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Glucose-lowering medication initiation in people with newly diagnosed type 2 diabetes in Scotland: A mixed-methods study

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Declaration

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgment, the work presented is entirely my own.

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Abstract

Background. Worldwide, clinical guidelines recommend the reduction of glucose levels in people with type 2 diabetes mellitus (T2DM) as necessary in order to reduce risk of complications. In Scotland, the national guidelines suggest a target of glycated haemoglobin (HbA1c) of 53 mmol/mol (7.0%) and recommend an individualised treatment approach that may include lifestyle and/or pharmacological interventions. For most patients, the initial treatment is recommended to be lifestyle changes: diet and physical activity. However, when glycaemic targets are not achieved by lifestyle changes, pharmacological treatment should be added, drug choices should be based on patient characteristics and preferences.

The literature review showed that the period after diagnosis is one of the critical points for optimal management for T2DM. However, it also showed that there is a lack of studies, which have focused on the initiation of pharmacological treatment in people with newly diagnosed T2DM. Thus, this study aimed to describe factors associated with the initiation of glucose-lowering medication (GLM) in people with newly diagnosed T2DM and the underlying reasons for starting pharmacological treatment in a Scottish primary healthcare context.

Methods. This study employed a convergent parallel mixed-methods design, comprising two strands: one quantitative and one qualitative. The quantitative strand comprised a retrospective cohort study design; participants were drawn from an extract of the SCI-Diabetes dataset, which included people who had been diagnosed with T2DM in Scotland between 2004 and 2012 and were followed up for at least two years after diagnosis. This strand explored factors associated with time to initiation of GLM amongst people with newly diagnosed T2DM. For the qualitative strand, interviews were undertaken with 16 healthcare professionals (HCPs) recruited from 12 practices in Scotland to identify and explore factors and considerations that might influence clinical decision-making in relation to initiation of GLM in

people with T2DM in a Scottish primary healthcare context, data were analysed thematically.

Results. The cohort, for the quantitative strand, consisted of 154,660 people with newly diagnosed T2DM. More than half of people (54.9%) received GLM prescription within two years after T2DM diagnosis. The results indicated that increased age, male sex, the least deprived Scottish Index of Multiple Deprivation (SIMD) quintiles and receiving antihypertensive medication were associated with longer time to drug treatment. Conversely, HbA1c >53 mmol/mol, body mass index (BMI) $\geq$30 Kg/m^2 and receiving antihypertensive medication were associated with shorter time to drug treatment. The findings from the qualitative strand revealed that a variety of interwoven factors and considerations influenced HCPs' decision-making about initiating medication to lower blood glucose. These fell into three main categories: individual-patient related considerations, HCP-patient related factors, and contextual factors. Individual patient-related considerations included physiological aspects such as patient's age and HbA1c, and psychological aspects, for instance, whether they were perceived to be motivated, their needs and expectations and cultural/ethnic background. HCP-patient related factors included historical contact with patients and, negotiation with patients. Contextual factors included time resources, division of labour within their practices, clinical guidelines (including the recent decommissioning of the Quality and Outcomes Framework; QOF), and HCPs' perceptions of how their own roles fitted in with those of other colleagues involved in delivering diabetes care.

Conclusions. The cohort showed that patients' baseline HbA1c, age, sex, and SIMD quintile were among the factors associated with the timing of GLM initiation in Scotland from 2004 to 2012. However, the interviews with HCPs highlighted the complex factors, which can influence and inform HCPs' decision-making. Thus, offering important insights into why prescription patterns for treatment of early type 2 diabetes vary across patients, practices and over time.

Lay Summary

The main aim of this study was to describe factors related to the initiation of medication to control type 2 diabetes and, the reasons behind starting this treatment. I particularly focused on people who had been recently diagnosed with type 2 diabetes in Scotland. In other words, I wanted to know if there were differences between people who received and did not receive medication to lower their glucose levels. Also, I was interested in knowing why some people received a drug prescription sooner than others.

To answer these queries, I analysed information on the people diagnosed with type 2 diabetes in Scotland between 2004 and 2012. Besides this, I also interviewed doctors and nurses working in different medical practices in Scotland. I found that just over half of people received a prescription for medication to control their diabetes after two years of being diagnosed with type 2 diabetes. People who were younger, had higher blood glucose, were obese and, lived in the most deprived areas (according to the Scottish Index of Multiple Deprivation) received a prescription for medication to control their diabetes sooner than those people with different circumstances.

The doctors and nurses who took part in the study described several factors, which influenced their decision to prescribe medication. Among others, doctors and nurses mentioned that the principal aspect they took into consideration when prescribing medication to control type 2 diabetes was their patient's characteristics such as age, blood glucose and, overall health condition. Yet, some other aspects like consultation length and staff shortage made their ability to focus on patients' circumstances rather challenging.

