19, DC18 considered 120 as overtreated, 61 as appropriately treated and 1 as undertreated. ADA21 considered all of these 182 patients as appropriately treated.

Table 2. Health status and glycaemic control appropriateness in the 318 geriatric patients with T2D according to the three major CPGs

	DC18	ES19	ADA21	Concordance estimation (κ)
Health status, n (%)				
Good	9 (2.8)	0 (0.0)	0 (0.0)	
Intermediate	108 (34.0)	105 (33.0)	105 (33.0)	0.858
Poor	201 (63.2)	213 (67.0)	213 (67.0)	
Glycaemic control appropriateness, n (%)				
Undertreated	53 (16.7)	57 (17.9)	57 (17.9)	
Appropriately treated	145 (45.6)	79 (24.8)	261 (82.1)	0.356
Overtreated	120 (37.7)	182 (57.2)	0 (0.0)	

DC18: Diabetes Canada 2018 [13]; ES19: Endocrine Society 2019 [12]; ADA21: American Diabetes Association 2021 [14].

DISCUSSION

This study found a minimal concordance in glycaemic control appropriateness, with a large discrepancy concerning detection of glycaemic control overtreatment between CPGs.

The criteria used to define patient's health status tier are very similar across the three CPGs [9], and even identical between ES19 and ADA21. The excellent agreement between CPGs in health status classification was therefore expected. As the definition of patient's health

status tier is determinant for the choice of appropriate HbA1c target, discrepancies found in glycaemic control appropriateness classification are not due to differences in health status.

The main reason for large discrepancies in glycaemic control appropriateness classification between CPGs lies in discrepancies between guidelines regarding values of HbA1c target range, and above all, the definition of a lower bound. DC18 and ES19 guidelines suggest indeed a lower bound to HbA1c target range when GLT includes insulin, sulfonylurea or glinide [12, 13], whereas ADA21 guidelines do not [9, 14] (Figure). Consequently, all patients considered as overtreated using DC18 or ES19 were considered as appropriately treated using ADA21. Interestingly, this pattern of mismatches was similarly highlighted between other former CPGs [15].

More than theoretical considerations, these discrepancies between CPGs about definition of glycaemic control appropriateness (and detection of overtreatment) may have major consequences in clinical practice. The purpose of setting HbA1c targets suggested by CPGs is to adjust patient's GLT, so that the glycaemic control corresponds to what is best suited to the patient according to his or her health characteristics [6, 7]. This proposal enables an individualised therapeutic approach, i.e. a treatment meeting the needs of each patient, while being as safe as possible. In clinical practice, these differences between the three major CPGs involve different attitudes to prescribing and adapting GLT, same patient being considered as overtreated or appropriately treated overtreated according to different CPG, triggering therefore GLT-deintensification or no adaptation to the GLT respectively. These differences may conduct to an opposite and/or unsafe GLT choice for geriatric patients, who are particularly sensitive to hypoglycaemic events and their morbid and fatal consequences.

For all these reasons, the choice of the CPG to follow is particularly important in clinical practice. Given that these three guidelines are supported by major scientific societies, are of good methodological quality and are based on same (and very limited) scientific evidence , it is therefore urgent, in the light of the results of this study, to plead for CPGs favouring the safest treatment for patient and of conducting research that provide high level of scientific evidence to rely on.

This study was limited by its retrospective design, preventing the collection of other data of interest, such as duration of diabetes or patient's and/or physician preferences. Strengths of this study are the use of the most recent version of major CPGs focussing on diabetes management in older adults, the use of real life patient's data allowing accurate health status definition, and the focus on a geriatric population.

CONCLUSION

A large discrepancy in glycaemic control appropriateness was found across the major CPGs on diabetes management in older adults, and mainly concerned the definition of diabetes overtreatment. This is an obstacle to the prevention of threatening hypoglycaemic events that ought to be avoided in this high-risk population.

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SECTION II -
Diabetes overtreatment in older patients with type 2 diabetes

Chapter 3. Poor health status, inappropriate glucose-lowering therapy and high one-year mortality in geriatric patients with type 2 diabetes

Chapter 4. Diabetes overtreatment in older multimorbid patients with type 2 diabetes

Chapter 5. Overtreatment of older people with type 2 diabetes – a high impact frequent occurrence in need of a definition

Chapter 3. Poor health status, inappropriate glucose-lowering therapy and high one-year mortality in geriatric patients with type 2 diabetes

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ABSTRACT

BACKGROUND. Glucose-lowering therapy (GLT) should be individualized in older patients with type 2 diabetes (T2D) according to their health status and their life expectancy. This study aimed at assessing the inappropriateness of GLT prescribing and the one-year mortality rate in geriatric patients with T2D.

METHODS. Retrospective cohort study of consecutive inpatients with T2D admitted to a geriatric ward of a Belgian university hospital. Inclusion criteria were age ≥ 75 years, T2D with GLT before admission, and HbA1c measurement during the hospital stay. Comorbidities and geriatric syndromes were collected. GLT agents were classified into hypoglycaemic and non-hypoglycaemic ones, and their dosages were expressed in daily defined dose (DDD). Health status (intermediate or poor) and GLT appropriateness (appropriate, overtreatment, undertreatment) were assessed according to the 2019 Endocrine Society guideline on diabetes treatment in older adults, in which GLT overtreatment requires the presence of hypoglycaemic therapy. One-year mortality was determined using the National Registry of vital status, and its associated factors were analysed using multivariable Cox' regression.

RESULTS. The 318 geriatric patients with T2D (median age 84 years; 46% female) were in intermediate (33%) or poor health (67%). These two groups reached similar low HbA1c values (median 6.9%) with similar GLT regimens. GLT overtreatment was frequent (57%) irrespectively of the geriatric features. One-year mortality rate was high (38.5%) and associated in multivariate analysis with poor health status (HR: 1.59, p=0.033), malnutrition (HR: 1.67, p=0.006) and GLT overtreatment (HR: 1.73, p=0.023). Patients with GLT overtreatment had a higher mortality rate (44.5%).

CONCLUSIONS. GLT overtreatment was present in more than half of these geriatric patients. Many of them were in poor health status and died within one-year. Special attention should be paid to individualisation of the HbA1c goals in the geriatric patients with diabetes, and to GLT de-intensification in those being over-treated.

BACKGROUND

In older people, those with a geriatric profile are among the frailest, the most dependent and those with the shortest life expectancy. In this population, type 2 diabetes (T2D) is prevalent [1] and the associated glucose-lowering therapy (GLT) can be complex to manage. The treatment should be moderate enough to avoid as possible hypoglycaemic events while remaining intense enough to control high-level hyperglycaemia related symptoms. In older patients with geriatric features, *i.e.* those with frail profile and complex or poor health status, the hypoglycaemic events are indeed particularly harmful as they increase risk of falls, falls-related fractures, coma, seizures and cognitive impairments as well as all causes mortality [2]. These geriatric patients are at higher risk of more frequent and severe hypoglycaemic events [2-5].

In recent years, Scientific Societies and expert panels published clinical practice guidelines addressing the need to individualise GLT in older patients with T2D in order to minimize the risk of GLT-associated hypoglycaemia. They recommended several HbA1c target ranges according to the patient's health status (American Geriatric Society 2013 [6], American Diabetes Association 2020 [7]), life expectancy (European Association for the Study of Diabetes 2015 [8]) or geriatric profile (frailty, dementia: International Diabetes Federation 2013 [9]). In 2019, the Endocrine Society (co-sponsored by the European Society of Endocrinology, The Gerontological Society of America, and The Obesity Society) released a clinical practice guideline for the treatment of diabetes in older people [10]. This guideline helps operationalising the tailoring of the HbA1c target range based on the patient's health status (good, intermediate or poor) and GLT regimen (presence of a hypoglycaemic agent or not). In this guideline, HbA1c should not be lower than 7%, 7.5% and 8% in patients on hypoglycaemic medications with, respectively, good, intermediate and poor health status. Patients on hypoglycaemic medications with HbA1c values lower than these cut-off values may therefore be considered as over-treated.

The aims of the present study was to assess (a) the prevalence of GLT inappropriate prescribing in geriatric patients with type 2 diabetes according to the 2019 Endocrine Society guideline [10] and (b) the one-year mortality rate and its associated factors.

METHODS

STUDY DESIGN AND PARTICIPANTS' INCLUSION

This retrospective study included all consecutive inpatients with type 2 diabetes admitted in a geriatric ward (24 beds) of an academic hospital (Brussels, Belgium) between 2008 and

2015. Inclusion criteria were age ≥ 75 years, type 2 diabetes, glucose lowering therapy (GLT) at home, and HbA1c measurement during the hospital stay. In patients with multiple hospital stay, only the first one was considered in this study.

DATA COLLECTION AND DEFINITION OF VARIABLES

Data was extracted from the patient's medical record and included general, geriatric and biomedical characteristics, as well as information about GLT at home. Type 2 diabetes was defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [11]. Geriatric characteristics included residence in a long-term nursing facility, chronic functional impairment defined by ≥ 2 impairments in 5 of the basic activities of daily living (*i.e.* eating, bathing, dressing, toileting and transferring) [10], malnutrition (diagnosed by a full-time dietician after taking an anamnesis about patient's appetite loss, weight loss, eating habits as their evolution over time), recent falls (≥ 2 falls within last year) and chronic cognitive impairment (dementia or MMSE < 24/30). Estimated glomerular filtration rate (eGFR) was computed using MDRD formula [12] based on the creatinine rate at the admission in geriatric ward; eGFR <30 $ml.min^{-1}$ defined severe renal failure. Glycated haemoglobin (HbA1c) was expressed in NGSP nomenclature (%). GLT agents were encoded according to the Anatomical Therapeutic Chemical (ATC) classification system [13]. Hypoglycaemic agents included insulins (A10A), sulfonylureas (A10BB) and glinides (A10BX02-03-05-08). Non-hypoglycaemic agents included biguanides (A10BA), GLP1-receptor agonists (A10BJ), DPP4-inhibitors (A10BH), alpha-glucosidase inhibitors (A10BF) and thiazolidinediones (A10BG). Doses of each GLT agent were converted into Defined Daily Dose (DDD), according to the ATC/DDD Index 2018 [13]. GLT was considered as intense when the dose was ≥ 1.0 DDD in this geriatric population. Finally, the patient's vital status was collected using the Belgian national Register one-year after the hospital admission, this time frame being suited for the study population.

OVERALL HEALTH STATUS

Patient overall health status was classified according to the 2019 Endocrine Society guideline criteria (comorbidities, functional status, cognitive status and residence) [10] as good (absence of diabetic comorbidities, ≤ 2 non-diabetes chronic illnesses, no basic ADL impairments and ≤ 1 instrumental ADL impairment), intermediate (≥ 3 non-diabetes chronic illnesses, mild cognitive impairment/early dementia or ≥ 2 IADL impairments), or poor (end-stage medical condition, moderate/severe dementia, ≥ 2/5 ADL impairments or residence in a long-term nursing facility).

APPROPRIATENESS OF GLUCOSE LOWERING THERAPY

The 2019 Endocrine Society Guideline [10] defines the patient's HbA1c target range based on the overall health status and the use of hypoglycaemic therapy (*i.e.* insulins, sulfonylureas or glinides). In the presence of hypoglycaemic therapy, the HbA1c range has a lower limit. In patients with good health status, the HbA1c target range is <7.5% in the absence of hypoglycaemic therapy and 7.0-7.5% in the presence of hypoglycaemic therapy. In patients with intermediate health status, the HbA1c target range is <8.0% and 7.5-8.0%, respectively, in the presence and the absence of hypoglycaemic therapy. In patients with poor health status, the HbA1c target range is <8.5% and 8.0-8.5% in the presence and the absence of hypoglycaemic therapy.

Participants were classified into one of three categories of GLT appropriateness, *i.e.* appropriate GLT (HbA1c value in the patient's target range), GLT undertreatment (HbA1c value higher than the patient's target range) and GLT overtreatment (HbA1c value lower than the patient's target range). As target ranges of HbA1c have a lower bound only for people using hypoglycaemic agents, GLT overtreatment concerned only patients receiving hypoglycaemic therapy. Table 1 presented the different cut-offs used to define the three categories of GLT appropriateness based on the suggested HbA1c target ranges.

The terms "appropriate" and "inappropriate" should be understood as "concordant with the guideline" and "non-concordant with the guideline" respectively.

Table 1. Definition of categories of GLT appropriateness (undertreatment, appropriate GLT and overtreatment) according to the concordance with the 2019 Endocrine Society Guidelines [10].

Use of hypoglycaemic agents*	Overall health status	GLT appropriateness category		
		Appropriate GLT	Undertreatment	Overtreatment
		HbA1c level	HbA1c level	HbA1c level
No	Good	< 7.5 %	≥ 7.5 %	/
	Intermediate	< 8.0 %	≥ 8.0 %	/
	Poor	< 8.5 %	≥ 8.5 %	/
		HbA1c level	HbA1c level	HbA1c level
Yes	Good	≥ 7.0 and < 7.5 %	≥ 7.5 %	< 7.0 %
	Intermediate	≥ 7.5 and < 8.0 %	≥ 8.0 %	< 7.5 %
	Poor	≥ 8.0 and < 8.5 %	≥ 8.5 %	< 8.0 %

* Hypoglycaemic agents include insulins, sulfonylureas or glinides; GLT: Glucose-lowering therapy

STATISTICAL ANALYSES

Continuous data were expressed as median [P25; P75] and categorical data as number and percentages. Comparisons between the three GLT appropriateness categories were performed using Kruskal-Wallis test for continuous variables and Pearson's chi-squared test or Fisher-Freeman-Halton test for categorical variables. Factors associated with GLT appropriateness categories were assessed using a multinomial logistic regression. All variables associated with a *p*-value <0.2 in univariate analysis were candidate for the multivariable model and a stepwise selection using Akaike information criterion (AIC) was performed to select the final multivariable model. Multicollinearity was assessed using variance inflation factor (VIF), a VIF value >5 indicating multicollinearity. Factors associated with 1-year mortality were assessed using a Cox's Proportional Hazards regression. The selection of the final multivariable model was performed in the same way as for the multinomial logistic regression above. Validity conditions were fulfilled, proportional hazards hypothesis was respected and censoring was non-informative. Statistical analyses were performed using R software (version 3.4.1). A *p*-value <0.05 was considered statistically significant.

ETHICAL CONSIDERATION

This study was approved by the Institutional Review Board Committee (Commission d'Ethique Hospitalo-Facultaire, Cliniques universitaires Saint-Luc, Brussels, Belgium, IRB agreement nb. IRB00001530 and IRB00008535).

RESULTS

This study included the 318 consecutive patients with T2D admitted to the geriatric ward. According to the 2019 Endocrine Society guidelines, the patient's overall health was poor (n=213, 67.0%) or intermediate (n=105, 33.0%), no patient with T2D admitted to the geriatric ward being in good health because of some medical comorbidities or/and functional dependencies.

PATIENTS' CHARACTERISTICS

The median age was of 84.0 years, 45.9% of the patients were female, and 22.3% lived in a long-term nursing facility (Table 2). Among T2D comorbidities, patients presented ischaemic heart disease (42.8%) and severe renal impairment (16.8%). The median number of daily drugs was 9 (P25-P75: 7-11). Geriatric features were prevalent, namely functional impairment (63.2%), cognitive impairment (57.5%), recent falls (53.1%), severe

polypharmacy (48.8%) and malnutrition (30.2%) (Table 2). Patients in poor health (n=213, 67.0%) did not differ from those in intermediate health (n=105, 33.0%) in age, sex, number of comorbidities or daily drugs, neither in features of glucose lowering therapy (GLT), *i.e.* use of hypoglycaemic agents (81.7% *vs.* 75.2%; p=0.180), use of metformin (38.5% *vs.* 46.7%; p=0.164), and overall GLT DDD (0.85 *vs.* 0.81 DDD; p=0.316).

APPROPRIATENESS OF GLUCOSE-LOWERING THERAPY

Table 2 compares the patients with appropriate GLT (24.8%), GLT overtreatment (57.2%) and GLT undertreatment (17.9%). These three groups did not statistically differ in socio-demographic characteristics, global health status, prevalence of ischemic heart disease and of geriatric features. Renal failure (eGFR < 30 ml/min) was more present in patients with GLT overtreatment (21.1%) than in patients with GLT undertreatment (16.1%) or appropriate GLT (7.9%) (Table 2; p=0.038).

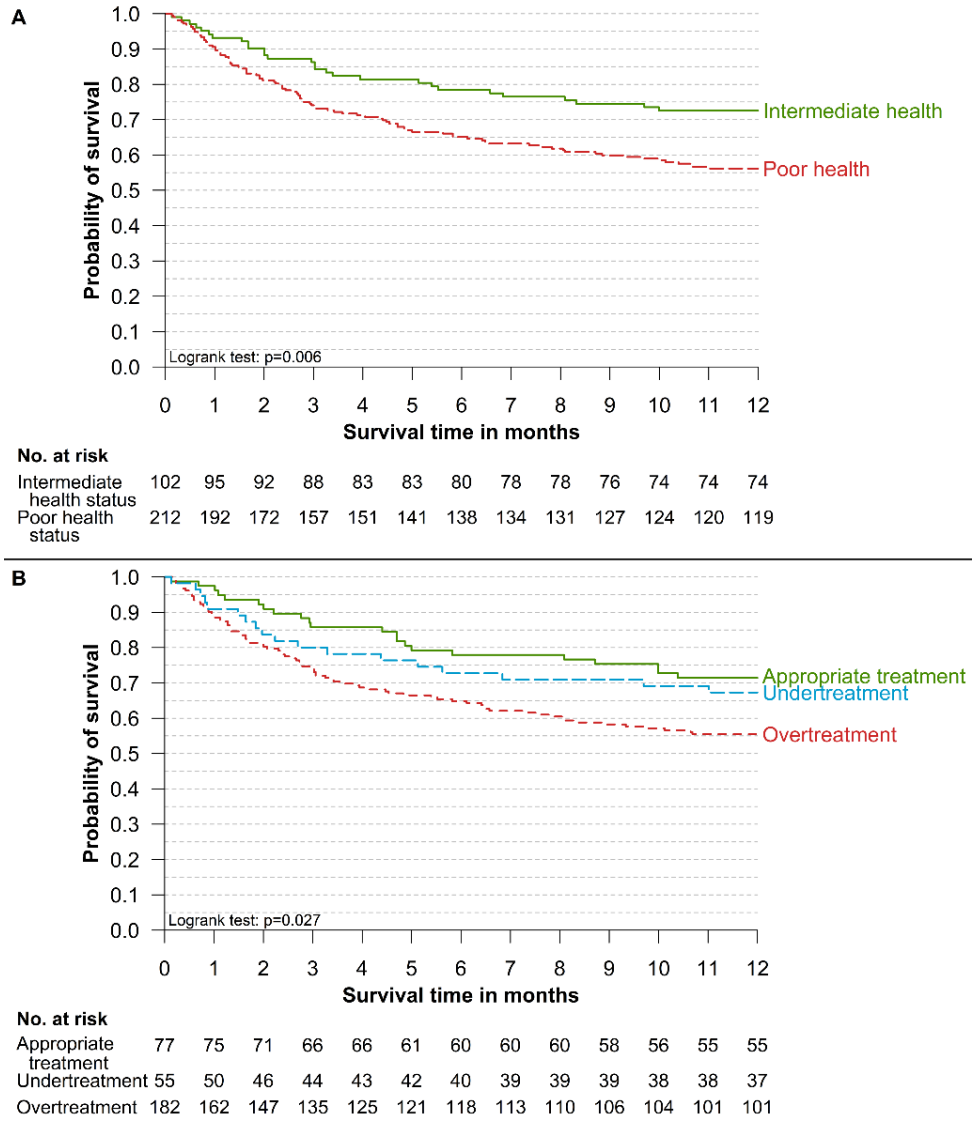
The three categories of GLT appropriateness differed in HbA1c values, GLT classes and GLT intensity (DDD) (Table 2). Patients with appropriate GLT (n=79) showed a median HbA1c of 6.9%, obtained with a simple GLT regimen (metformin 83.5%; monotherapy 84.8%). They were infrequently on hypoglycaemic agents (25.3%) or on GLT ≥ 1.0 DDD (29.1%). Patients with GLT undertreatment (n=57) had median HbA1c value of 9.2% despite the frequent prescribing of hypoglycaemic agents (89%) and of intense GLT (DDD ≥ 1.0: 61.4%). Patients with GLT overtreatment (n=182) were prescribed a more intense GLT regimen than those with appropriate GLT, with a lower use of metformin use (25.3 vs. 83.5%, p<0.001) and a high use of intense GLT (DDD ≥ 1.0: 46.2 vs. 29.1%, p=0.015). In the logistic regression model comparing GLT overtreatment to appropriate GLT [Additional file 1], GLT overtreatment was associated with severe renal failure (OR [95%CI] = 3.49 [1.38; 8.81]), poor health status (OR 1.96 [1.10; 3.51]) and GLT bi- or tri-therapy (OR 2.41 [1.18; 4.94]).

Table 2. Patient's and glucose-lowering therapy (GLT) characteristics, according to GLT appropriateness (N = 318)

Variable	All patients *n* = 318 Median [P25;P75] or n (%)	Appropriate GLT *n* = 79 (24.8%) Median [P25;P75] or n (%)	GLT Overttt *n* = 182 (57.2%) Median [P25;P75] or n (%)	GLT Underttt *n* = 57 (17.9%) Median [P25;P75] or n (%)	*p*-value
Age, in years	84 [80 ; 88]	84 [80 ; 87]	84 [81 ; 88]	83 [80 ; 87]	0.544
Female	146 (45.9)	34 (43.0)	89 (48.9)	23 (40.4)	0.443
Overall health category					0.107
Intermediate health	105 (33.0)	33 (41.8)	52 (28.6)	20 (35.1)	
Poor health	213 (67.0)	46 (58.2)	130 (71.4)	37 (64.9)	
Comorbidities					
Ischaemic heart disease	136 (42.8)	29 (36.7)	77 (42.3)	30 (52.6)	0.177
Renal failure (n=303)*	51 (16.8)	6 (7.9)	36 (21.1)	9 (16.1)	0.038
Geriatric features					
Nursing home residency	71 (22.3)	18 (22.8)	45 (24.7)	8 (14.0)	0.238
Functional impairment **	201 (63.2)	44 (56.7)	123 (67.6)	34 (59.6)	0.155
Severe polypharmacy ***	139 (43.7)	33 (48.8)	82 (45.1)	24 (42.1)	0.855
Cognitive impairment	183 (57.5)	46 (58.2)	106 (58.2)	33 (57.9)	0.999
Recent falls	169 (53.1)	43 (54.4)	93 (51.1)	33 (57.9)	0.646
Malnutrition	96 (30.2)	28 (35.4)	52 (28.6)	16 (28.1)	0.501
GLT characteristics					
HbA1c, in %	6.9 [6.1 ; 7.8]	6.8 [6.1 ; 7.6]	6.7 [6.1 ; 7.2]	9.2 [8.6 ; 10.1]	<0.001
Use of GLT classes					
Metformin	131 (41.2)	66 (83.5)	46 (25.3)	19 (33.3)	<0.001
Other NHGA****	9 (2.8)	5 (6.3)	3 (1.6)	1 (1.8)	0.101
Hypoglycaemic agents	253 (79.6)	20 (25.3)	182 (100.0)	51 (89.5)	<0.001
Bi- or tri-therapy	78 (24.5)	12 (15.2)	49 (26.9)	17 (29.8)	0.076
GLT total intensity, in DDD	0.9 [0.5 ; 1.4]	0.8 [0.4 ; 1.0]	0.8 [0.5; 1.3]	1.2 [0.8 ; 2.0]	0.014
0-0.4 DDD	73 (23.0)	27 (34.2)	40 (22.0)	6 (10.5)	0.002
0.5-0.9 DDD	103 (32.4)	29 (36.7)	58 (31.9)	16 (28.1)	
≥ 1 DDD	142 (44.7)	23 (29.1)	84 (46.2)	35 (61.4)	

GLT: Glucose-lowering therapy; HbA1c: Glycated haemoglobin; DDD: Defined daily dose; NHGA: Non-hypoglycaemic agents; Overttt: Overtreatment; Underttt: Undertreatment; Hypoglycaemic agents include insulin, sulfonylureas and glinides; *defined as estimated glomerular filtration rate <30ml/min; ** defined as ≥2 impairments in basic activities of daily living, including eating, bathing, toileting, transferring and dressing; *** defined as ≥10 drugs/day; **** Other non-hypoglycaemic agents were DPP4-inhibitors, thiazolidinediones and alpha-glucosidase inhibitors.

Fig. 1. One-year survival of geriatric patients with T2D according to (A) Health status and (B) GLT-appropriateness.



Kaplan-Meier survival curves at one year of geriatric patients with type 2 diabetes according to (A) their overall health status (Intermediate or Poor) and (B) their category of GLT appropriateness (Appropriate, Undertreatment or Overtreatment).

Table 3. Factors associated with one-year mortality in Cox Proportional Hazards regression (N = 314)

Variables	Univariate model		Multivariable model	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Socio-demographic characteristics				
Category of ages				
Age < 80 years	1.00			
Age 80-84 years	0.89 [0.53 ; 1.50]	0.660		
Age 85-89 years	1.04 [0.62 ; 1.76]	0.879		
Age ≥ 90 years	1.41 [0.80 ; 2.49]	0.234		
Sex (male *vs.* female)	1.26 [0.88 ; 1.80]	0.207		
Health status, comorbidities and geriatric characteristics				
Health status (poor *vs.* intermediate)	1.80 [1.18 ; 2.74]	0.007	1.59 [1.04 ; 2.43]	0.033
Ischaemic heart disease	1.44 [1.01 ; 2.06]	0.045	1.39 [0.97 ; 1.98]	0.074
Nursing home residency	1.67 [1.13 ; 2.48]	0.010		
Malnutrition	1.65 [1.15 ; 2.38]	0.007	1.67 [1.16 ; 2.42]	0.006
Recent falls	0.64 [0.45 ; 0.92]	0.015	0.63 [0.44 ; 0.91]	0.013
Functional impairment*	1.65 [1.11 ; 2.46]	0.014		
Polypharmacy				
Absent (0-4 drugs/day)	1.00			
Moderate (5-9 drugs/day)	2.08 [0.83 ; 5.19]	0.117		
Major (≥ 10 drugs/day)	2.41 [0.97 ; 6.01]	0.059		
GLT characteristics				
Appropriateness				
Present	1.00		1.00	
Undertreatment	1.22 [0.65 ; 2.27]	0.534	1.22 [0.65 ; 2.28]	0.542
Overtreatment	1.80 [1.12 ; 2.89]	0.015	1.73 [1.08 ; 2.79]	0.023
Category of HbA1c				
HbA1c < 6.5%	1.82 [1.02 ; 3.22]	0.042		
HbA1c 6.5-7.4%	1.05 [0.58 ; 1.92]	0.866		
HbA1c 7.5-8.4%	1.00			
HbA1c ≥ 8.5%	1.16 [0.58 ; 2.33]	0.672		
Use of hypoglycaemic agents	1.71 [1.03 ; 2.86]	0.040		
Use of metformin	0.62 [0.42 ; 0.91]	0.015		

HR: Hazard Ratio; CI: Confidence interval; GLT: Glucose-lowering therapy; *Functional impairment was defined as ≥2/5 impairments in basic activities of daily living (eating, bathing, dressing, toileting and transferring).

FACTORS ASSOCIATED WITH ONE-YEAR MORTALITY

At one year, more than one-third of these geriatric patients with T2D had died (38.5 %; n=121/314, 4 missing values). As expected, the one-year mortality rate was higher in

patients with poor health status (43.9%) than in those with intermediate health status (27.5%) (Fig. 1A, Logrank test p = 0.006). The one-year mortality rate also differed in patients with appropriate GLT (28.6%), GLT undertreatment (32.7%) and GLT overtreatment (44.5%) (Fig. 1B, Logrank test p = 0.027). In the multivariable model (Table 3), one-year mortality was not associated with older age, was lower in patients with recent falls (HR: 0.63, p=0.013) and was higher in patients with poor health status (HR: 1.59, p=0.033), malnutrition (HR: 1.67; p=0.006) and GLT overtreatment (*vs.* appropriate GLT; HR: 1.73, p=0.023). Finally, it was not associated with GLT-undertreatment.

DISCUSSION

In this study of older old patients admitted to a geriatric ward, GLT at home was appropriately prescribed in only 1 in 4 patients. GLT appropriateness was not associated with any patient's characteristic but with GLT prescribing, i.e. lower use of hypoglycaemic agents (i.e. insulins, sulfonylureas or glinides) and of intense dose. GLT undertreatment concerned 1 in 6 geriatric patients, in whom HbA1c was too high despite high dose of GLT. GLT overtreatment, i.e. patients prescribed with hypoglycaemic agents with a HbA1c value below the target range, was detected in 1 in 2 patients. GLT overtreatment was associated with poor health status, severe renal failure and use of bi-or tri-therapy of GLT. Importantly, one-year mortality was higher in patients with GLT overtreatment (44%) than those with appropriate GLT, independently of the patient's health status and of the age of the patient.

GLT overtreatment, which potentially leads to hypoglycaemia [14, 15] and thus to associated comorbidities and mortality [2], was surprisingly not less frequent in patients with geriatric syndromes or poor health status than others. This finding highlights in this population a clear lack of individualisation of GLT according to these characteristics. This is even more surprising since older patients with geriatric features or/and in poor health status are at higher risk of more frequent and severe hypoglycaemic events, due to frequent misdiagnoses, unawareness and atypical presentations [2]. In our study, GLT overtreatment was more frequent in patients with severe renal failure (eGFR<30ml/min), most of whom (n=47/51; 92.2%) received at least one hypoglycaemic agent (*i.e.* insulins, sulfonylureas or glinides). One potential explanation is the contra-indication of metformin in patients with severe renal failure. In addition to the fact that some hypoglycaemic agents can accumulate in case of severe renal failure (*e.g.* sulfonylureas [16]), other non-hypoglycaemic GLT agents are preferable, such as DPP4-inhibitors, the safety of which (with adjusted doses for some) has been studied in case of severe renal impairment even in older patients [10, 17].

Patients with GLT undertreatment might benefit from GLT intensification in order to avoid discomfort of hyperglycaemia-related symptoms. Beyond the value of HbA1c, the decision to intensify the treatment should be taken with caution. Indeed, hypoglycaemic events can also occur despite high HbA1c values in patients receiving intensive hypoglycaemic therapy [18]. Therefore, in the geriatric patients with a HbA1c over the target level, GLT intensification should be achieved on a case-by-case basis, considering a risk-benefit balance between the discomfort of hyperglycaemia and the risk of hypoglycaemic events. Furthermore, considering that the very old and frail population of this study received highly conservative GLT agents (largely composed by metformin and hypoglycaemic agents), non-hypoglycaemic agents other than metformin could be an interesting option, if further intensification of the treatment is deemed necessary.

The one-year mortality rate was high in these patients (38.5%). In the multivariate model, one-year mortality was higher in the presence of poor health status, low weight and GLT overtreatment, but lower in the presence of multiple falls. The latter association might be explained by the fact that the very dependent geriatric patients do not walk anymore. Falls might indicate a somewhat preserved functional status. The association between one-year mortality and GLT overtreatment is important to discuss. This observation does not mean that GLT overtreatment increases mortality in geriatric patients, as it has been demonstrated in other studies involving younger old and healthier patients [19-21]. Indeed, the observational design of our study does not allow any causal conclusion. Frailty and severe renal failure might be confounding factors, as they are associated to both GLT overtreatment and mortality. However, the observed association between one-year mortality and GLT overtreatment highlights the pointlessness and the risk of intense GLT in geriatric patients with poor health status with a poor one-year life expectancy. It is indeed useless to prescribe an intense GLT therapy with the aim to avoid long-term T2D complications in patients with a short life expectancy, especially since such a therapy induces hypoglycaemic events.

This study was limited by its retrospective design. The duration of diabetes is not known. Data related to the GLT prescribers (*e.g.* motivations for initiating/continuing this treatment, knowledge about the guidelines on diabetes in older adults) could not be collected. The association of GLT appropriateness with other outcomes that matter to the geriatric patients, *i.e.* impaired quality of life, hypoglycaemic episodes, functional decline, should be studied in the future. This study was finally limited by its single-centre inclusion, which, despite the risk of selection bias, is to be put into perspective given the continuous inclusion of patients over a long period of time during which several different medical teams succeeded one another.

A strengths of this study is the focus on geriatric patients with type 2 diabetes ≥75 years in the setting of a geriatric ward of a university hospital. Geriatric patients are the most dependent with the most unfavourable health status among older patients (*e.g.* no patients in this study was in good health status). Therefore, these data cannot be generalised to the general older population ≥75 years. However, these data are important for patients from this particular setting, especially as these patients are not commonly represented in the scientific literature on the treatment of type 2 diabetes. Other strengths were the collection of data on the main geriatric syndromes, the tailoring of HbA1c targets according to the 2019 Endocrine Society guideline, and the analysis of the residual life expectancy (vital status at one year).

This study confirms the need for an improvement in GLT prescribing in the geriatric patients with T2D. Several actions should be considered. Firstly, the prescribing physician should individualise the HbA1c targets in each older patient based on the health status and the use of hypoglycaemic therapy (*i.e.* insulins, sulfonylureas or glinides), as suggested by the Endocrine Society. As pointed by most of the recent clinical guidelines on older adults with diabetes, the tailoring of HbA1c is the most effective way to reduce inappropriate therapy and the ensuing risk of hypoglycaemia [10, 22-24]. It is acknowledged that the implementation of guidelines takes time. However, the results of this study highlight the existence and relevance of guidelines related to the individualised management of glucose-lowering therapy, in particular the 2019 Endocrine Society guideline, and to use patients' health status and the use of hypoglycaemic agents to individualise GLT according the patient's target HbA1c level. Secondly, the patients should be involved in the decision making process as much as possible [10]. Finally, in the numerous geriatric patients with GLT overtreatment, de-intensification of hypoglycaemic agents (*i.e.* stopping the medication, reducing the dose or switching to another and safer drug) should be performed especially in patients with a poor overall health status (with frail profile, dementia, cognitive impairment) [25]. Actually, life expectancy of these patients is reduced and the benefit of intensive glucose lowering therapy is therefore absent. Interventional studies are deeply needed to clarify the modalities of GLT de-intensification in older people with type 2 diabetes.

CONCLUSIONS

Inappropriateness of GLT prescribing (*i.e.* non-concordance with the guideline) was very frequent in these geriatric patients with type 2 diabetes, mainly due to too low HbA1c value with hypoglycaemic agents, *i.e.* GLT overtreatment. One year-mortality was high and associated with poor health status, low body weight and GLT overtreatment. As the majority

of such geriatric patients with diabetes are in poor health and overtreated with GLT, a GLT reassessment should be carried out, in order to improve the appropriateness of GLT prescribing in the geriatric patients with type 2 diabetes.

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APPENDICES

Table S.1. Factors associated with Overtreatment and Undertreatment of GLT (*vs.* Appropriate-GLT) in multivariable multinomial logistic regression analysis (n = 303)

Variables	Overtreatment *vs.* Appropriate GLT		Undertreatment *vs.* Appropriate GLT	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Overall health status (poor *vs.* intermediate)	1.96 [1.10 ; 3.51]	0.022	1.34 [0.65 ; 2.76]	0.420
Renal failure [a]	3.49 [1.38 ; 8.81]	0.008	2.51 [0.83 ; 7.60]	0.103
Bi- or tri-therapy of GLT	2.41 [1.18 ; 4.94]	0.016	2.34 [0.99 ; 5.51]	0.051

OR: Odds Ratio; CI: Confidence interval; GLT: Glucose-lowering therapy; [a]15 missing values; *defined as estimated glomerular filtration rate <30ml/min.

Chapter 4. Diabetes overtreatment in older inpatients with type 2 diabetes, polypharmacy and multimorbidity: a substudy of a European multicentre study.

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ABSTRACT

BACKGROUND. Diabetes overtreatment is a frequent and severe issue in multimorbid older patients with type 2 diabetes (T2D). This study aimed at assessing the association between diabetes overtreatment and one-year mortality, hospitalisation rate and functional decline in older inpatients with polypharmacy and multimorbidity.

METHODS. Substudy of the European multicentre OPERAM trial of multimorbid patients aged ≥70 years, with T2D and glucose-lowering treatment (GLT). Diabetes overtreatment was defined according to the 2019 Endocrine Society guideline with the HbA1c target range individualised according to patient's overall health status and the use of a GLT with high risk of hypoglycaemia. Multivariable regressions were used to assess factors associated with the three outcomes at one year.

RESULTS. Among the 490 patients with T2D (median age: 78 years; 38% female), 168 (34.3%) had diabetes overtreatment. The mortality rate was higher in patients with diabetes overtreatment than in not overtreated patients (31.8 vs. 20.1/100 patient-years, p=0.023). In multivariable analyses, diabetes overtreatment was independently associated with a higher mortality rate (HR [95%CI]: 1.61 [1.07;2.41]), a lower hospitalisation rate (IRR [95%CI]: 0.78 [0.63; 0.95]), but not with functional decline at one year.

DISCUSSION. Diabetes overtreatment is common among older people with T2D, multimorbidity and polypharmacy, and was independently associated with higher mortality rate and lower hospitalisation rate at one year. The results of this study confirmed that diabetes overtreatment is an important clinical problem in this vulnerable population. Meanwhile, GLT de-intensification should be considered in older patients with diabetes overtreatment.

BACKGROUND

Type 2 diabetes is a prevalent condition in older people, reaching almost 20% of patients aged ≥ 65 years in European countries [1], and severely affecting their quality of life and functional status [2]. The treatment of diabetes usually includes a control of glycaemia by a glucose-lowering therapy (GLT), reducing long-term complications from chronic exposure to hyperglycaemia (such as microvascular complications) [3]. However, some glucose-lowering drugs induce a high risk of hypoglycaemia (such as insulins, sulfonylureas or glinides), especially if they are used to achieve a tight glycaemic control, i.e. diabetes overtreatment [4-6].

In older patients, hypoglycaemic events are more frequent, more challenging to diagnose (due to the unawareness and their insidious clinical presentation), more severe, and more frequently complicated, in particular in those with frailty or poorer health status [5, 7, 8]. These harmful hypoglycaemic events increase falls-related fractures, cardiovascular events, cerebral events (comas and seizure), while they reduce cognitive status, functional status and life expectancy [9-12].

Recent clinical practice guidelines (CPGs) from major scientific societies strongly recommend avoiding hypoglycaemia and diabetes overtreatment in older patients. They suggest that GLT should be individualised, in particular by using individualised HbA1c goals according to the patients' health status and the type of GLT used (inducing high risk of hypoglycaemia or not) in order to define an individualised treatment objective [13-16]. Individualisation of treatment objective allows the benefit-risk balance of the glycaemic treatment prescribed to older patients to be more accurately adjusted to their health status and life expectancy, i.e. the balance between the potential long-term benefits of GLT vs. the risks of short-term complications.

However, there is limited data on the prevalence of overtreatment of diabetes in older patients and its consequences, particularly in populations usually less represented in studies, such as multimorbid older people [17, 18]. This study aimed at assessing the association of diabetes overtreatment with three outcomes at one year: mortality, hospitalisation rate and functional decline.