This study provides knowledge about the differences in prescription of medication to control type 2 diabetes. Although this study helps to explain why the prescription of medication to control type 2 diabetes varies, I recognise that more studies, which use more recent patients' information, need to be carried out.

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Glossary

Abbreviation	Key term
AACE	American Association of Clinical Endocrinologists
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	American College of Endocrinologists
ADA	American diabetes organization
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CCA	Complete case analysis
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes education and self-Management for ongoing and newly diagnosed type 2 diabetes
DPP-4	Dipeptidyl peptidase-4
FPG	Fasting venous plasma glucose
GLM	Glucose-lowering medication
GLM-2Y	The group of people who received glucose-lowering medication prescription within two years of T2DM diagnosis.
GLP-1	Glucagon-like peptide 1
GP	General practitioner
GPRD	General practice research database
HbA1c	Glycated Haemoglobin
HCP	Healthcare professional
IDF	International diabetes federation
IFCC	International federation of clinical chemists
IQR	Interquartile range
MAR	Missing at random

MCAR	Missing completely at random
MNAR	Missing not at random
NCDs	Non-communicable diseases
NHANES	National and health nutrition examination survey
NHS	National health service
NICE	The National Institute for health and care excellence
NM-2Y	The group of people who did not receive glucose-lowering medication prescription within two years of T2DM diagnosis.
NPT	Normalisation process theory
OGTT	Oral glucose tolerance test
QOF	Quality and outcomes framework
RCT	Randomised controlled trial
RWD	Real-world data
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Social-ecological model
SGTL2	Sodium-glucose co-transporter-2
SIGN	The Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
THIN	The health improvement network
UK	United Kingdom
UKPDS	UK prospective study group
US	United States
WHO	World health organization
YLDs	Years lived with disability

Chapter 1 Introduction and Background

1.1 Introduction

This thesis describes the factors associated with glucose-lowering medication (GLM) initiation in people with type 2 diabetes (T2DM) and, views of healthcare professionals (HCPs) working in primary care in Scotland about when to initiate GLM in people with T2DM. A mixed-methods research design was adopted, which means that a quantitative and a qualitative component were included.

Diabetes is a public health concern; the World Health Organization (WHO) estimated that in 2014, 8.5% of the global adult population had diabetes (World Health Organization, 2016a). T2DM is the most common type of diabetes, elevated levels of glucose in people with T2DM can lead to life-changing complications such as retinopathy, neuropathy, foot ulcers and amputation, kidney failure, heart disease, and stroke. These complications can have significant economic consequences for both health systems and, individuals and their families (American Diabetes Association, 2019a, World Health Organization, 2016a, World Health Organization, 2018a).

According to clinical guidelines, early diagnosis and optimal control of blood glucose levels can delay the long–term complications of T2DM and reduce related costs (International Diabetes Federation, 2017a, American Diabetes Association, 2019a). Treatment for T2DM includes a healthy lifestyle, which encompasses a healthy diet and physical activity in order to attempt to achieve or maintain a healthy weight[1]. However, when clinically recommended levels of glucose are not achieved by following a healthy lifestyle, oral medication is usually required (International Diabetes Federation, 2017a).

[1] Healthy weight to reduce risk of T2DM is defined by the WHO as a BMI in the range of 18.5-24.9 Kg/m^2 WORLD HEALTH ORGANIZATION 2019a. Body mass index - BMI. *A healthy lifestyle.* Denmark: WHO Regional Office for Europe, WORLD HEALTH ORGANIZATION 2019c. Mean Body Mass Index (BMI). *Global Health Observatory (GHO) data.*

By conducting a retrospective cohort study looking at factors associated with the initiation of GLM within two years of T2DM diagnosis that are recorded in routine clinical care of people with T2DM, and interviewing HCPs about their reasons for starting (or not) GLM, this mixed-methods research seeks to provide a deeper understanding of factors associated with GLM initiation and clinical decision-making.