METHODS

STUDY DESIGN AND PATIENTS' INCLUSION

This study was a substudy of a European multicentre cluster randomised controlled trial (Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM)) [19, 20]. The OPERAM trial was designed to assess the effect of pharmacological treatment optimisation on drug related hospital admissions in older inpatients with multimorbidity and polypharmacy. It included 2008 patients aged ≥ 70 years with multimorbidity (≥ 3 conditions) and polypharmacy (≥ 5 different drugs/day) admitted to a university hospital in four countries, namely Switzerland (Bern), Netherlands (Utrecht), Belgium (Louvain) and Republic of Ireland (Cork). Patients were excluded when admitted to palliative care within 24 hours after hospital admission. Clusters were 1:1 randomised to standard of care (control group) or a structured pharmacotherapy optimisation intervention (evidence-based structured medication review using the Dutch Systematic Tool to Reduce Inappropriate Prescribing (STRIP) [21], based on the STOPP/START.v2 criteria [22]). Besides the discontinuation of long-acting sulfonylureas (STOPP J1) and the discontinuation of thiazolidinediones in the presence of cardiac failure (STOPP J2) in STOPP/START.v2 criteria and the fact that the physician-pharmacist pairs could make recommendations on GLT if thought to be relevant, no other specific intervention was required to the GLT. All patients were followed-up for a duration of 1 year after the inclusion.

The present substudy included all patients with type 2 diabetes prescribed a GLT before the hospitalisation and a concomitant value of HbA1c.

DATA COLLECTION

The collected data at index hospitalisation were related to patients' socio-demographic characteristics (age, sex, place of residency), main trial characteristics (site of inclusion and group of allocation – intervention or control arm), clinical, biological and functional characteristics. Among them, comorbidities were collected to compute the Charlson comorbidity index [23]. Functional status was assessed using the Barthel index (total score/100 [24]), scoring the independence in 10 activities of daily living (ADL). Cognitive impairment was defined as a diagnosed dementia. Quality of life was assessed using EQ-5D score [25]. Severe frailty was defined as a score of ≥7 on the Clinical Frailty Scale [26]. Severe polypharmacy was defined as prescribed ≥10 drugs daily at the usual place of living for at least 30 days before admission.

HbA1c, expressed in National Glycohemoglobin Standardization Program (NGSP) nomenclature (%), was retrospectively collected after inclusion of patients (data from medical records). We considered the value of HbA1c, which was closest to the enrolment date in OPERAM trial within a year. The glucose-lowering treatment (GLT) concomitant to the HbA1c value was collected as well. Glucose-lowering agents were encoded according to the Anatomical Therapeutic Chemical classification system (ATC) [27]. Glucose-lowering agents included hypoglycaemic drugs (insulins (A10A), sulfonylureas (A10BB) and glinides (A10BX02–03–05-08)) and non-hypoglycaemic agents (biguanides (A10BA), GLP1-receptor agonists (A10BJ), DPP4-inhibitors (A10BH), alpha-glucosidase inhibitors (A10BF), thiazolidinediones (A10BG) and SGLT2-inhibitors)).

OUTCOMES

The occurrences of outcomes of interest were investigated in the year of follow-up after admission: all-cause mortality, hospitalisation rate and functional decline (measured at 2 and 12 months). Functional decline was defined as a loss (loss of ≥10%) in Barthel index (activities of daily living).

OVERTREATMENT

Diabetes overtreatment refers in this study to overtreatment of glycaemic control. This is defined based on the Clinical Practice Guidelines (CPG) of the 2019 Endocrine Society [15] about the management of diabetes in older adults, i.e. according to the patients' health status, hypoglycaemic drugs, and HbA1c.

The patient's health status was assessed, according to their number of comorbidities, functional status, cognitive status and place of residency (see Fig. S.1. in Appendices). Each patient was classified into one of three tiers: good, intermediate or poor health status.

Diabetes overtreatment was defined as having a GLT including a glucose-lowering agent at high risk of hypoglycaemia (i.e. insulin, sulfonylurea or glinide) while having an HbA1c < 7.0% for patients in good health, < 7.5% for patients in intermediate health and < 8.0% for those in poor health.

STATISTICAL ANALYSIS

Categorical data were expressed as absolute frequency (n) and relative frequency (%). Continuous variables were expressed as medians and interquartile range (median [1st quartile; 3rd quartile]).

The incidence rates of hospitalisation and mortality during 1 year after the index hospitalisation were expressed as number of events per 100 patient-years at risk. The comparison of incidence rates between groups (overtreated vs. not overtreated) were performed using a z-test. The percentage of functional decline was computed among patients with at least 2 measurements of the Barthel index and defined as a loss of at least 10% of Barthel index. The percentage of functional decline was compares between groups (overtreated vs. not overtreated) using a Pearson's Chi-squared test.

Factors associated with mortality at one year were assessed using a multivariable Cox's Proportional Hazards regression. For this model, the absence of multicollinearity was checked using the variance inflation factor (VIF; a VIF value > 5 indicated multicollinearity) and the conditions of validity of the model were fulfilled: the proportional hazards assumption was checked using Schoenfeld residuals, nonlinearity was assessed using Martingale residuals and influential observations were examined using Deviance residuals. Factors associated with hospitalisation rate were assessed using a multivariable Poisson regression computing the incidence rate ratio. Finally, factors associated with functional decline based on measures of Barthel index at baseline, 2 months and 12 months of follow up, were assessed using a multivariable linear mixed effects regression. For all models, a stepwise selection using the Akaike information criterion (AIC) was performed to select the final multivariable model, and interactions between variables within models were assessed and included in the model if necessary.

For all analyses, a p-value < 0.05 was considered as statistically significant. All statistical analyses were performed using R statistical software (version 4.0.2).

ETHICAL CONSIDERATION

The OPERAM trial was approved by the independent research ethics committees at each site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016-01200; Medical Research Ethics Committee Utrecht, Netherlands, ID 15-522/D; Comité d'Ethique Hospitalo-Facultaire Saint-Luc-UCL: 2016/20JUL/347–Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland; ID ECM 4 (o) 07/02/17), and Swissmedic as responsible regulatory authority [19].

RESULTS

Of the 2008 older patients included in the OPERAM trial, 519 (25.8%) had type 2 diabetes. Among them, 490 patients had glucose-lowering treatment (GLT) before the index hospital

admission with a concomitant HbA1c measurement, and were included in the present analyses.

BASELINE CHARACTERISTICS

The 490 older patients with type 2 diabetes had a median age of 78 years and 38.0% of them were women (Table 1). The median number of comorbidities was 5, resulting in a median Charlson comorbidity index of 7. The median number of daily drugs was 11 and severe polypharmacy (≥ 10 drugs daily) was observed in 63.7% of the patients

Three in ten (30.6%) of the patients had ≥ 2 impairments in basic activities of daily living (bathing, dressing, eating, toileting and transferring), 9.8% had cognitive impairment, and 6.9% lived in a nursing home. These features resulted in a health status being poor in 41.4%, intermediate in 42.9% and good in 15.7% of the patients. Severe frailty was found in 20.4% of the patients.

As far as GLT was concerned, half of the patients (52.9%) received a daily bi- or tritherapy. The most frequent GLT regimen was a bi- or tritherapy including hypoglycaemic drug(s) (46.7%) followed by monotherapy with non-hypoglycaemic drug (30.2%). The median HbA1c was 7.0% [6.3%; 7.8%].

Diabetes overtreatment was found in 168 patients (34.3%) (Table 1).

Table 1. General characteristics at baseline (N=490)

Variable	All patients (n = 490; 100%) n (%) or median [P25 ; P75]	Overtreated (n = 168; 34.3%) n (%) or median [P25 ; P75]	Not overtreated (n = 322; 65.7%) n (%) or median [P25 ; P75]
Age, *years*	78 [74 ; 82]	76 [73 ; 83]	78 [74 ; 82]
Age ≥80 years	197 (40.2)	67 (39.9)	130 (40.4)
Female	186 (38.0)	59 (35.1)	127 (39.4)
Site			
Bern	184 (37.6)	60 (35.7)	124 (38.5)
Cork	72 (14.7)	11 (6.5)	61 (18.9)
Louvain	123 (25.2)	58 (34.5)	65 (20.2)
Utrecht	111 (22.7)	39 (23.2)	72 (22.4)
Group intervention	207 (42.2)	73 (43.5)	134 (41.6)
Number of comorbidities	5 [2 ; 7]	5 [3 ; 7]	4 [2 ; 7]
Charlson comorbidity index	7 [5 ; 8]	7 [5 ; 8]	6 [5 ; 8]
Number of drugs/day	11 [8 ; 14]	11 [9 ; 14]	11 [8 ; 14]
Severe polypharmacy (>=10 drugs/day)	312 (63.7)	116 (69.0)	196 (60.9)
Functional status			
≥ 2 impairments in ADL	150 (30.6)	59 (35.1)	91 (28.3)
Barthel index (12 missing values)	90 [75 ; 100]	90 [70 ; 100]	95 [80 ; 100]
Cognitive impairment	48 (9.8)	19 (11.3)	29 (9.0)
Fall (≥2 in the last year)	54 (11.0)	14 (8.3)	40 (12.4)
Nursing home residency	34 (6.9)	12 (7.1)	22 (6.8)
Severe frailty (CFS ≥ 7)	100 (20.4)	40 (23.8)	60 (18.6)
Health status			
Good	77 (15.7)	19 (11.3)	58 (18.0)
Intermediate	210 (42.9)	68 (40.5)	142 (44.1)
Poor	203 (41.4)	81 (48.2)	122 (37.9)
Quality of life (EQ-5D)	0.89 [0.67 ; 1.00]	0.86 [0.60 ; 0.97]	0.91 [0.72 ; 1.00]
Number of glucose-lowering drugs/day	2 [1 ; 2]	2 [1 ; 2]	1 [1 ; 2]
Bi-therapy or more	259 (52.9)	119 (70.8)	140 (43.5)
Glucose-lowering treatment			
Monother. non-hypoglycaemic drug	148 (30.2)	0 (0)	148 (46.0)
Monother. hypoglycaemic drug	83 (16.9)	49 (29.2)	34 (10.6)
Bi or trither. non-hypoglycaemic drug	30 (6.1)	0 (0)	30 (9.3)
Bi or trither. hypoglycaemic drug	229 (46.7)	119 (70.1)	110 (34.2)
HbA1c, *%*	7.0 [6.3 ; 7.8]	6.7 [6.2 ; 7.2]	7.5 [6.5 ; 8.3]
< 6.5%	136 (27.8)	65 (38.7)	71 (22.0)
6.5 – 7.49 %	167 (34.1)	86 (51.2)	81 (25.2)
7.5 – 8.49 %	113 (23.1)	17 (10.1)	96 (29.8)
≥ 8.5 %	74 (15.1)	0 (0)	74 (23.0)

ADL: Activities of daily living; CFS: Clinical Frailty Scale; Monother.: Monotherapy; Trither.: Tritherapy; HbA1c: Glycated haemoglobin; Health status was defined according to criteria of the Endocrine Society Guidelines (2019) [15]. Patients were considered as overtreated when glucose-lowering treatment with high risk of hypoglycaemia (i.e. including insulin, sulfonylurea or glinide) was taken and HbA1c was < 7.0 % (for patients in good health), < 7.5 % (for patients in intermediate health) or < 8.0 % (for patients in poor health).

OUTCOMES AT ONE-YEAR (ALL-CAUSE MORTALITY, HOSPITALISATION AND FUNCTIONAL DECLINE) AND ASSOCIATED FACTORS

The all-cause mortality rate (23.9 per 100 patient-years during the year after the inclusion) was higher in patients with diabetes overtreatment than in the others (31.8 vs. 20.1 per 100 person-years; p=0.023) (Fig. 1 & Table 2). In multivariable analysis, the risk of death at one year was 1.61 times higher in overtreated patients as compared to those without overtreatment (Hazard Ratio (HR) (95%CI): 1.61 (1.07; 2.41), p=0.023). Other factors associated with higher one-year mortality rate were higher Charlson comorbidity index (HR: 1.12 per point increase p=0.011), poor health status (as compared to good health status (HR (95%CI): 4.71 (1.21; 16.25), p=0.014), inclusion at site 4 (as compared to site 1 : HR (95%CI): 1.72 (1.09 ; 2.76), p=0.025), and severe frailty (HR (95%CI): 1.70 (1.03; 2.80), p=0.039) (Fig. 2(a) & Table S.1 in Appendices).

Fig. 1. One-year survival of older multimorbid patients with type 2 diabetes (n=490) with (n = 168) and without (n = 322) diabetes overtreatment

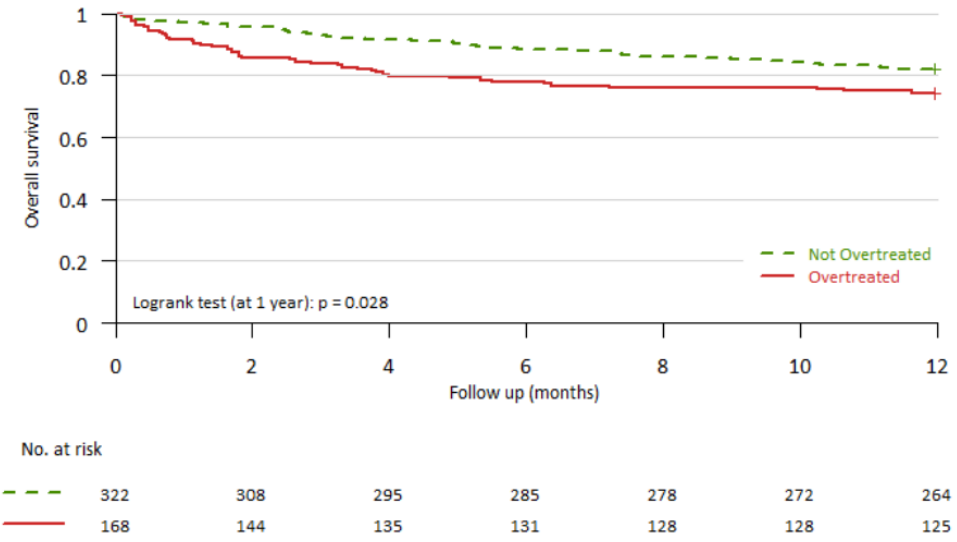


Table 2. Incidence of outcomes (mortality, hospitalisation and functional decline) according to overtreatment

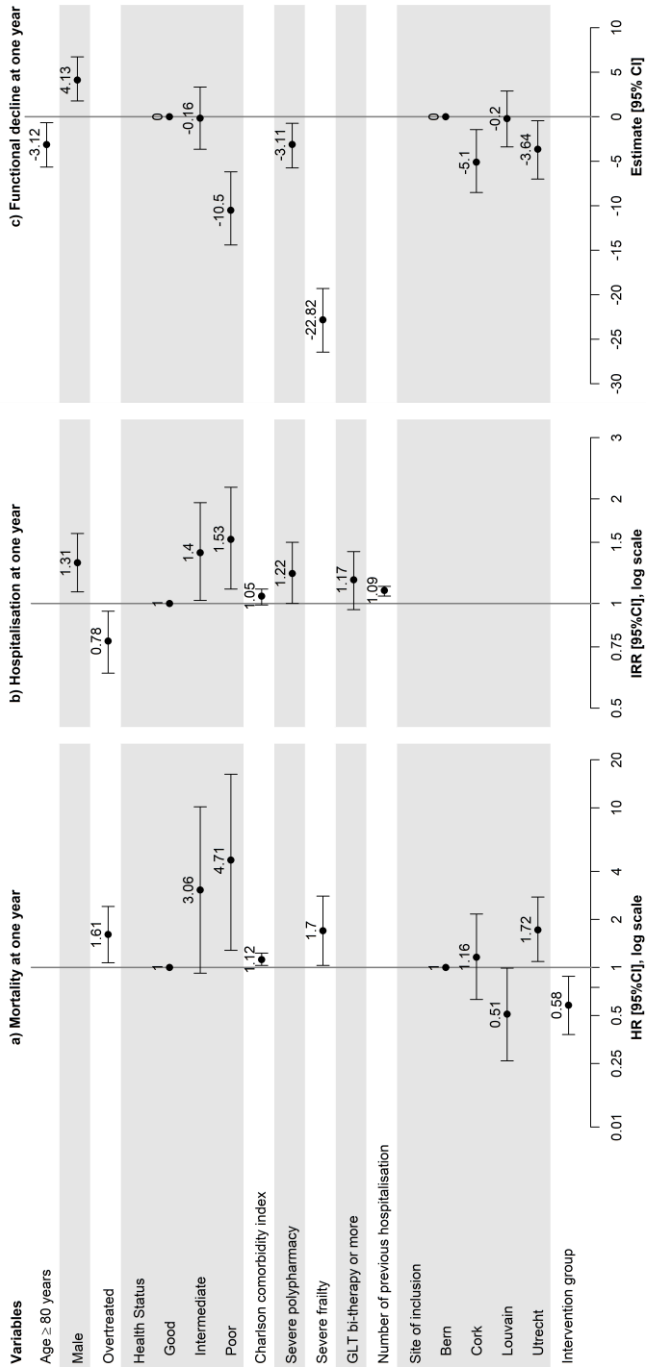
Outcomes at one year	All patients (n = 490) IR and 95% CI (cases per 100 patients-year) or % and 95%CI	Overtreated (n = 168; 34.3%) IR and 95% CI (cases per 100 patients-year) or % and 95%CI	Not overtreated (n = 322; 65.7%) IR and 95% CI (cases per 100 patients-year) or % and 95%CI	p-value
Mortality, *IR*	23.9 (19.4; 29.0)	31.8 (23.0; 42.8)	20.1 (15.3; 26.0)	0.023
Hospitalisation, *IR*	117.0 (106.9; 127.7)	104.3 (87.8; 123.0)	122.9 (110.4; 136.4)	0.099
Functional decline, *%* [a]	35.1 (30.5; 40.0)	29.3 (21.9; 37.9)	38.0 (32.2; 44.0)	0.087

[a] Defined as a loss of ≥ 10% of Barthel index occurring during the follow up among patients with at least 2 measurements of Barthel index (n = 407); IR: Incidence rate (cases per 100 patients-year); CI: confidence interval.

The hospitalisation incidence (117 hospitalisations per 100 patients-year during the year after inclusion) was not different between patients with and those without overtreatment (Table 2). As compared to patients in good health, the patients in intermediate health and those in poor health had a significant higher rate of hospitalisation, which was respectively 1.40 and 1.53 higher. In the same way, males (as compared to females) and patients with higher number of hospitalisation in the last year had a higher mean number of hospitalisation during the follow-up. On the contrary, as compared to patients not overtreated, patients with overtreatment had a lower hospitalisation rate (Fig. 2(b); see Table S.2. in Appendices).

Functional decline during the 1-year follow up was associated with severe frailty, poor health status, severe polypharmacy, age ≥80 years, sites of inclusion 2 and 4, and inversely associated with sex male (Fig. 2(c); see Table S.3. in Appendices). There was no effect of time in the model.

Fig. 2. Forest plot of characteristics associated with outcomes at 1 year: (a) All-cause mortality; (b) Hospitalisation; (c) Functional decline.



95%CI: confidence interval at 95%; HR: Hazard ratio; IRR: Incidence rate ratio; Severe frailty: Clinical Frailty Scale ≥ 7; Severe polypharmacy: ≥ 10 drugs/day; Health status was defined according to criteria of the Endocrine Society Guidelines (2019) [15]. Patients were considered as overtreated when GLT with high risk of hypoglycaemia (insulin, sulfonylureas and/or glinides) was taken and HbA1c was < 7.0 % (for patients in good health), <7.5 % (for patients in intermediate health) or < 8.0 % (for patients in poor health).

DISCUSSION

In this study of the older hospitalised multimorbid patients with type 2 diabetes, diabetes overtreatment was detected in a third of the patients. Diabetes overtreatment was associated with a 61% increase mortality risk within one year in multivariate analysis even after adjusting for multiple confounders, e.g. Charlson index, poor health status, severe frailty. Even if almost all confounding factors are available, observational studies not allow to draw conclusions about causal relationships. However, the high one-year mortality rate (32 par 100 person-years) in patients with glycaemic overtreatment is an important argument for GLT de-intensification.

The prevalence of overtreatment in this older multimorbid population was high (34.3 %), which is of concern given the high sensitivity of this population to hypoglycaemic events and their adverse consequences [5, 28, 29]. This finding demonstrates a lack of implementation of the individualisation of diabetes treatment according to the patient's health status as recommended by major clinical practice guidelines [13-16]. Using the same definition of diabetes overtreatment, its prevalence was even higher (57 %) in another cohort study conducted in 318 geriatric inpatients ≥75 years (median age: 84 years) who were all in intermediate or poor health status [30]. Definitions of diabetes overtreatment are widely heterogeneous in scientific literature, hampering further comparisons of the present results with those of other studies [31-33].

This study shows that mortality at one year was independently associated with diabetes overtreatment, after controlling for health status, clinical frailty, Charlson comorbidity index and age. Similar results were found in another cohort study of patients admitted to a geriatric ward [30]. No causal link between diabetes overtreatment and mortality can be established, given the potential of other confounding factors. As highlighted by this study, it is of concern that overtreatment, known to induce hypoglycaemic events, is more frequent in patients with a short life expectancy, i.e. those who have no benefit to expect from an intensive glycaemic treatment aimed at preventing long-term diabetic complications. The present results could however support the hypothesis that overtreatment is directly increasing mortality in multimorbid old diabetic patients. Overtreatment indeed induces hypoglycaemic events that may be fatal [6, 34]. Patients in poorer health or with severe frailty are more sensitive to hypoglycaemic events and their consequences [5]. Thus, in any case, individualisation of the treatment of type 2 diabetes, in particular the glycaemic control, must be implemented.

In this study, diabetes overtreatment was a protective factor for hospitalisation. However, these results should be interpreted with caution. Indeed, despite the fact that the

competitive risk related to one-year mortality was taken into account in the association analyses with hospitalisation (by considering the incidence rate of hospitalisation rather than the raw number of hospitalisations), patients who died early also had more hospitalisations in the year of follow-up (incidence rate (95%CI) of hospitalisations of 284.6 (231.8; 345.8) *vs* 101.6 (91.8; 112.2) per 100 patients-year for those who were still alive at 1 year). The risk of hospitalisation was therefore probably underestimated in patients who died in the year of follow-up, who are also the patients overtreated. Concerning functional decline, the interpretation is probably limited by the important number of missing values in the follow up.

This study was limited by the retrospective use of data collected prospectively, which did not allow us to access key variables on diabetes (diabetes complications, age at diagnosis or presence of hypoglycaemia) or GLT use (e.g. patient's preferences and prescriber's profile), by the single measure of overtreatment over the time, and by the fact that the main study was not designed for these aims. This study has also strengths: the use of data collected among patients usually poorly represented in studies, and the use of a definition of overtreatment based on individualised definition of diabetes overtreatment, based on the 2019 Endocrine Society guideline, both patient-centred (individualisation) and safe (avoidance of hypoglycaemia), in the absence of a standardised definition.

Further studies are needed in order to improve the knowledge in this area. Better knowledge is required for better therapeutic management of older patients with type 2 diabetes. In particular, interventional studies, conducted in representative populations, should be undertaken on selecting the best HbA1c targets, prescribing newer oral glucose-lowering medications (such as SGLT2 inhibitors) or de-intensifying glucose-lowering treatment.

In conclusion, avoiding diabetes overtreatment is a major medical priority in older multimorbid patients, in particular in those in poor health status, as the harms of intensive treatment likely exceeds the benefits. This can be achieved by individualising the management of glucose-lowering treatment according to patient's health status and de-intensifying glucose-lowering treatment in older patients with diabetes overtreatment.

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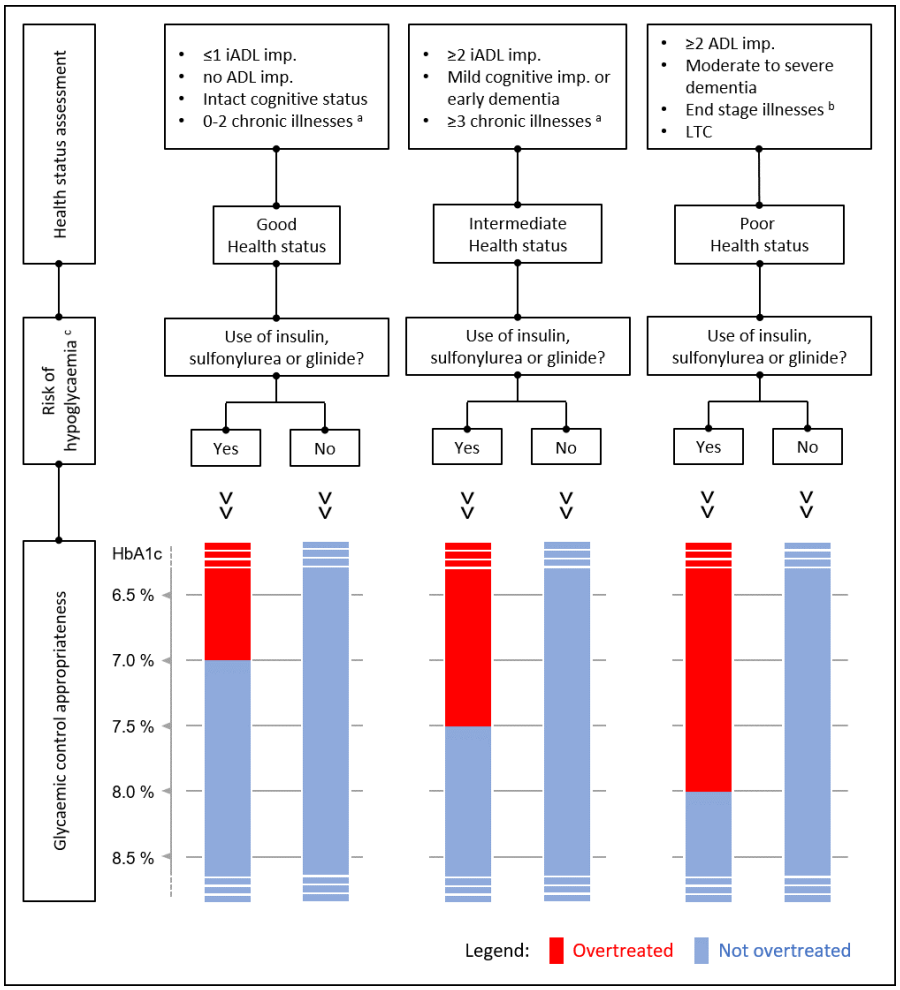
APPENDICES

Fig. S.1. Algorithm for classification of patients as overtreated or not overtreated, according to their health status and the risk of hypoglycaemia induced by glucose-lowering treatment (adapted from [15]).



Legend: [a] Chronic illnesses may include: arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage ≥ 3 chronic kidney disease, myocardial infarction, stroke. [b] End-stage chronic illnesses: stage 3–4 congestive heart failure, oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer. [c] High risk of hypoglycaemia is defined by the presence of insulin, sulfonylureas or glinides. LTC: long-term care; iADL = instrumental activities of daily living; ADL = activities of daily living. Imp. = impairment; Adapted according to [15].

Table S.1. Factors associated with all-cause mortality at 1 year in Proportional Hazards Cox's regression (N = 490)

Variable	Univariable analysis		Multivariable analysis	
	HR [95%CI]	p-value	HR [95%CI]	p-value
Age ≥ 80 years	1.62 [1.10 ; 2.40]	0.015		
Male	0.96 [0.64 ; 1.44]	0.849		
Overtreated	1.55 [1.05 ; 2.30]	0.029	1.61 [1.07 ; 2.41]	0.023
Health status				
Good	1.00		1.00	
Intermediate	4.38 [1.35 ; 14.27]	0.014	3.06 [0.92 ; 10.14]	0.067
Poor	9.63 [3.03 ; 30.65]	<0.001	4.71 [1.28 ; 16.25]	0.014
Charlson comorbidity index	1.23 [1.14 ; 1.33]	<0.001	1.12 [1.03 ; 1.23]	0.011
Severe polypharmacy	1.84 [1.17 ; 2.89]	0.008		
Severe frailty	2.58 [1.72 ; 3.87]	<0.001	1.70 [1.03 ; 2.80]	0.039
GLT bi-therapy or more	0.81 [0.55 ; 1.20]	0.289		
Number of hospitalisation during last year	1.09 [1.01 ; 1.17]	0.028		
Site				
Bern	1.00		1.00	
Cork	0.82 [0.45 ; 1.49]	0.513	1.16 [0.63 ; 2.16]	0.633
Louvain	0.39 [0.21 ; 0.74]	0.004	0.51 [0.26 ; 0.99]	0.045
Utrecht	1.30 [0.82 ; 2.05]	0.267	1.72 [1.09 ; 2.76]	0.025
Group intervention	0.68 [0.45 ; 1.03]	0.069	0.58 [0.38 ; 0.88]	0.011

Severe frailty: Clinical Frailty Scale ≥ 7; Severe polypharmacy: ≥ 10 drugs/day; GLT: Glucose-lowering treatment; HR: Hazard ratio; 95%CI: confidence interval at 95%; Health status was defined according to criteria of the Endocrine Society Guidelines (2019) [15]. Patients were considered as overtreated when glucose-lowering treatment with high risk of hypoglycaemia (i.e. including insulin, sulfonylurea or glinide) was taken and HbA1c was < 7.0 % (for patients in good health), < 7.5 % (for patients in intermediate health) or < 8.0 % (for patients in poor health).

Table S.2. Factors associated with hospitalisation at 1 year in Poisson regression (N = 490)

Variable	Univariable analysis		Multivariable analysis	
	IRR (95%CI)	p-value	IRR (95%CI)	p-value
Age ≥ 80 years	1.11 (0.92 ; 1.32)	0.268		
Male	1.38 (1.14 ; 1.68)	<0.001	1.31 (1.08 ; 1.59)	0.006
Overtreated	0.85 (0.70 ; 1.03)	0.099	0.78 (0.63 ; 0.95)	0.016
Health status				
Good	1.00		1.00	
Intermediate	1.70 (1.27 ; 2.33)	<0.001	1.40 (1.02 ; 1.95)	0.039
Poor	1.99 (1.49 ; 2.72)	<0.001	1.53 (1.10 ; 2.16)	0.013
Charlson comorbidity index	1.09 (1.05 ; 1.13)	<0.001	1.05 (0.99 ; 1.10)	0.057
Severe polypharmacy	1.44 (1.19 ; 1.75)	<0.001	1.22 (1.00 ; 1.50)	0.052
Severe frailty	1.24 (0.99 ; 1.53)	0.056		
GLT bi-therapy or more	1.10 (0.92 ; 1.31)	0.304	1.17 (0.96 ; 1.41)	0.114
Number of hospitalisation during last year	1.11 (1.08 ; 1.14)	<0.001	1.09 (1.05 ; 1.12)	<0.001
Site				
Bern	1.00			
Cork	0.90 (0.69 ; 1.17)	0.453		
Louvain	0.65 (0.51 ; 0.83)	<0.001		
Utrecht	0.97 (0.77 ; 1.22)	0.796		
Group intervention	0.98 (0.82 – 1.17)	0.797		

Severe frailty: Clinical Frailty Scale ≥ 7; Severe polypharmacy: ≥ 10 drugs/day; GLT: Glucose-lowering treatment; Health status was defined according to criteria of the Endocrine Society Guidelines (2019) [15]. Patients were considered as overtreated when glucose-lowering treatment with high risk of hypoglycaemia (i.e. including insulin, sulfonylurea or glinide) was taken and HbA1c was < 7.0 % (for patients in good health), < 7.5 % (for patients in intermediate health) or < 8.0 % (for patients in poor health). IRR: Incidence rate ratio. CI: confidence interval.

Table S.3. Factors associated with functional decline at 1 year in linear mixed-effects models (N = 488)

Variable	Univariable analysis		Multivariable analysis	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age ≥ 80 years	-5.69 (-9.26 ; -2.37)	0.001	-3.12 (-5.66; -0.67)	0.013
Male	4.32 (1.06 ; 8.06)	0.015	4.13 (1.77; 6.72)	0.001
Overtreated	-0.22 (-3.88 ; 3.27)	0.902		
Health status				
Good	0.00		0.00	
Intermediate	-0.27 (-3.83 ; 3.59)	0.894	-0.16 (-3.66; 3.33)	0.928
Poor	-22.25 (-26.29 ; -17.76)	<0.001	-10.50 (-14.41; -6.19)	<0.001
Charlson comorbidity index	-1.42 (-2.29 ; -0.55)	<0.001		
Severe polypharmacy	-6.73 (-10.24 ; -3.00)	<0.001	-3.11 (-5.75; -0.74)	0.015
Severe frailty	-30.97 (-34.26 ; -27.78)	<0.001	-22.82 (-26.45; -19.31)	<0.001
GLT bi-therapy or more	-1.39 (-5.03 ; 2.16)	0.419		
Number of hospitalisation during last year	0.66 (-0.26 ; 1.61)	0.188		
Site				
Bern	0.00		0.00	
Cork	-0.64 (-5.48 ; 4.41)	0.806	-5.10 (-8.52; -1.45)	0.006
Louvain	6.86 (2.40 ; 11.32)	0.002	-0.20 (-3.39; 2.89)	0.910
Utrecht	2.06 (-3.21 ; 6.65)	0.368	-3.64 (-7.01; -0.45)	0.026
Group intervention	0.42 (-3.02 ; 3.82)	0.810		
Time	0.05 (-0.14 ; 0.23)	0.610		

Functional decline = decline in Barthel index between two consecutive measures during the one-year follow-up. Severe frailty: Clinical Frailty Scale ≥ 7; Severe polypharmacy: ≥ 10 drugs/day; GLT: Glucose-lowering treatment; Health status was defined according to criteria of the Endocrine Society Guidelines (2019) [15]. Patients were considered as overtreated when glucose-lowering treatment with high risk of hypoglycaemia (i.e. including insulin, sulfonylurea or glinide) was taken and HbA1c was < 7.0 % (for patients in good health), < 7.5 % (for patients in intermediate health) or < 8.0 % (for patients in poor health).

Chapter 5. Overtreatment of older people with type 2 diabetes – a high impact frequent occurrence in need of a new definition

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Manuscript in preparation [*Internal review*].

ABSTRACT

Diabetes overtreatment is a frequent and major issue in older people with type 2 diabetes. This critical review aimed at reporting the definitions of diabetes overtreatment in older people used in research studies. Searching in PubMed database and screening records, we found twenty-two research studies providing a definition of diabetes overtreatment in people aged ≥65 years. Overall, 12 different definitions of diabetes overtreatment were used. All studies defined overtreatment according to a HbA1c threshold (varying from <6.0% (<42mmol/mol) to <8% (<64mmol/mol)). Among them, 2 definitions had no consideration about glucose-lowering (GL) treatment, 6 required the prescribing of ≥1 GL agent(s), and 4 the prescribing of ≥1 GL agent(s) inducing high risk of hypoglycaemia (i.e. sulfonylurea(s) or insulin(s)). Only 4 of the 12 definitions (four studies) were individualised, using varying HbA1c thresholds according to patients' age or health status. Definitions of diabetes overtreatment are heterogeneous across research studies, which is confusing. A standardised definition, based on the individual risk of hypoglycaemia and/or its complications must be promoted in order to add evidence in this field, as well as to improve the quality of the management of diabetes in older patients.

INTRODUCTION

Type 2 diabetes (T2D) is one of the most prevalent chronic condition in older people. In European countries, the prevalence of T2D in older people (age ≥ 65 years) is estimated at 20.1% and expected to rise in the next 25 years [1, 2]. In older patients, T2D is often associated with multiple comorbidities, disability or functional impairment, promoting frailty and being complicated by more frequent hospitalisation, decreased quality of life and increased mortality [3, 4]. T2D is therefore a real burden for patients, as well as for public health due to the high health-costs associated with T2D in older patients [5]. Appropriate therapeutical management of T2D is crucial in older people. Overtreatment should be avoided particularly when managing glycaemic control through glucose-lowering treatment (GLT) [6, 7].

Given the wide heterogeneity of this population in terms of overall health status and life expectancy, the potential long-term benefits of an intensive GLT largely considerably differ between patients. Furthermore, older patients are more sensitive and vulnerable to GLT adverse events (such as hypoglycaemic events), which are particularly harmful to older patients and costly to the health care system [8-11]. Hypoglycaemic events have serious consequences for older patients, especially for those being more vulnerable (patients with frailty or impaired awareness), namely increases in cardiovascular events, cognitive impairment, frailty, falls with fracture, disability and mortality [12-15]. Hypoglycaemia occurs especially in the context of (too) intense treatment, which is referred as “diabetes overtreatment”.

Few clinical practice guidelines (CPGs) on the management of T2D in older people have been released by Scientific Societies. They all recommend to avoid hypoglycaemia [16-19]. However, none of these recent guidelines provides any definition of glycaemic overtreatment. Such a definition seems crucial for delivering quality research and appropriate management of older patients. This review aimed at reporting and critically discussing the definitions of diabetes overtreatment used in clinical research studies.

METHODS

This review was conducted through a comprehensive search of the literature.

SEARCH STRATEGY AND INCLUSION CRITERIA

The literature search was carried out on the 31/03/2021 using a search equation designed to identify the studies of interest [Appendix 1], in all scientific journals indexed in MEDLINE®.

This search equation used keywords belonging to the field of "older patient", "diabetes" and "overtreatment". The search was not limited to some designs of studies, publication date or language. Duplicates were removed.

Inclusion criteria were original research studies addressing diabetes overtreatment in older people (≥ 65 years) with type 2 diabetes and providing a clear definition of "overtreatment". "Diabetes overtreatment" was understood as "overtreatment by glucose-lowering drugs".

The selection of the studies followed a 2-step process, and was carried out by one author (AC). Firstly, the titles and abstracts were screened and all records not meeting the inclusion criteria were excluded. Secondly, the full-papers of the remaining studies were examined. Studies were included if they were confirmed to be eligible on the basis of the inclusion criteria.

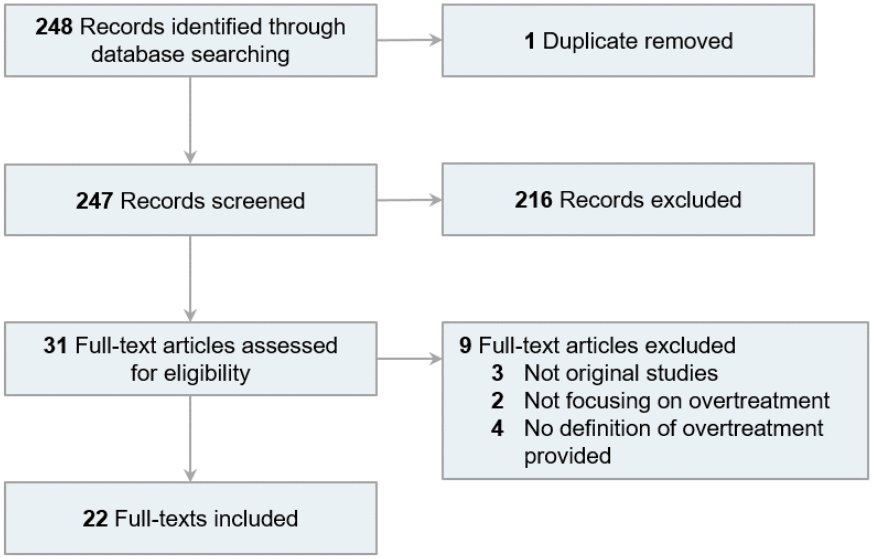
DATA EXTRACTION

General information was extracted from the included studies (year of publication, country, study design, setting, patients' inclusion criteria, number of patients). Definitions of diabetes overtreatment were extracted and summarised. Among existing glucose-lowering agents, those inducing a high risk of hypoglycaemia were insulins, sulfonylureas and glinides.