This thesis is divided into six chapters plus appendices, and is structured as follows:

- Chapter 1. Sets the scene for the thesis by providing general information about T2DM and its management, including the provision of healthcare in Scotland.
- Chapter 2. Reviews the literature on GLM prescription patterns, time to pharmacological treatment initiation, and glycaemic control in people with a recent diagnosis of T2DM. It also includes a review of qualitative research focused on HCPs' perspectives and experiences in diabetes care, particularly about factors influencing clinical decision-making.
- Chapter 3. Provides an introduction to mixed-methods research, and describes the mixed-method design chosen and the rationale for this research. In addition, the specific methods followed for each strand of the study (quantitative and qualitative) are presented.
- Chapter 4. Presents the results of the quantitative strand of the study, which consisted of a retrospective cohort study based on secondary analysis of diabetes register data from 2004 to 2012.
- Chapter 5. Presents the findings from interviews undertaken with HCPs about factors and aspects they take into consideration to decide when to initiate GLM in people with T2DM.
- Chapter 6. Provides a summary of the main findings and the overall discussion. In this chapter the study strengths and limitations are discussed, as well as the implications of the work and directions for future research.

1.2 Diabetes and non-communicable diseases

Non-communicable diseases (NCDs) are usually those of long duration and slow progression (World Health Organization, 2018b). The most common types of NCDs include cardiovascular diseases (CVDs), cancer, chronic respiratory diseases and diabetes; these diseases have modifiable risk factors in common such as physical inactivity, unhealthy diet, tobacco use and the harmful use of alcohol, and are estimated to be responsible for 80% of premature NCD deaths (World Health Organization, 2018b, World Health Organization, 2019e). Premature NCD death is described by the WHO as the death occurred from 30 to under 70 years from a major NCD (World Health Organization, 2019d, World Health Organization, 2020b).

In the United Kingdom (UK), NCDs are estimated to account for 89% of total deaths (World Health Organization, 2018d). Furthermore, in the UK, NCDs are important causes of years lived with disability (YLDs). However, diabetes is the only NCD, that in ten years (2007 to 2017) the ranking has increased, from 8th to 5th most common estimated cause of YLDs (Institute for Health Metrics and Evaluation, 2019b). Diabetes is also listed as one of the top 25 causes of disability-adjusted life years (DALYs) in the world.

YLDs are a measure of the burden of a disease; the term is used to refer to the number of years lived in less than optimal health. YLDs are calculated by multiplying the prevalence of a disease by the disability weight associated with that disease. The WHO defines DALYs as the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability: one DALY equals one lost year of healthy life. These units permit the estimation of the total number of years lost due to specific causes and risk factors and the comparison of health conditions over time and across different populations. Thus, in the UK, diabetes has been identified as one of the conditions that causes the most disability after lower back pain, headache disorders, depressive disorders and neck pain (Institute for Health Metrics and Evaluation, 2019b, Institute for Health Metrics and Evaluation, 2019a, World Health Organization, 2019b, National Institute of Mental Health, 2019).

Diabetes is a metabolic disorder that occurs when the pancreas does not produce insulin, the production is insufficient or when the body is not able to use the insulin produced effectively (World Health Organization, 2018a). Globally, diabetes is an important cause of premature mortality and disability (World Health Organization, 2016a, World Health Organization, 2014). Recently, the prevalence of T2DM has increased, and this increase is driven by ageing of the population and modifiable risk factors, such as lack of physical activity resulting in increasing prevalence of overweight and obesity; which are key risk factors (World Health Organization, 2014, World Health Organization, 2018a).

Diabetes has two main forms: type 1 or type 2, with the latter form of diabetes resulting from the body's ineffective use of insulin and accounting for 90-95% of all cases and is characterised by a progressive loss of insulin secretion with simultaneous insulin resistance (American Diabetes Association, 2019a, World Health Organization, 2016a, World Health Organization, 2018a). As the focus of this research is on people with T2DM, the following sections and sub-sections are concerned with this type of diabetes.

1.3 Type 2 diabetes

T2DM was previously referred to as "adult-onset" or "non-insulin dependent" diabetes. However, these terms are not accurate as nowadays T2DM is increasingly occurring in young adults, adolescents and children. Furthermore, insulin is often used in the management of T2DM (International Diabetes Federation, 2017a, American Diabetes Association, 2019a, World Health Organization, 2018a). In the following four sub-sections, I will describe the aetiology and epidemiology, diagnosis, monitoring of glycaemic control, and complications T2DM.

1.3.1 Aetiology and epidemiology

Although the aetiology of T2DM are complex, two key risk factors are age and being overweight or obese, increased percentage of body fat, principally

in the abdominal region is an important contributor to the risk of developing T2DM (Shanik et al., 2008, American Diabetes Association, 2019a, International Diabetes Federation, 2017a). Ethnic differences exist but populations with a high prevalence of obesity generally also have the highest prevalence of diabetes and, conversely, populations with a low prevalence of obesity have a low prevalence of diabetes (Shaw and Sicree, 2008). In addition, factors such as increasing urbanisation, and economic development have been associated with increased prevalence of T2DM at the population level (Shaw and Sicree, 2008, American Diabetes Association, 2019a).