RESULTS

A total of 248 records were identified. After removal of 1 duplicate, titles and abstracts of 247 records were screened, of which 216 were excluded (Fig. 1). Of the 31 full-texts further assessed for eligibility, 22 fitted with the inclusion criteria.

Figure 1. PRISMA flow diagram



CHARACTERISTICS OF THE STUDIES

The majority of the 22 studies were from Europe (n = 13) and North America (n = 6). None was published before 2010 and three-quarter were from the last five years (Table 1). Thirteen studies (59%) were conducted in the outpatient settings (geriatric medicine unit, diabetes centres or general practice). Sample sizes varied widely across studies, with three of them (registered-based, from North America) including a very large number of patients (42,000 – 108,000). All but two were cross-sectional or retrospective cohort studies. All but one study had a retrospective design (cross-sectional or cohort).

Table 1. Characteristics of the twenty-two clinical research studies addressing diabetes overtreatment

Author, Year	Country	Inclusion criteria	Setting	N	Study type
Lega, 2021 [20]	Canada	≥75 + T2D + GLT	Outpatients (GP)	108,620	RCS
Christiaens, 2020 [21]	Belgium	≥75 + T2D + GLT	Inpatients (Geriatrics)	318	RCS
Gotfredsen, 2020 [22]	Denmark	>80 + T2D	Inpatients	5,172	RCS
Niznik, 2020 [23]	USA	Veteran + T2D + limited LE and/or advanced dementia	LTC	6,960	RCS
Quilot, 2020 [24]	France	≥65 + T2D	LTC	148	RCS
Sonmez, 2020 [25]	Turkey	≥65 + T2D	Inpatients (DbC)	1,264	CSS
Tran, 2020 [26]	Norway	≥65 + T2D	Outpatients (GP)	10,233	CSS
Akin, 2019 [27]	Turkey	≥65; T2D ≥5 years; perfect attendance in ctl (<2 years)	Outpatients (DbC)	755	CSS
Wojszel (1), 2019 [28]	Poland	Older* + T2D	Inpatients (Geriatrics)	213	CSS
Wojszel (2), 2019 [29]	Poland	Older* + T2D	Inpatients (Geriatrics)	213	CSS
Arnold, 2018 [30]	USA	≥75 + T2D	Outpatients (DbC)	42,669	CSS
Bruce, 2018 [15]	Australia	≥75 + T2D	Outpatients (GP and DbC)	367	PCS
Formiga, 2017 [31]	Spain	≥65 + T2D	In and outpatients (GP)	7,269	CSS
Hambling, 2017 [32]	UK	≥70 + T2D + SUH/insulin	Outpatients (GP)	1,379	RCS
Hart, 2017 [33]	The Netherlands	≥70 + T2D	Outpatients (GP)	1,002	RCS
Maciejewski, 2017 [34]	USA	≥65 + T2D	Outpatients	78,792	RCS
Vimalananda, 2017 [35]	USA	[>74 OR dementia] + SUH/insulin + HbA1c <7%	Outpatients	2,830	Uncontrolled interventional study
Deletre, 2016 [36]	Switzerland	≥75 + T2D + GLT	Inpatients (Geriatrics)	257	RCS
Müller, 2016 [37]	Germany	≥65 + T2D	Outpatients	4,459	CSS
Lipska, 2015 [38]	USA	≥65 + T2D	Outpatients (GP)	1,288	CSS
Penfornis, 2015 [39]	France	≥75 + T2D + CKD	Outpatients (GP + DbC)	980	CSS
Bouillet, 2010 [40]	France	≥65 + T2D	LTC	100	CSS

DbC: Diabetes Centre; GP: General practice; T2D: Type 2 diabetes ; GLT : Glucose-lowering treatment ; SUH: Sulfonylureas ; LE: Life expectancy ; LTC: Long term care; RCS: Retrospective cohort study; PCS: Prospective cohort study; CCS: Cross-sectional study; * Age not provide

DEFINITIONS OF OVERTREATMENT

Overall, the twenty-two studies used 12 different definitions of diabetes overtreatment. The definitions were classified into non-individualised definitions ("the same for all patients": 8 definitions shared by eighteen studies) and individualised definitions ("the definition varies according to patient's characteristics": 4 definitions used in four studies)

Non-individualised definitions (n=8)

The 8 non-individualised definitions of diabetes overtreatment were all based on a HbA1c threshold and for the 6 of them, additionally on the presence of a GLT (Table 2). Indeed, 2 definitions took only HbA1c values into account [28, 29, 31, 40], 4 definitions required the use of any GL agent(s) [22, 23, 25, 27, 34] and 2 definitions required the use of a GLT inducing a high risk of hypoglycaemia, i.e. a GLT including insulin, sulfonylurea or glinide [15, 20, 24, 30, 32, 35, 37-39]. The HbA1c threshold considered by the different definitions varied from < 6% (42 mmol/mol) to < 7.5% (58 mmol/mol). The most frequent definition of diabetes overtreatment, shared by eight different studies, was HbA1c < 7% (53 mmol/mol) in patients prescribed a GLT inducing higher risk of hypoglycaemia.

Table 2. Summary of the 12 definitions of diabetes overtreatment (twenty-two studies)

		Criterion = Glucose-lowering treatment		
		No consideration about GLT	GLT use, any	GLT inducing high risk of hypoglycaemia
Criterion = HbA1c values	HbA1c < 6.0 % (42 mmol/mol) for all patients		[22]	
	HbA1c < 6.5 % (48 mmol/mol) for all patients	[40]	[25, 34][a]	
	HbA1c < 7.0 % (53 mmol/mol) for all patients	[28, 29, 31]	[27]	[15, 20, 24, 30, 32, 35, 37, 38]
	HbA1c < 7.5 % (58 mmol/mol) for all patients		[23]	[39][b]
	Individualised thresholds of HbA1c		[33]	[21]
			[36]	[26]

Numbers in brackets indicate the study reference (see table 1). GLT = Glucose-lowering treatment. [a] in Sonmez et al. [25]: GLT including ≥ 2 glucose-lowering agents ; [b] in Perfornis et al [39]: GLT including ≥ 2 glucose-lowering agents, including at least 1 agent inducing high risk of hypoglycaemia (Sulfonylurea and/or insulin).

Individualised definitions (n=4)

Four studies provided individualised definitions of diabetes overtreatment [21, 26, 33, 36], i.e. definitions with different criteria according to patients' characteristics (Table 3). These studies defined diabetes overtreatment as a HbA1c value lower than a given threshold in the presence of a GLT (with high hypoglycaemic risk for 2 studies) [21, 26]. In the individualised definitions, this HbA1c threshold varied according to specific patients characteristics: patients' age [26] or patients' health status [21, 33, 36]. Each of the three latter definitions was based on the recommendations of clinical practice guidelines for the treatment of type 2 diabetes in older patients (American Diabetes Association 2020 [41], Nederlands Huisartsen Genootschap – Standaard 2013 [42] and Endocrine Society 2019 [17]).

Table 3. Summary of the 4 individualised definitions of diabetes overtreatment (four studies)

Studies	Individualised definitions of diabetes overtreatment
Christiaens et al. (2020) [21]	Use of sulfonylurea or/and insulin + HbA1c cut-off individualised according to patient's health status tier: - Poor health: < 8 % (64 mmol/mol) - Intermediate health: < 7.5 % (58 mmol/mol) - Good health: < 7 % (53 mmol/mol) [Based on Endocrine Society 2019 targets and health status classification] [17]
Deletre et al. (2016) [36]	Use of any GLT + HbA1c cut-offs individualised according to patient's health status tier: - Poor health: < 8 % (64 mmol/mol) - Intermediate health: < 7.5% (58 mmol/mol) - Good health: < 7 % (53 mmol/mol) [Based on American Diabetes Association 2020 guidelines: (targets – 0.5%) and health status] [41]
Hart et al. (2017) [33]	Use of any GLT + HbA1c cut-offs individualised according to patient's health status tier: - ≥ 70 years + GLT other than metformin monotherapy + Db duration ≥10 years: < 7 % (53 mmol/mol) - ≥ 70 years + GLT other than metformin monotherapy + Db duration <10 years: < 7 % (53 mmol/mol) - < 70 years or Metformin monotherapy or no GLT: No overtreatment [Based on Nederlands Huisartsen Genootschap 2013 guidelines] [42]
Tran et al. (2020) [26]	Use sulfonylurea or/and insulin + HbA1c cut-offs individualised according to patient's age only: - > 75 years: < 7 % (53 mmol/mol) - 64-75 years: < 6.5 % (48 mmol/mol)

SUH: Sulfonylureas; GLT: Glucose-lowering therapy; ADA20: American Diabetes Association 2020; ES19: Endocrine Society 2019

DISCUSSION

This study found that twelve different definitions of diabetes overtreatment were used in the twenty-two original research articles addressing diabetes overtreatment. These definitions were all based on HbA1c threshold and, for the most of them, on glucose-lowering drug regimen. Among these 12 definitions, 8 were non-individualised definitions (the same definition for all patients), whereas 4 definitions were individualised according to patients' characteristics (age or health status).

The studies were all published after 2010. This observation probably results from the beginning of the medical consideration of a potential risk of too strict glycaemic control in older patients with T2D [8, 43]. The concept of diabetes overtreatment in older patients is therefore relatively recent. Nevertheless, in the past 10 years of clinical research, only 22 publications addressed diabetes overtreatment in older people, despite the high relevance of this issue for patients and public health. The lack of research on this issue is correlated with the overall paucity of research on diabetes in older patients [44, 45].

The definitions of overtreatment used by the 22 studies are very heterogeneous, being based on different combinations of various criteria. Among those, a HbA1c value below a defined threshold (i.e. a "too tight glycaemic control") is shared by all definitions, but threshold values ranges from 6% (42 mmol/mol) to 7.5% (58 mmol/mol). However, the recent major clinical practice guidelines on T2D management in older patients, because of the large clinical heterogeneity of this population, recommend to individualise the treatment goal for each patient by setting an individualised HbA1c target according to her/his health status [16]. It would therefore be logical to consider an individualised definition of a "too tight glycaemic control" according to the patient's health status, as proposed in only 3 of the 12 definitions [21, 33, 36]. However, the values of these thresholds are not based on high-level evidence but mostly on expert opinion [44, 45].

The majority of the 22 studies also included the presence of a glucose-lowering treatment as a required condition to define diabetes overtreatment. It seems indeed expected that being overtreated first requires being pharmacologically treated. Some glucose-lowering agents induce a higher risk of hypoglycaemia (insulin, sulfonylureas or glinides), while others (e.g. biguanides, DPP4-inhibitors, etc.) have a negligible risk of hypoglycaemia [17]. Four definitions (shared by half of the studies included) considered overtreatment only when a glucose-lowering agent with a high-risk of hypoglycaemia (insulin, sulfonylureas or glinides) was prescribed.

This wide variety of definitions can be confusing for clinicians and researchers working on diabetes overtreatment. At the very least, this makes hardly comparable the results of studies that do not share a same definition of this concept, thereby diluting the little existing evidence for addressing a problem of great importance to older patients with diabetes. The prospect of a consensual definition of overtreatment therefore seems attractive. In our view, the new definition of diabetes overtreatment should correspond to a level of glycaemia that is inappropriate to a patient's health status that places a high risk of unwanted side effects of GLT, such as hypoglycaemia and/or its harmful consequences.

At this stage, we can only speculate on what might be the ideal criteria for defining overtreatment. Among these, it seems important to consider individualised HbA1c thresholds according to the patient's health status (functional status and main diseases), and the use of anti-hyperglycaemic treatment as necessary. While the definitions provided by the 22 studies do not propose any other criteria to define diabetes overtreatment, we believe that additional criteria should be considered in a future and more effective definition. As already stated, such definition should follow the purpose of reflecting the risk of hypoglycaemia induced by GLT. Therefore, known risk factors for hypoglycaemia in older patients could be indeed used as criteria to modulate the definition of diabetes overtreatment, such frailty, care home residency, polypharmacy (≥10 drugs/day) or undernutrition [9, 13]. This would enable the overtreatment of some patients to be considered more severe than that of others, alerting to the greater risk of hypoglycaemia to which this overtreatment exposes.

This new definition should be developed carefully, based on the strongest available evidence. Research in this field needs to progress to provide new evidence [45, 46]. Furthermore, while the detection of overtreatment is a key issue in the management of diabetes in older patients, there is also a need to consider its treatment,, i.e. the management of GLT deprescribing/de-intensification. The available evidence in this area is currently too poor and recommendations provided by CPGs, if any, are mainly based on expert opinions [47, 48]. Finally, this new definition should be validated by trials, so that it is not an empirical definition, as is the case for all the studies included in this review.

Finally, it should be remembered that the concept of "overtreatment of diabetes" as discussed here relates only to the overtreatment of glycaemic control. Overtreatment with anti-hypertensive or lipid-lowering therapy is also possible and may also have adverse consequences for older patients, but is not the subject of this review.

In conclusion, the prospect of a new consensual definition of overtreatment is attractive, especially given the heterogeneity of definitions in the current scientific literature. We

believe that this advance would contribute to better evidence in the field of diabetes in older people, while directly improving the quality of therapeutic management for those patients.

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APPENDICES

Appendix 1. Search equation and results

("older"[Title/Abstract] OR "oldest"[Title/Abstract] OR "old"[Title/Abstract] OR "elder*"[Title/Abstract] OR "geriatr*"[Title/Abstract]) AND ("diabetes"[Title/Abstract] AND "diabetes"[Title/Abstract]) AND ("over treat*"[Title/Abstract] OR "overtreat*"[Title/Abstract] OR "inappropriat*"[Title/Abstract] OR "PIM"[Title/Abstract] OR "overuse*"[Title/Abstract]) AND ("glucose-lowering"[Title/Abstract] OR "anti-

diabetic"[Title/Abstract] OR "antihyperglyc*"[Title/Abstract] OR "glucose-lowering"[Title/Abstract] OR "GLT"[Title/Abstract] OR "treatment"[Title/Abstract])

N	Search equation	Records found
#1	("older"[Title/Abstract] OR "oldest"[Title/Abstract] OR "old"[Title/Abstract] OR "elder*"[Title/Abstract] OR "geriatr*"[Title/Abstract])	1,738,935
#2	(diabetes[Title/Abstract])	561,217
#3	#1 AND #2	64,070
#4	((over-treat*[Title/Abstract]) OR (overtreat*[Title/Abstract]) OR (inappropriat*[Title/Abstract]) OR (PIM[Title/Abstract]) OR (overuse*[Title/Abstract]))	93,039
#5	#3 AND #4	546
#6	((glucose-lowering[Title/Abstract]) OR (anti-diabetic[Title/Abstract]) OR (antihyperglyc*[Title/Abstract]) OR (glucose lowering[Title/Abstract]) OR (GLT[Title/Abstract]) OR (treatment[Title/Abstract]))	4,533,720
#7	#5 AND #6	248

SECTION III - Metabolic heterogeneity among older patients with type 2 diabetes

Chapter 6. Distinction of cardiometabolic profiles among people ≥ 75 years with type 2 diabetes: A latent profile analysis

Chapter 6. Distinction of cardiometabolic profiles among people ≥ 75 years with type 2 diabetes: A latent profile analysis

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ABSTRACT

BACKGROUND. Older patients with type 2 diabetes mellitus represent a heterogeneous group in terms of metabolic profile. It makes glucose-lowering-therapy (GLT) complex to manage, as it needs to be individualised according to the patient profile. This study aimed to identify and characterize subgroups existing among older patients with diabetes.

METHODS. Retrospective observational cohort study of outpatients followed in a Belgian diabetes clinic. Included participants were all aged ≥75 years, diagnosed with type 2 diabetes, Caucasian, and had a Homeostasis Model Assessment (HOMA2). A latent profile analysis was conducted to classify patients using the age at diabetes diagnosis and HOMA2 variables, i.e. insulin sensitivity (*HOMA2%-S*), beta-cell-function (*HOMA2%-β*), and the product between both (*HOMA2%-βxS*; as a measure of residual beta-cell function). GLT was expressed in defined daily dose (DDD).

RESULTS. In total, 147 patients were included (median age: 80 years; 37.4% women; median age at diabetes diagnostic: 62 years). The resulting model classified patients into 6 distinct cardiometabolic profiles. Patients in profiles 1 and 2 had an older age at diabetes diagnosis (median: 68 years) and a lesser decrease in *HOMA2%-S,* as compared to other profiles. They also presented with the highest *HOMA2%-βxS* values. Patients in profiles 3, 4 and 5 had a moderate decrease in *HOMA2%-βxS*. Patients in profile 6 had the largest decrease in *HOMA2%-β* and *HOMA2%-βxS*. This classification was associated with significant differences in terms of HbA1c values and GLT total DDD between profiles. Thus, patients in profiles 1 and 2 presented with the lowest HbA1c values (median: 6.5%) though they received the lightest GLT (median GLT DDD: 0.75). Patients in profiles 3 to 5 presented with intermediate values of HbA1c (median: 7.3% and GLT DDD (median: 1.31). Finally, patients in profile 6 had the highest HbA1c values (median: 8.4%) despite receiving the highest GLT DDD (median: 2.28). Other metabolic differences were found between profiles.

CONCLUSIONS. This study identified 6 groups among patients ≥75 years with type 2 diabetes by latent profile analysis, based on age at diabetes diagnosis, insulin sensitivity, absolute and residual β-cell function. Intensity and choice of GLT should be adapted on this basis in addition to other existing recommendations for treatment individualisation.

BACKGROUND

Type 2 diabetes is one of the most prevalent chronic diseases worldwide, especially among older people aged ≥ 75 years, in whom prevalence reached 20% in 2017, and is poised to increase over the coming decades [1]. In Europe, the cost per patient per year with diabetes mellitus was estimated at US Dollar 3,100 in 2017. Moreover, diabetes was responsible for 10% of total health care expenditure in 2010 [2]. Diabetes in older patients has therefore a major impact on healthcare systems.

Current classification of diabetes mellitus considers 4 different categories: type 1 diabetes, type 2 diabetes, gestational diabetes and specific rare types of diabetes [3]. In older age, type 2 diabetes is reported to represent 85-90% of all-cause diabetes, ahead of type 1 diabetes, which includes latent autoimmune diabetes in adults [4, 5].

Type 2 diabetes induces specific acute or chronic complications (e.g. microvascular complications from chronic hyperglycaemia) and increases the incident risk of macrovascular complications from various cardiometabolic abnormalities promoting the occurrence of atherosclerosis [6]. These vascular complications promote and intensify the development of several geriatric syndromes in older patients, such as falls, polymedication, cognitive disorders or sensorial disorders [6, 7]. The aim of glucose lowering therapy (GLT) in these patients is to control hyperglycaemia and its associated morbidity and mortality. Nevertheless, in older patients with type 2 diabetes, GLT should be adapted according to patient's characteristics in order to be intense enough to avoid microvascular complications but light enough to prevent potential side-effects of GLT, mainly hypoglycaemia, as it also increases morbidity and mortality [7]. These considerations offer only a narrow frame to perform a safe and effective GLT management in patients aged 75 years or more with type 2 diabetes. Several recent guidelines provide recommendations about GLT management in older patients with diabetes, in terms of hyperglycaemia, risk factors and complications [8, 9]. These guidelines and other reports all insist on treatments' individualisation in order to give tailored medication for each patient [8, 10-15]. At present, factors currently considered in this treatment individualisation are related to the type of diabetes [3], but also to prevalent comorbidities, geriatric syndromes, nutrition issues, physical activity, age-specific aspects of pharmacotherapy, ethnic disparities and estimated life expectancy [8, 11].

Indeed, type 2 diabetes is a complex condition with marked heterogeneity in pathophysiological mechanisms leading to hyperglycaemia and cardiometabolic comorbidities between patients. Ageing process enhances this heterogeneity, adding other

conditions, such as nutritional deficits, sarcopenia, additional stresses on pancreatic beta-cells and micro-inflammation [16-18].

Yet, current guidelines for older patients do not suggest taking into account characteristics related to the pathophysiology of diabetes or severity of residual beta-cell function (BCF) loss. Therefore, it is of interest to consider these factors in GLT individualisation in order to improve the quality, efficacy and safety of GLT management in older patients.

Therefore, the aim of the present study was to assess the heterogeneity of cardiometabolic features in patients aged 75 years or more with type 2 diabetes and to classify them into relevant cardiometabolic profiles using mixture models as Latent Profile Analysis (LPA).

METHODS

STUDY DESIGN AND PATIENT SELECTION

A retrospective cohort study of outpatients followed by the same investigator (MPH) between 2000 and 2017 and attending a Belgian university diabetes clinic was conducted. Among the 266 Caucasian patients followed in the diabetes clinic and aged ≥75 years at the last two visits to the endocrinologist, 147 participants had a Homeostasis Model Assessment (HOMA2) after the diagnosis of their type 2 diabetes. All 147 participants were GAD-antibodies-negative. Type 2 diabetes was defined according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [3].

This study was approved by the local Ethics Committee (Commission d'Ethique Hospitalo-Facultaire, Cliniques universitaires Saint-Luc, Brussels, Belgium; ref. B403/2017/16NOV/521).

DATA COLLECTION

A first part of the data was collected at the time of the HOMA2 assessment. Data included anthropometric (weight, body mass index and fat mass proportion), biochemical (HbA1c) and ongoing GLT (drug molecules and doses).

Body mass index (BMI; kg/m^2) was calculated as [Weight(kg)×Height(m)$^{-2}$]. Body fat mass (%) was measured using a BodyFat Analyser (Omron BF 500; Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). HbA1c was expressed in NGSP nomenclature (%) and was converted to IFCC nomenclature (mmol/mol) using the NGSP convertor (*www.ngsp.org/convert1.asp*).

Insulin sensitivity and beta-cell function were assessed using the computer-based homeostasis model assessment (HOMA2, *http://www.dtu.ox.ac.uk*) [19]. HOMA2 parameters were calculated from triplicates of fasting glucose and insulin level, sampled after a sufficient period of GLT washout (i.e. between 1 to 5 days, according to the molecules involved). Values of insulin secretion (*HOMA2%-β (%)*; normal 100%) were plotted as a function of insulin sensitivity (*HOMA2%-S (%)*; normal 100%), defining a *hyperbolic product area* (*HOMA2%-βxS (%²)*; normal 100%). This product described the interaction between insulin sensitivity and insulin secretion, or more precisely, the true latent beta-cell function (BCF) indexed by insulin sensitivity. It approximates the magnitude of glucose homeostasis deficit and the required GLT intensity [20].

GLT data corresponded to the treatment taken one week before the HOMA2 realization. Drugs were transcribed into Anatomical Therapeutic Chemical (ATC) codes and grouped by GLT classes (A10A-Insulin, A10BA-biguanides, A10BB-sulfonylureas, A10BF-alpha-glucosidase-inhibitors, A10BG-thiazolidinediones, A10BH-DPP4-inhibitors, A10BJ-GLP1-receptor agonists, A10BX-other). Sulfonylureas and repaglinide were considered as "*Oral hypoglycaemic agents (OHA)"* and insulin and OHA were considered as "*Hypoglycaemic agents (HA)"*. Patients with no GLT were considered as "*Lifestyle changes only*". Treatment doses were collected and converted into Defined Daily Dose (DDD), according to the ATC/DDD Index 2018 [21]. For each patient, a sum of the GLT drugs doses, expressed in DDD, was computed and described hereafter as "*GLT's total doses"*.

The second part of the data was collected at the time of the last consultation at the diabetes clinic, at which all patients were ≥ 75 years, and included socio-demographic (age, sex) and diabetes-related data (age at diabetes diagnosis, comorbidities, vascular complications). Micro-angiopathic complications were defined as: neuropathy (clinical examination of knee and ankle reflexes; Semmes-Weinstein monofilament test, confirmed by lower-limbs electromyography) and diabetic retinopathy (based on retinal examination by an experienced ophthalmologist and/or fluorescein angiography). Diabetic nephropathy was not taken into account in this study because of its high prevalence in older age and its multiple aetiologies that cannot be attributed *de facto* to chronic hyperglycaemia.

Macro-angiopathic complications included coronary artery disease (CAD: myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography), cerebrovascular disease (CVD) or peripheral artery disease (PAD). CVD was defined according to *UK Prospective Diabetes Study* criteria: any neurological deficit ≥ 1 month, without distinction between ischemic, embolic and haemorrhagic events [22]. PAD was diagnosed from medical history of lower-limb

claudication; clinical or imaging evidence for ischemic diabetic foot; history of angioplasty, stenting, revascularization surgery; and/or lower-limb artery stenosis at Doppler ultrasonography or angiography.

STATISTICAL ANALYSIS

Continuous data were expressed as medians (P25, P75). Categorical data were expressed as number of people and percentages. Continuous variables were compared between 2 groups using Mann Whitney test, and between ≥3 groups using Kruskal-Wallis test. Categorical variables were compared between groups using Pearson's χ^2 test, Pearson's χ^2 test with Yates correction, Fisher's exact test or Fisher Freeman Halton's test, according to the conditions of validity of each test.

In order to identify profiles of patients with type 2 diabetes a latent profile analysis (LPA) was performed using the following continuous discriminant variables (indicators): insulin sensitivity (*HOMA2%-S*), BCF (*HOMA2%-β*), hyperbolic product *βxS* (*HOMA2%-βxS*) and age at diabetes diagnosis. Models with 2 to 7 profiles were ran. Evaluative information was used to select the best model, e.g. the model with the lowest Akaike information criteria, Bayesian Information Criterion (BIC) and Log Likelihood (LL) [23]. In addition, the likelihood ratio test was used to compare a model with k-1 profiles with a model with k profiles. Finally, posterior probabilities, i.e. the probability of each patient of belonging to each profile, were computed for the final selected model. An average posterior probability per group ≥ 0.70 was used to consider whether profiles were sufficiently separated from each other.

Statistical analyses were performed using IBM SPSS Statistics 25® software or R software (R x64 version 3.4.1). A p-value<0.05 was considered statistically significant.

RESULTS

PATIENTS' CHARACTERISTICS

The 147 older patients (≥ 75 years of age; 37% women) had a median age of 62.0 years at diabetes diagnosis and a median duration of diabetes of 19.0 years at the last visit at the diabetes clinic (Table 1, left column). According to HOMA2-modeling, median insulin sensitivity was 47.4% and median BCF was 49.3%. Median hyperbolic product of insulin sensitivity and beta-cell function *βxS*) was 25.0% and median HbA1c was 7.1% (54 mmol/mol) at the time of the HOMA2 testing.

Table 1. Patients' characteristics by cardiometabolic profiles created in latent profile analysis (N=147)

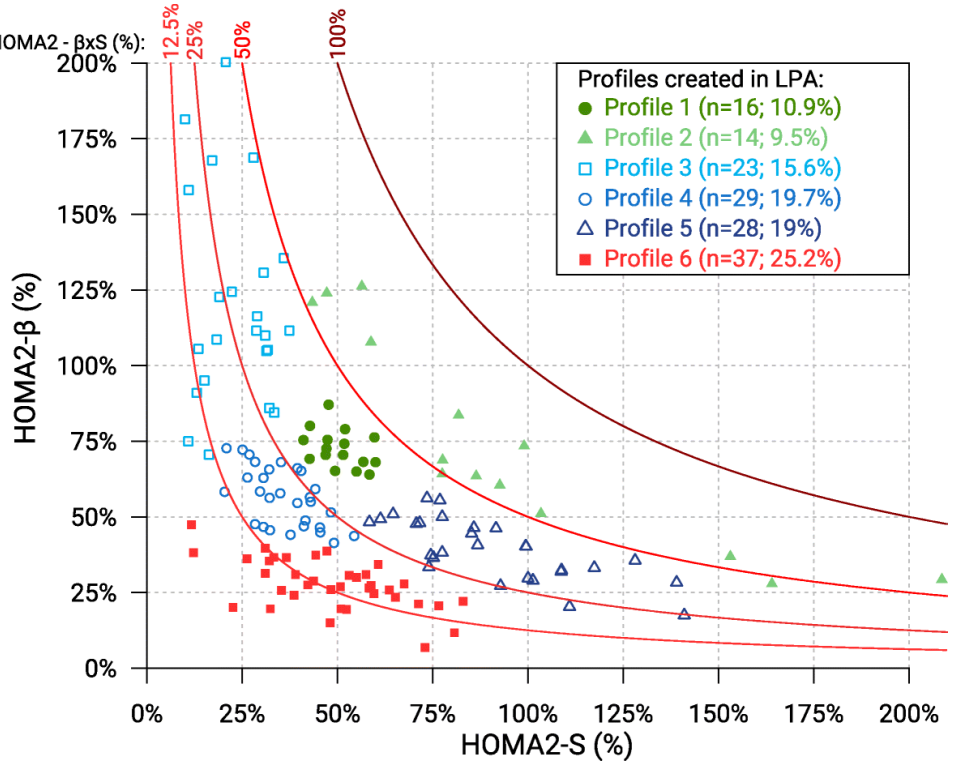
Variables	Total (N=147) Median [P25; P75] *or* n (%)	Profile 1 (n=16) Median [P25; P75] *or* n (%)	Profile 2 (n=14) Median [P25; P75] *or* n (%)	Profile 3 (n=23) Median [P25; P75] *or* n (%)	Profile 4 (n=29) Median [P25; P75] *or* n (%)	Profile 5 (n=28) Median [P25; P75] *or* n (%)	Profile 6 (n=37) Median [P25; P75] *or* n (%)	p-value
Characteristics at the time of the last consultation								
Age, in years	80.0 [77.0; 83.0]	80.5 [76.0; 82.8]	80.0 [78.0; 84.0]	77.0 [76.0; 81.0]	79.0 [76.0; 82.0]	80.0 [77.0; 83.8]	81.0 [77.0; 84.0]	0.545
Women	55 (37.4)	6 (37.5)	4 (28.6)	12 (52.2)	14 (48.3)	7 (25.0)	12 (32.4)	0.278
Family history of diabetes*	52 (35.4)	4 (25.0)	4 (30.8)	5 (21.7)	11 (37.9)	11 (39.3)	17 (49.6)	0.348
Diabetes duration, *in years*	19.0 [12.0; 27.0]	12.0 [3.3; 14.8]	15.0 [9.8; 20.3]	12.0 [5.0; 23.0]	20.0 [15.5; 28.0]	23.5 [17.3; 29.0]	22.0 [14.5; 27.5]	<0.001
Characteristics at the time of HOMA2								
Age at HOMA2, *in years*	72.0 [69.0; 76.0]	73.5 [70.3; 76.5]	72.0 [70.0; 73.3]	71.0 [64.0; 76.0]	71.0 [66.0; 77.0]	71.0 [68.3; 74.8]	73.0 [68.0; 77.0]	0.714
BMI, in kg/m²	28.3 [25.7; 31.2]	26.8 [24.9; 29.6]	26.2 [24.7; 33.1]	28.0 [25.8; 33.3]	29.6 [26.6; 34.6]	27.9 [25.7; 29.6]	28.2 [25.5; 31.7]	0.037
BMI [18-25[kg/m²	33 (22.4)	4 (25.0)	5 (35.7)	3 (13.0)	8 (27.6)	9 (32.1)	4 (10.8)	
BMI [25-30[kg/m²	68 (46.3)	10 (62.5)	6 (42.9)	9 (39.1)	8 (27.6)	14 (50.0)	21 (56.8)	
BMI ≥30 kg/m²	45 (30.6)	2 (12.5)	3 (21.4)	11 (47.8)	13 (44.8)	4 (14.3)	12 (32.4)	
HbA1c†, *in %*	7.1 [6.4; 8.2]	6.6 [6.0; 7.9]	5.4 [5.2; 6.6]	7.0 [6.4; 7.9]	7.4 [7.1; 8.0]	6.8 [5.8; 7.2]	8.4 [7.8; 9.1]	<0.001
Indicators used in latent profile analysis								
Age at diagnosis, *in years*	62.0 [54.0; 70.0]	70.5 [63.3; 74.0]	68.0 [61.0; 70.5]	64.0 [58.0; 74.0]	58.0 [54.5; 62.0]	55.5 [47.8; 67.8]	61.0 [52.0; 65.0]	<0.001‡
HOMA2%-S, *in %*	47.4 [32.1; 73.0]	50.5 [47.0; 56.4]	84.1 [58.2; 115.8]	22.3 [15.1; 31.4]	35.2 [29.1; 42.9]	86.3 [74.1; 106.9]	48.3 [34.3; 40.2]	<0.001‡
HOMA2%-β, in %	49.3 [32.4; 72.6]	71.6 [68.1; 76.1]	66.5 [47.6; 111.1]	111.6 [95.1; 135.5]	56.5 [46.8; 65.5]	39.2 [32.0; 47.9]	27.3 [21.7; 34.9]	<0.001‡
HOMA2%-βxS, *in %*	25.0 [16.0; 37.0]	36.0 [33.3; 40.5]	56.0 [52.8; 64.3]	28.0 [17.0; 34.0]	20.0 [17.0; 24.0]	34.5 [28.3; 39.8]	13.0 [9.0; 16.0]	<0.001‡

HOMA2%-S: insulin sensitivity assessed by Homeostasis Model Assessment 2 (HOMA2); HOMA2%-β: beta-cell function assessed by HOMA2; HOMA2%-βxS: Hyperbolic product between beta-cell function and insulin sensitivity. BMI: body mass index ($kg.m^{-2}$).* 3 missing values (2.0%). †1 missing value (0.7%). ‡: Differences were expected as these indicators were included in the LPA to create the 6 profiles.

PROFILES OF OLDER PATIENTS WITH TYPE 2 DIABETES

Using latent profile analysis, a 6-profile model was the best-fitting model based on evaluative information (see Additional file 1). In addition, in this model, the average probability of each patient to belong to each group ranged from 0.904 in profile 4 to 0.977 in profile 2, showing good separation between profiles (see Additional file 2).

Fig. 1. Distribution of patients on HOMA2 graph according to the profiles created in latent profile analysis



Distribution of older patients with type 2 diabetes on HOMA2 graph, labeled according to the 6 profiles obtained from the Latent Profile Analysis (LPA). This graph represents insulin sensitivity (*HOMA2%-S*) on the x-axis and beta-cell function (*HOMA2%-β*) on the y-axis, both calculated by Homeostasis Model Assessment (HOMA2). The product of *HOMA2%-S* and *HOMA2%-β* is represented on the hyperbolic axis (*HOMA2%-βxS*) at four levels (100%, 50%, 25%, 12.5%).

Table 2. Patients' glucose-lowering therapy at the time of HOMA2 by pathophysiologic profiles (N=147)

Variable	Total (N=147) Median [P25; P75] *or* n (%)	Profile 1 (n=16) Median [P25; P75] *or* n (%)	Profile 2 (n=14) Median [P25; P75] *or* n (%)	Profile 3 (n=23) Median [P25; P75] *or* n (%)	Profile 4 (n=29) Median [P25; P75] *or* n (%)	Profile 5 (n=28) Median [P25; P75] *or* n (%)	Profile 6 (n=37) Median [P25; P75] *or* n (%)
Number of GLT drugs*	2.00 [1.00; 2.00]	1.00 [1.00; 1.75]	1.00 [0.00; 2.00]	1.00 [0.00; 2.00]	2.00 [1.00; 2.00]	1.00 [1.00; 2.00]	2.00 [2.00; 2.00]
Lifestyle changes only	21 (14.3)	3 (18.8)	4 (28.6)	7 (30.4)	1 (3.4)	6 (21.4)	0 (0.0)
Monotherapy	52 (35.4)	9 (56.3)	5 (35.7)	8 (34.8)	12 (41.4)	11 (39.3)	7 (18.9)
Bitherapy	61 (41.5)	3 (18.8)	5 (35.7)	6 (26.1)	13 (44.8)	11 (39.3)	23 (62.2)
Tritherapy	13 (8.8)	1 (6.3)	0 (0.0)	2 (8.7)	3 (10.3)	0 (0.0)	7 (18.9)
GLT's total dose, in DDD	1.50 [0.75; 2.28]	0.75 [0.35; 1.11]	0.71 [0.11; 1.33]	0.85 [0.00; 2.59]	1.50 [1.15; 2.10]	1.14 [0.41; 1.79]	2.28 [1.67; 2.85]
GLT's total dose among users, in DDD	1.67 [0.89; 2.58]	0.85 [0.50; 1.43]	0.79 [0.69; 1.69]	1.81 [0.83; 2.86]	1.53 [1.21; 2.11]	1.52 [0.85; 2.07]	2.28 [1.67; 2.85]
GLT classes							
Biguanides							
Use	79 (53.7)	8 (50.0)	5 (35.7)	9 (39.1)	18 (62.1)	16 (57.1)	23 (62.2)
DDD among users	0.85 [0.57; 1.28]	0.68 [0.48; 0.85]	0.50 [0.43; 0.50]	0.85 [0.85; 1.28]	0.85 [0.50; 1.17]	0.85 [0.85; 1.28]	0.85 [0.80; 1.28]
Insulin							
Use	29 (19.7)	1 (6.3)	4 (28.6)	3 (13.0)	11 (37.9)	0 (0.0)	10 (27.0)
DDD among users	1.00 [0.60; 1.35]	0.75	0.34 [0.31; 0.41]	1.95 [1.40; 2.16]	1.05 [0.73; 1.24]	NA	1.28 [0.93; 1.46]
OHA							
Use	79 (53.7)	8 (50.0)	5 (35.7)	10 (43.5)	15 (51.7)	12 (42.9)	29 (78.4)
DDD among users	1.50 [1.00; 1.89]	1.00 [0.94; 1.00]	1.43 [1.00; 1.50]	1.00 [0.56; 2.04]	1.50 [0.88; 1.50]	1.21 [0.94; 1.57]	1.50 [1.43; 2.00]
Hypoglycaemic agents							
Use	101 (68.7)	9 (56.3)	6 (42.9)	13 (56.5)	24 (82.8)	12 (42.9)	37 (100.0)
DDD among users	1.43 [1.00; 1.79]	1.00 [0.75; 1.00]	1.38 [0.81; 1.77]	1.00 [0.75; 2.14]	1.24 [0.97; 1.50]	1.21 [0.94; 1.57]	1.50 [1.35; 2.00]

GLT: glucose-lowering therapy; DDD: defined daily dose; OHA: Oral hypoglycemic agents (=Sulfonylureas or Glinides); Hypoglycemic agents: Insulin and/or OHA. * Statistically significant difference between groups (p-value < 0.001). NA: not applicable

PROFILES' CHARACTERISTICS COLLECTED AT THE HOMA2 ASSESSMENT

HOMA2 was realized at similar median ages in the 6 profiles, between 71.0 and 73.5 years (p=0.714) (Table 1). All participants' values were plotted on a HOMA2 graph presenting the relationship between *HOMA2%-β* and *HOMA2%-S* (Fig. 1). Each profile of patients was distinctly delimited in terms of *HOMA2%-β*, *HOMA2%-S*. *HOMA2%-βxS* values were different (p<0.001) across the six profiles (Table 1; Fig 2C).

No significant difference was found in the six profiles in terms of sex ratio (p=0.278).

Patients in profiles 1 (n=16; 10.9%) and 2 (n=14; 9.5%) had an older age at diabetes diagnosis (median: 70.5 years and 68.0 years, respectively) and had a slight decrease in *HOMA2%-βxS* (median: 36.0% and 56.0%, respectively) (Table 1; Fig. 2C). Patients in profile 2 had a higher insulin sensitivity than patients in profile 1 (Table 1; Fig. 2A). As profile 2 also had preserved *beta-secretion (66.*5 %), its *HOMA2%-βxS* was the highest (56%). From profiles 3 (n=14) to 5 (n=29), insulin sensitivity increased, and beta-cell function decreased inversely, resulting in a moderate decrease in *HOMA2%-βxS* in all 3 profiles (median: 28.0%, 20.0% and 34.5%, respectively; Table 1; Fig. 2C). Profile 6 (n=37) had the lowest beta-cell function (27.3%) and thereby the lowest *HOMA2%-βxS* (median: 13.0%) (Table 1; Fig. 2C).

The six profiles were also significantly different in terms of BMI (p=0.037). Profiles 1 and 2 had the lowest median BMI, while profile 3 and 6 had the highest median values. Obesity (i.e. BMI ≥ 30.0kg/m^2) was less prevalent in profiles 1 (12.5%), 2 (21.4%) and 5 (14.3%) than in profiles 3 (47.8%), 4 (44.8%) and 6 (32.4%) (p=0.028). There was no significant difference in fat mass proportion between profiles (p=0.137), nor in abdominal circumference (p=0.129) (Table 1; Fig. 2; Fig. 3). Finally, the median HbA1c value was higher in profile 6 than in profiles 1, 2, 3 and 5 (p<0.001) (Table 1).

Regarding the use of GLT in the six profiles, significant difference was observed in terms of number of glucose-lowering agents (p<0.001) (Table 2). Profiles 1, 2, 3 and 5 had lower number of GLTs than profile 6. Moreover, a higher prevalence of GLT-bi- and -tri-therapy was found in profile 6. There were no differences in the proportions of patients receiving biguanides, except in profiles 2 and 3 (those with higher residual beta-secretion) (Fig. 1). Insulin was prescribed more frequently in profiles 2, 4 and 6 than in other profiles, as was prescription of hypoglycaemic agents or oral hypoglycaemic agents (Table 2).

Table 3. Diabetes complications and comorbidities according to subgroups created from the latent profile analysis (N=147)

Variable	Total (N=147) n (%)	Group 1 (n=16) n (%)	Group 2 (n=14) n (%)	Group 3 (n=23) n (%)	Group 4 (n=29) n (%)	Group 5 (n=28) n (%)	Group 6 (n=37) n (%)	p-value
Nephropathy	97 (66.0)	13 (81.3)	7 (50.0)	15 (65.2)	20 (69.0)	17 (60.7)	25 (67.6)	0.584
Microangiopathy	68 (46.3)	5 (31.3)	4 (28.6)	9 (39.1)	13 (44.8)	12 (42.9)	25 (67.6)	0.060
Diabetic retinopathy	43 (29.3)	2 (12.5)	1 (7.1)	4 (17.4)	10 (34.5)	8 (28.6)	18 (68.6)	0.015
Diabetic neuropathy	52 (35.9)	3 (18.8)	4 (28.6)	7 (30.4)	11 (39.3)	9 (32.1)	18 (50.0)	0.297
Macroangiopathy	81 (55.1)	4 (25.0)	6 (42.9)	14 (60.9)	15 (51.7)	14 (50.0)	28 (75.7)	0.017
Coronary artery disease	52 (35.4)	3 (18.8)	6 (42.9)	8 (34.8)	7 (24.1)	9 (32.1)	19 (51.4)	0.149
Cerebro-vascular disease	28 (23.0)	1 (6.7)	1 (7.7)	7 (35.0)	6 (23.1)	4 (19.0)	9 (33.3)	0.208
Peripheral artery disease	25 (17.0)	1 (6.3)	1 (7.1)	3 (13.0)	3 (10.3)	7 (25.0)	10 (27.0)	0.252

Microangiopathy = diabetic retinopathy and/or diabetic neuropathy; Macroangiopathy = coronary artery disease and/or cerebrovascular disease and/or peripheral artery disease.

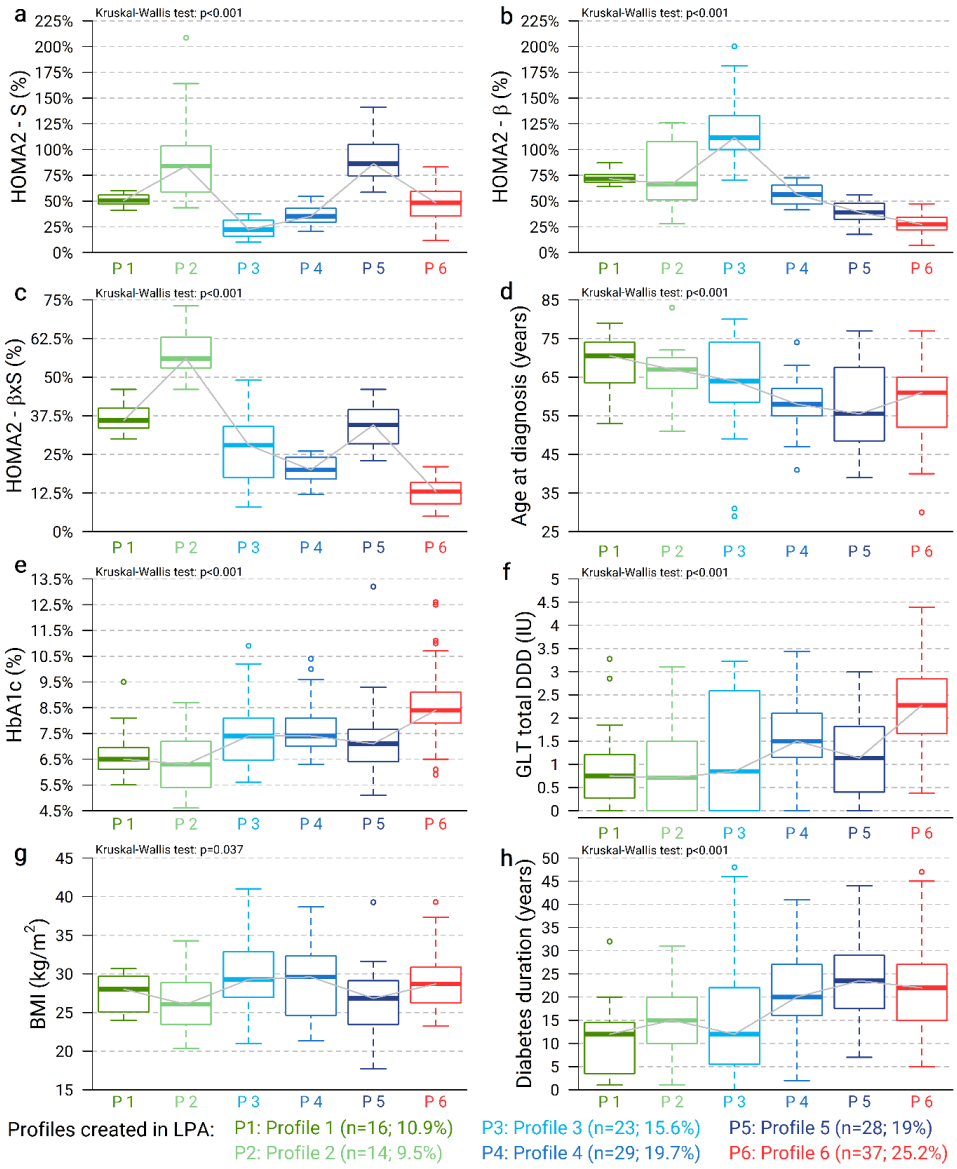
In addition to differences within profiles in GLT agents, the median GLT total doses, expressed as daily defined doses (DDD), were different between profiles (p<0.001). Profile 1 and 2 had the lowest median DDD, profiles 3 to 5 had intermediate median DDD and profile 6 had the highest median DDD (Table 2). Profile 6 was significantly different in that respect from profiles 1, 2, 3 and 5 (p<0.001).

DIABETES COMPLICATIONS AND COMORBIDITIES OF EACH PROFILE AT THE TIME OF THE LAST CONSULTATION

At the date of the last consultation to the diabetes clinic, profiles 1 and 2 had the lowest prevalence of diabetic retinopathy (13% and 7%, respectively), and profile 6 the highest prevalence (68.6%) (p=0.015; Table 3; Fig. 3). Profiles 1 and 2 also had the lowest prevalence of diabetic neuropathy and all-cause-microangiopathy (diabetic retinopathy and neuropathy), and profile 6 the highest one, without statistically significant differences (Table 3; Fig. 3).

Differences were also found in terms of all-cause macroangiopathy prevalence (p=0.017). Profile 6 had the highest prevalence of macroangiopathy (75.7%), unlike profile 1 (25.0%). Profiles 2 to 5 had intermediate prevalence of macroangiopathy (42.9%, 60.9%, 51.7% and 50.0% respectively). Finally, a familial history of type 2 diabetes was less prevalent in profile 3 (21.7%) and profile 1 (25.0%) than in other profiles, in particular profile 6 (48.6%), but no significant difference was found between profiles (p=0.348). Among the 6 profiles, no significant difference was found in terms of age at the time of last consultation (p=0.545) (Table 1; Fig. 3; Table 3).

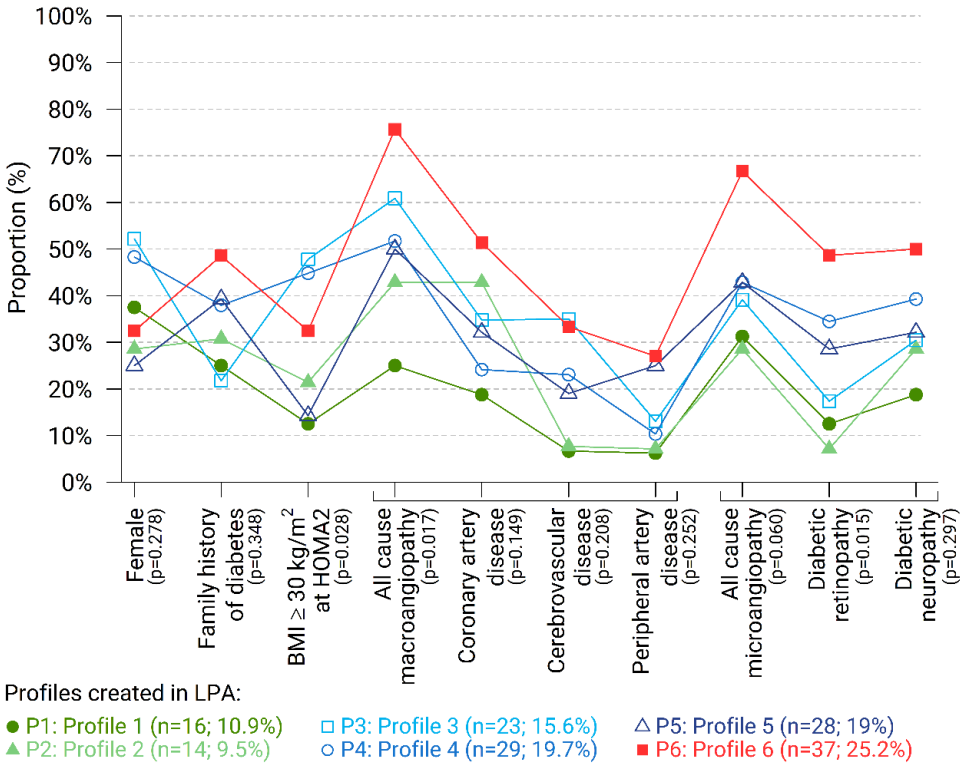
Fig. 2. Distribution of patients' diabetes characteristics according to the 6 profiles created in latent profile analysis



Boxplot of patients' (A) insulin sensitivity (*HOMA2%-S*) calculated by Homeostasis Model Assessment (HOMA2), (B) beta-cell function (*HOMA2%-β*) calculated by Homeostasis Model Assessment (HOMA2), (C) hyperbolic product of insulin sensitivity and beta-cell function (*HOMA2%-βxS*), (D) Age at diagnosis of type 2 diabetes mellitus, (E) HbA1c collected at the time of HOMA2 assessment, (F) Glucose-lowering therapy (GLT) total dose, used just before the HOMA2 assessment,

and expressed in Defined Daily Dose (one unrepresented outlier patient in profile 6 whose GLT total DDD = 6.88), (G) BMI (kg/m² ; one unrepresented outlier patient in profile 3 whose BMI = 58.56kg/m²), and (H) duration of diabetes until the last endocrinology consultation, according to the 6 profiles created by the Latent Profile Analysis (LPA). Statistical comparisons between profiles were performed using a Kruskal-Wallis test.

Fig. 3. Prevalence of women, diabetes family history, comorbidities and complications according to the 6 profiles.



Prevalence of women, family history of diabetes, BMI ≥30 kg/m², all cause macroangiopathy (coronary artery disease, cerebro-vascular disease and peripheral artery disease) and all cause microangiopathy (diabetic retinopathy and diabetic neuropathy) in each of the 6 profiles created by LPA. Statistical comparisons between profiles were performed using Pearson's χ^2 test, Pearson's χ^2 test with Yates correction or Fisher Freeman Halton's test according to the conditions of validity of each test.

DISCUSSION

The aim of the present study was to classify older patients with type 2 diabetes into profiles using a LPA methodology based on their metabolic features, in order to select more appropriate GLT in terms of their diabetes attributes and metabolic phenotype, and doing so to add another dimension to treatment individualisation [8] based on diabetes characteristics.

The indicators used as discriminant variables input for LPA were selected on the basis of recent literature. First, as suggested in several studies, age at diabetes' diagnosis is a major determinant of metabolic differences. Cardio-metabolic profile is usually less severe in patients with an older age at diabetes diagnosis than in those who are diagnosed younger. The former have lower HbA1c, fasting plasma glucose, fasting insulin, insulin resistance, triglyceride levels, LDL-cholesterol, BMI, obesity prevalence and family history of diabetes [24-26]. Patients diagnosed with diabetes at an older age also have a lower risk of developing diabetic retinopathy, regardless of known diabetes duration [27]. This suggests that their diabetes might have a lower propensity of generating microvascular complications.

Furthermore, *HOMA2%-S* and *HOMA2%-β* were used in order to distinct patients in terms of intrinsic glucose homeostasis characteristics, allowing to better select among GLT alternatives. One advantageous feature of our model is to have *HOMA2%-βxS* among input variables, bringing essential information on residual BCF to better identify patients whose needs and intensity of GLT escalation are more marked [19].

The use of these indicators allowed classifying patients into six distinct profiles. It highlights important phenotypic differences across patients sharing a common and seemingly unambiguous diagnosis of type 2 diabetes. Firstly, patients of profiles 1 and 2 had both the highest age at diabetes diagnosis combined with the highest *βxS*, whereas profile 6 patients had the youngest age at diabetes diagnosis and the lowest *βxS*. A link seems to exist between age at diabetes diagnosis and magnitude of glucose homeostasis' impairment, as shown in previous studies [24, 25]. This also implies that patients with an older age at diabetes diagnosis may need less intensive GLT, in terms of dose and drug of choice (e.g. use of hypoglycaemic agent). Inappropriate prescribing of hypoglycaemic agents in patients with late-onset type 2 diabetes may induce severe hypoglycaemic events.

Secondly, cardiometabolic risk, as shown by indices of insulin resistance, macrovascular comorbidities and BMI was very different between profiles. Some patients' profiles had lower BMI, lower insulin resistance and few macrovascular complications (e.g. profile 1), while other profiles had higher values of these variables (e.g. profile 6). Profiling older

patients with type 2 diabetes thus confirms the rationale of bringing under control modifiable risk factors taking into account the cardiometabolic risk profile for the corresponding profile of individual patients.

The LPA method used allowed for distinguishing patients based on degree of insulin resistance and/or BCF loss. The quantification of these variables provides useful information to individualise GLT (e.g. hypoglycaemic agents when impaired BCF is the major driver of hyperglycaemia or biguanides when insulin resistance is in the foreground). This is all the more relevant given the absence of phenotypic overlap of different profiles of type 2 diabetes in older patients.

The strengths of the present study are twofold. First, all patients were followed by the same endocrinologist and data were prospectively collected by one dedicated clinician. This allows for standardization of all bioclinical measurements, increases as such data's quality and accuracy. Second, the HOMA2 was based on triplicates of fasting glucose and insulin levels sampled after a sufficient period of GLT washout. However, this sample of patients, most of whom Caucasians from a well-off Brussels suburb, was followed at a single-centre diabetes clinic, and may not *de facto* be representative of other populations of older patients with type 2 diabetes of various ethnicities.

Recently, Ahlqvist et al. provide a refined classification of diabetes using a data-driven cluster analysis [28], realised on a large cohort of Swedish patients with diabetes (ANDIS cohort, N = 8980) and replicated on three independent cohorts (N = 5795). It classified patients into five clusters. Despite some similarities in the aims and variables chosen to classify patients, the study of Ahlqvist et al. differed from the present study in many ways.

First, the data used in ANDIS cohort were collected on incident cases at the time of the diabetes diagnosis (median time at inclusion = 40 days after diagnosis) in adult patients aged from 18 to 96 years, with a mean age at diagnosis of 60.2 years. Our study included prevalent cases of patients diagnosed with type 2 diabetes ≥75 years, with a median age at diagnosis of 62.0 years. Then, the inclusion criteria of Ahlqvist et al. were not restricted to type 2 diabetes but included all types of diabetes. The analytical method was a data-driven clustering, a classification method based on different theoretical approach as compared to latent profile analysis used in the present study. Finally, Ahlqvist et al. used six variables classifying patients into subgroups: three were identical to those used in the present study (HOMA2%-β, HOMA2%-S and age at diabetes onset), while two were not used (body mass index (BMI), GAD-antibodies and HbA1c). In the present study, BMI was not used, as it is not an optimal measure for obesity in older patients [29]. GAD-antibodies were not used, as the present study included only patients with type 2 diabetes. Regarding HbA1c, the

present study used HOMA2%-βxS instead, assessing the blood glucose control in patients taking glucose lowering therapies.

In the future, it might be of interest to assess the reproducibility of this study by increasing the number of patients, by recruiting older patients with diabetes followed by general practitioners and/or by running a study with a prospective design. It would allow predicting whether patients are ascribed to their appropriate profile and, accordingly, to propose therapeutic recommendations based on the patient's cardiometabolic profile, keeping in mind that such recommendations could only serve as complements to existing criteria for standards of care individualisation and current guidelines [8].

CONCLUSIONS

In conclusion, our study confirms the heterogeneity of cardiometabolic profiles in older type 2 diabetes patients, generating six profiles by LPA. The characterization of six distinct profiles could serve as decision-support indicators for choosing GLT, combined with existing criteria of therapeutic individualisation for older patients. Such classification could contribute to refine the current decision processes related to the control of hyperglycaemia, while limiting the risk of side effects such as hypoglycaemic episodes or therapeutic failure, aiming at a better overall management of the disease and its complications.

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APPENDICES

ADDITIONAL FILE 1. Latent profile analysis: Model fit statistics

Evaluative information (Goodness-of-fit statistics) for each k-profile model, including Log likelihood, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and Log Likelihood Ratio Test (LLRT). These statistics were used to select the best fitting number of profiles for the final latent profile anlaysis model.

Model	Goodness-of-fit statistics			
	Log Likelihood	AIC	BIC	LLRT p-value*
1-profile	-2616.4	5248.8	5272.7	
2-profile	-2548.7	5131.5	5182.3	<0.001
3-profile	-2503.6	5059.1	5136.9	<0.001
4-profile	-2475.1	5020.2	5124.9	<0.001
5-profile	-2446.4	4980.8	5112.4	<0.001
6-profile	-2416.9	4939.8	5098.3	<0.001
7-profile	-2409.7	4943.4	5128.8	0.111

AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; LLRT = Log Likelihood Ratio Test. *A p-value <0.05 indicates that a k profile model provides better fit than a k-1 profile model.

ADDITIONAL FILE 2. Posterior probabilities associated with each profile in the six-profile model (N=147).

Profile	n (%)	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
1	16 (10.9)	0.935	0.020	0.005	0.025	0.016	0.000
2	14 (9.5)	0.000	0.977	0.011	0.000	0.012	0.000
3	23 (15.6)	0.001	0.016	0.962	0.021	0.000	0.000
4	29 (19.7)	0.001	0.000	0.045	0.904	0.025	0.024
5	28 (19.0)	0.000	0.030	0.000	0.005	0.963	0.002
6	37 (25.2)	0.000	0.000	0.015	0.028	0.010	0.946

GENERAL DISCUSSION

Summary of the findings

Discussion

Strengths and limitations

Perspectives

Summary of the findings

The SECTION I (CHAPTERS 1 and 2) of this thesis focused on recommendations from Guidelines for the individualisation of glucose-lowering treatment in older patients with diabetes.

CHAPTER 1 is a systematic review of clinical practice guidelines about type 2 diabetes management in older people comparing their **recommendations** regarding the individualisation of glucose-lowering treatment in older patients. This review focused on 4 relevant aspects for this individualised approach: (i) health assessment, (ii) targets for glycaemic control, (iii) lifestyle management and (iv) glucose-lowering therapy. In this systematic review, we included the CPGs on type 2 diabetes management in older people published in English after 2015 by western scientific societies. Three CPGs met the inclusion criteria, namely those from the American Diabetes Association 2020 [1], the Endocrine Society 2019 [2] and the Diabetes Canada Expert Committee 2018 [3]. These three CPGs are of high methodological quality. They all address the four relevant aspects concerning the individualised approach of glycaemic management, for which they make overall 27 recommendations (40% being of high level of evidence). The comparison between these CPGs identified discrepancies in the individualised values of HbA1c targets. The 13 strong recommendations concern ten **key clinical messages**, five of them being shared by all three CPGs, i.e. assess health status, screen for cognitive impairment, avoid hypoglycaemia, prioritise drugs with low hypoglycaemic effects, and simplify complex drug regimens.

Using real data from older patients hospitalised in a geriatric ward, large **discrepancy** was found between the 3 CPGs in terms of glucose-lowering appropriateness classification, particularly in overtreatment detection (CHAPTER 2). These findings from the clinical practice emphasised the differences we have detected between the major CPGs regarding individualisation of the HbA1c targets for older patients with diabetes.

The SECTION II (CHAPTERS 3, 4, 5) of this thesis aimed at assessing the implementation of the HbA1c targets individualisation among older patients with type 2 diabetes, and focused specifically on the assessment of **diabetes overtreatment**.

CHAPTER 3 studied the inappropriateness of GLT prescribing (including overtreatment), the factors associated with GLT inappropriateness and the one-year mortality rate in older patients with type 2 diabetes. This retrospective cohort study included 318 inpatients admitted to a geriatric ward (single-centre), aged ≥ 75 years, with type 2 diabetes, a GLT

before hospital admission and HbA1c measurement during the hospital stay. In these patients, the prevalence of overtreatment was high (57%), GLT overtreatment was independently associated with poor health status, and the mortality rate at one year was higher in patients overtreated as compared to patients appropriately treated (45% vs. 29%). Mortality at one year was independently associated with GLT overtreatment (HR: 1.73, p=0.023).

CHAPTER 4 aimed at externally validating the results reported in the CHAPTER 3, using data from a large European multicentre cluster randomised controlled trial (OPERAM trial [4]), and including inpatients aged ≥ 70 years, with multimorbidity, polypharmacy, type 2 diabetes, a GLT before hospital admission and a concomitant HbA1c measurement. Overtreatment was present in a third (34.3%) of the 490 patients included with type 2 diabetes. Mortality at one year was higher in patients overtreated (31.8 patients per 100 person-years) than in others (20.1 patients per 100 person-years, p=0.023). Mortality at 1 year was independently associated with overtreatment (HR: 1.61, p=0.023). These results confirmed the findings obtained with the smaller cohort of CHAPTER 3. Both studies highlight that (i) diabetes overtreatment is very prevalent in older patients, (ii) individualisation of HbA1c targets is not sufficiently achieved, and (iii) patients who are overtreated have a higher risk of mortality at one year.

CHAPTER 5 reports our critical review of the **definitions of diabetes overtreatment** in older people that were used in recent research studies. Through a comprehensive literature search of all original research studies addressing diabetes overtreatment in older people, this review identified 12 different definitions used by 22 studies. All these definitions are based on HbA1c cut-off values varying from 6% to 8%. Among the 12 definitions, 4 definitions are individualised (HbA1c cut-off values vary according to the patient's characteristics); 4 definitions require that a glucose-lowering treatment (any drug) is prescribed; and 6 that the glucose-lowering treatment includes a drug inducing high risk of hypoglycaemia (i.e. insulin, sulfonylureas or glinides). There is obviously no consensus on diabetes overtreatment definition across research studies, which is impacting the quality of research in this field, as well as the management of older people with type 2 diabetes.

The SECTION III of this thesis (CHAPTER 6) examined the **cardiometabolic heterogeneity** among the older patients with type 2 diabetes, using data from an outpatient's diabetes centre of our university hospital. A wide heterogeneity was found concerning metabolic and diabetes characteristics in this selected population. This study identified six profiles of patients based on age at diabetes diagnosis, insulin sensitivity, and absolute and residual β-cell function.

Discussion

INDIVIDUALISATION OF DIABETES MANAGEMENT: HOW TO IMPROVE THE CURRENT RECOMMENDATIONS?

Given the results of CHAPTER 1 and CHAPTER 2 highlighting some weaknesses of the recommendations provided by the most recent CPGs, suggestions may be formulated to improve their quality.

Firstly, the overall level of evidence (LOE) of the recommendations should be increased. There is an urgent need to move away from expert advice recommendations based on extrapolations of results from studies in younger patients. This evidence must be established by conducting quality research, using data from sample of patients that are representative of the older population. There are several fields of research that need to be covered and many questions that remain unanswered [5, 6].

Secondly, the guidelines should be more patient-minded rather than disease(diabetes)-centred. In particular, this would ensure that the recommendations are safer for the older patient (taking into account the risks associated with GLT), that they make more sense (taking into account the actual expected benefit for the patient), and that they respect the specific needs of the older patient [6]. For example, the absence of a lower bound on the HbA1c target range in one of the three CPGs of our systematic review is clearly an unsafe aspect in the management with potential harmful consequences for older patients (CHAPTER 1 and CHAPTER 2).

Thirdly, a possibility would be to diversify the authors and experts on the writing committees of guidelines on the management of diabetes in older adults, by including for example geriatricians, general practitioners or nurses, alongside the usual diabetologists or endocrinologists. Another one would be to take greater account of patients' opinions in the formulation of guidelines. These aspects are in fact key elements of the methodological quality of the guidelines set out by AGREE-II guidelines [7], and it therefore seems essential to follow them.

Finally, it should be ensured that the recommendations provided by the guidelines can be concretely implemented. For example, one of the major clinical message extracted in the systematic review of CPGs was to avoid overtreatment [8]. However, no definition of overtreatment has been provided by CPGs, which makes the recommendation difficult (impossible) to apply and reduces its impact.

DIABETES OVERTREATMENT: WHY DID WE USE THIS DEFINITION?

In our two studies reported in SECTION II (CHAPTER 3 and CHAPTER 4), diabetes overtreatment referred to the overtreatment of glycaemic control. The definition of diabetes overtreatment (and extensively of inappropriate glycaemic management; see CHAPTER 3) largely determined the results of these studies. Despite some recommendations about overtreatment provided by clinical practice guidelines, no standard definition of diabetes overtreatment has been proposed.

In the studies included in these chapters, we defined diabetes overtreatment as having a GLT including a glucose-lowering agent which induces a high risk of hypoglycaemia (i.e. insulin, sulfonylurea or glinide) and an HbA1c below the lower target value (< 7.5% for patients in good health, < 8% for patients in intermediate health and < 8.5% for those in poor health status). This definition was derived from the recommendations about HbA1c target ranges for older people with type 2 diabetes provided by the 2019 Endocrine Society clinical practice guidelines [2].

The choice of this definition was justified in our opinion as this definition:

- was derived from recent, high quality and dedicated clinical practice guidelines for older people with diabetes [2],
- was individualised according to patients' health status (taking into account the health status heterogeneity existing among older people with type 2 diabetes),
- considered the risk of hypoglycaemic events associated with some glucose-lowering agents (i.e. insulins, sulfonylureas and glinides).

LACK OF IMPLEMENTATION OF GUIDELINES: WHY AND HOW TO IMPROVE?

The results displayed in SECTION II showed that individualisation of glucose lowering treatment was not, or poorly applied, at least the individualised choice of HbA1c targets according to patient's health status. Patients were treated in the same way, with the same glucose-lowering agents, achieving the same HbA1c, regardless of their characteristics (frailty, life expectancy, etc), following a "one-size fits all" strategy.

However, the paradigm shift (from a one-size-fits-all strategy to an individualised strategy) was initiated almost 20 years ago. Among the first guidelines or expert advices, recommending individualised management of diabetes in older people (since 2000), the

European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus is probably the forehead [9, 10].

These expert advice were provided based on the observation of the wide clinical heterogeneity in the older population with type 2 diabetes [11], and driven by the findings of large longitudinal studies about glycaemic control performed in general population. The relationship between risk of mortality and HbA1c follows a U-shaped curve, showing that all-cause mortality increases with high and low values of HbA1c, [12-16]. This relationship is partly explained by the occurrence of hypoglycaemia when hypoglycaemic treatment is prescribed.

Since these recommendations have been released and disseminated for more than 10 years, it is pertinent asking why this concept is not more widely applied. This could be due to a lack of dissemination of the CPGs, an overly conservative attitude on the part of prescribers, a difficulty in de-prescribing, or/and the place left to the shared-decision making with patients.

Interestingly, the CHAPTER 4 of this thesis reported that the individualisation of HbA1c targets were differently applied between the four countries participating to the OPERAM trial (Switzerland, Republic of Ireland, Belgium, The Netherlands). This may suggest that the guidelines are applied differently as a result of differences in the dissemination of the guidelines between these countries, differences in the degree of shared decision making or socio-cultural differences. The understanding of these differences found between countries deserves further investigations.

Finally, a perspective would be how to motivate physicians to individualise the management of glycaemic control according to the older patient's health status. Furthermore, it is also and perhaps more importantly, necessary to seek to improve the CPGs by increasing the level of evidence of these recommendations. This would, among other things, strengthen the healthcare professionals' confidence in these recommendations and thus improve adherence to them.

TOWARDS A SAFER GLUCOSE-LOWERING TREATMENT: WHICH PLACE FOR CARDIOMETABOLIC PROFILING?

The study reported in the SECTION III (CHAPTER 6) of this thesis aimed at classifying older patients with type 2 diabetes indifferent profiles according to their metabolic characteristics [17]. Besides a few studies that have demonstrate clinical differences between older patients according to the age at diabetes onset (adult-onset vs. elderly-onset) [18-22], the existence

of different metabolic profiles had never been shown before specifically in the older population.

Our study [17] is in the line of other studies, carried out in the last few years, highlighting the existence of a significant heterogeneity of metabolic characteristics in adult patients with type 2 diabetes, and the possibility of classifying them into different profiles according to these characteristics [23, 24]. The purpose of this work was to propose a new approach for the individualisation of the GLT according to patient's metabolic profile [23, 25-27]. According to Ahlqvist et al., the methodology of cluster-based classification provides a better holistic view of the disease than the empirical aetiologically-based classification does, and allows therefore a more precise and safer management, following the development of 'precision medicine' [26].

Despite these significant advances in the classification of patients (adults or older adults) according to their metabolic profile, no strategy for treatment choice has yet been proposed on this basis, as the evidence to support such a therapeutic approach simply does not exist. Moreover, the variables used by these classifications [17, 23], in particular insulin sensibility and β-cell function (computed by HOMA2) are not easily available in clinical practice. In order to make these classifications accessible to routine clinical practice, proxies should be found as a first step.

While this is an interesting way to improve the management of glucose-lowering treatment in older patients, it should be considered as a complementary approach to the individualisation currently proposed in the CPGs. This is an opportunity to ensure the safety of the treatment by targeting more precisely the GLT, and therefore decreasing the risk of hypoglycaemia.

Finally, it should be kept in mind that the future of precision medicine in the choice of treatment will probably not only involve the metabolic profile of patients, but also genetic and other 'omics' data, as already envisaged in many studies [26, 28]. Furthermore, the use of artificial intelligence and in particular machine learning has an important place to take in precision medicine in the coming years [26, 29].

Strengths and limitations

Our systematic review of clinical practice guidelines (CPGs) sought recent publications by a Scientific Society addressing the care of diabetes in older adults. Such criteria have limited the number of included CPGs (n=3) but increased their validity. This systematic review have also a limited scope, focusing only on key aspects of individualised glycaemic management

of older adults. The strengths of this systematic review were first its methodological rigour and the extensive literature search, following guidance on designing systematic review of CPGs. This systematic review promotes also the dissemination of the CPGs and their recommendations to the prescribers. Finally, to our knowledge, this is the first systematic review on this relevant issue for older people.

Our research on diabetes overtreatment in older people encountered some limitations. Firstly, diabetes overtreatment has no standardised definition. We chose a definition based on the 2019 Endocrine Society guidelines, which was both patient-centred (individualisation) and safe (avoidance of hypoglycaemia). Secondly, the retrospective design of this research, both in local geriatric patients (CHAPTER 3) and in European multi-morbid patients (CHAPTER 4), did not allow us to access key variables on GLT use (e.g. patient's preferences and prescriber's profile). In the same way, no data on the occurrence of hypoglycaemic events were available. Furthermore, health status and diabetes overtreatment were assessed on a one-time basis only, even though these conditions are subject to change over time. Our research on diabetes overtreatment had several strengths. The cohort design with the assessment of the vital status at one-year allowed us to disclose a positive association between overtreatment and mortality, both in bivariate and multivariable analyses (CHAPTER 3). The opportunity to further study diabetes overtreatment in the OPERAM multi-morbid older diabetic patients (CHAPTER 4) led us to an external (and international) validation of the positive association between overtreatment and mortality, after adjustment for important confounding factors (age, comorbidity / Charlson index; global health status / severe frailty). Both studies of CHAPTERS 3 and 4 used data from patients usually underrepresented in other studies of the literature (older, multimorbid, and/or geriatric).

Our project on the metabolic heterogeneity among older patients with type 2 diabetes (CHAPTER 6) was limited to a series of outpatients followed at our diabetes clinic, where detailed cardio-metabolic data are collected. Our attempt to collaborate with other research teams having collected detailed cardio-metabolic in older patients with type 2 diabetes did not succeed.

Perspectives

This thesis highlights the lack of available scientific evidence for the individualisation of glycaemic management in older patients with diabetes, which is in stark contrast to the epidemiological importance of this topic and the pressure of this medical condition on

healthcare systems. Recommendations in current clinical practice guidelines, even if established by major scientific societies, are indeed often based on a low level of evidence (LOE) and are mostly expert opinions. The LOE of recommendations should be globally increased to improve the quality of CPGs and therefore the confidence in them.

There is obviously a considerable need for quality research in this area, as claimed for many years by numerous experts [5, 6]. Some research questions remain unclear, despite the burden of type 2 diabetes on older patients and health care systems. In line with the questions studied throughout this thesis, some research should be undertaken which would relate to health assessment (e.g. "Is there a better phenotypic classification of older patients, including more specifically frailty?" or "What is the place of sarcopenia diagnosis in health assessment?"), to specific glycaemic goals (e.g. "What individualised HbA1c target ranges should be recommended to minimise poor outcomes in older people?" or "What could be an alternative measure of glycaemic control to HbA1c?") or to appropriate glucose-lowering strategy (e.g. "What is the optimal sequence of glucose-lowering drugs for older patients with type 2 diabetes, according to their health assessment?") [5].

As highlighted in CHAPTER 5 (the critical review), it is important to establish a common definition of diabetes overtreatment. Although elements of an ideal definition have been discussed in the thesis, more work is needed to construct a comprehensive definition with consistent criteria that would make sense in terms of poor outcomes occurrence. One way forward could be to develop an overtreatment score, defining several levels of overtreatment according to the actual risk of hypoglycaemia for the patient. Such score should be tested in a representative sample of older population.

Given the high prevalence of diabetes overtreatment, the importance of deprescribing in the optimal management of diabetes treatment should not be underestimated. Research in the field of de-prescription/de-intensification of glucose-lowering drugs should be conducted more ambitiously. There is a significant lack of evidence in this area, making it difficult to establish optimal recommendations for deprescribing [5, 30, 31].

In any case, such research should be carried out, as far as possible, on representative samples of the older population, not limited to the youngest or most functionally independent patients, besides all the challenges likely to be expected [5, 32]. Moreover, patients' preferences should be taken into account in the recommendations of clinical practice guidelines. This is consistent with the idea that for older patients, care should be more patient-minded than disease-centred.

Furthermore, the diabetes management could not be limited to the control of glycaemia. The interest of individualising the anti-hypertensive or lipid-lowering therapy should be explored as well. As already mentioned, the motivations and choices of physicians and other healthcare professionals must be investigated more deeply. Finally, patients' choice and their quality of life should be embed in all research, as it is ultimately the very substance of the whole issue discussed in this thesis.

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Scientific communications

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Abstract

Type 2 diabetes (T2D) is one of the most prevalent chronic condition in older people, a heterogeneous population in terms of health status. Consequently, risks and benefits of glycaemic control by glucose-lowering treatment may differ considerably between patients and must be wisely balanced to avoid harmful consequences, i.e. hypoglycaemic events. This can be achieved by individualising treatment goals according to patient's characteristics. This thesis (i) reviewed recommendations from recent Clinical Practice Guidelines for individualised glycaemic management in older people with T2D, (ii) assessed the application of these recommendations in clinical practice, and (iii) described the metabolic heterogeneity in older people with T2D. The results provide strong encouragement to follow more assiduously recommendations for individualising the glycaemic management in older patients with T2D, and to continue research in this field to provide high-level evidence recommendations.

Résumé

Le diabète de type 2 (DT2) est une pathologie prévalente chez les personnes âgées, une population hétérogène en termes de santé. Par conséquent, les risques et avantages du contrôle glycémique par un traitement anti-hyperglycémiant diffèrent considérablement d'un patient à l'autre et les objectifs du traitement doivent être individualisés pour en éviter les conséquences néfastes, comme la survenue d'hypoglycémies. Cette thèse (i) a revu les recommandations des récents guides de pratique clinique pour la gestion glycémique individualisée chez les personnes âgées avec DT2, (ii) a évalué l'application de ces recommandations en pratique clinique, et (iii) a décrit l'hétérogénéité métabolique chez ces patients. Les résultats encouragent fortement à suivre davantage les recommandations pour l'individualisation de la gestion glycémique chez les patients âgés avec DT2, et à poursuivre la recherche dans ce domaine afin de fournir des recommandations de haut niveau de preuve.