In order to implement actions to reduce their risk, it is important to identify people who might be at risk of developing T2DM such as those who have a first-degree relative with T2DM, who are overweight or obese, not physically active, smokers, with previous history of gestational diabetes, and those previously identified as having glucose intolerance (Ghosh S. and Collier A., 2012, World Health Organization, 2018a, World Health Organization, 2016a, International Diabetes Federation, 2012).

In 2016, the WHO estimated an overall prevalence of diabetes in the UK of 7.7% for people over 30 years of age. However, men had a higher age-standardised prevalence (8.4%) than females (6.9%) (World Health Organization, 2016b). The 2018 Scottish Diabetes Survey reported a crude prevalence of T2DM of 4.9%. Furthermore, it was reported that 81.7% of people with T2DM had a record of their body mass index (BMI), of whom 31.8% were overweight (BMI 25 – 29.9 Kg/m^2) and 55.2% were obese (BMI $\geq$30 Kg/m^2) (Scottish Diabetes Data Group, 2018).

1.3.2 Diagnosis

Usually, the presence of symptoms such as polyuria, polydipsia and lack of energy leads to the screening and diagnosis of T2DM. However, as generally the onset of T2DM is slow, some people with T2DM can live for years without developing symptoms and the diagnosis may be made as an incidental finding (Scottish Intercollegiate Guidelines Network (SIGN), 2017a,

International Diabetes Federation, 2017a). The diagnosis of T2DM may be based on plasma glucose or by measuring glycated haemoglobin (HbA1c). According to the WHO (World Health Organization, 2018a), T2DM is diagnosed when one or more of the following criteria are met on two separate occasions among people without symptoms:

1. Fasting venous plasma glucose (FPG) ≥7.0 mmol/l (126mg/dl)
2. Oral glucose tolerance test (OGTT): Glucose two hours after a 75g of oral glucose load ≥11.0 mmol/l (200mg/dl)
3. HbA1c ≥ 48 mmol/mol (6.5%)

However, it is important to consider that, as research conducted in the United States (US) suggests, the validity of HbA1c as a diagnostic tool can vary with ethnicity, particularly among African American populations. The evidence suggests that African Americans tend to have higher levels of HbA1c than non-Hispanic whites. Likewise, conditions such as sickle cell disease, pregnancy, and HIV among others, can alter the relationship between HbA1c and glycaemia. Similarly, some conditions such as diet, gastrointestinal disorders, stress, and medications can produce abnormal results of an OGTT (American Diabetes Association, 2019a, World Health Organization, 2016a, Ghosh S. and Collier A., 2012). Thus, these aspects and considerations need to be taken into account in the diagnosis of T2DM and monitoring of glucose levels.

In general, health outcomes are more likely to be unfavourable the longer a person lives with untreated T2DM. The implementation of universal screening for diabetes is not currently encouraged or recommended due to the lack of evidence that it is cost-effective. In the UK, the National Screening Committee recently reviewed the evidence on the effectiveness of screening for T2DM. The review showed a scarcity of high quality randomised controlled trials (RCTs) that have studied screening programmes' effect on mortality or morbidity. Hence, there is currently no evidence that strongly supports the benefit of universal screening compared to the current

opportunistic approach to diagnosis (UK National Screening Committee, 2019). However, England has introduced screening through the Health Check and NHS Diabetes prevention programme (NHS DPP). The NHS health check is for people in England aged 40 to 74 and who do not have pre-existing health conditions such as heart disease, high blood pressure or chronic kidney disease (NHS, 2019). The NHS DPP is a programme jointly developed by NHS England, Public Health England and Diabetes UK in which people who are at risk of developing T2DM are referred to a face-to-face programme where they receive tailored education about a healthy lifestyle (NHS England, 2019). Moreover, the IDF recommends the provision of advice on a healthy lifestyle to people who are at risk of developing T2DM (International Diabetes Federation, 2012).

1.3.3 Monitoring glycaemic control

Currently, the preferred method for assessing glycaemic control among people with a diagnosis is by measuring HbA1c which reflects the average plasma glucose over the previous 8 to 12 weeks (World Health Organization, 2011). This test requires a blood sample, and the patient does not need to be in a fasting state (World Health Organization, 2016a). HbA1c levels are reported either as a value in mmol/mol or as percentage depending on whether the International Federation of Clinical Chemists (IFCC) or the Diabetes Control and Complications Trial (DCCT) standards are used. In Scotland, HbA1c is now reported in mmol/mol since 2012 (Scottish Diabetes Group, 2009, Scottish Clinical Biochemistry Managed Diagnostic Network, 2012).

1.3.4 Complications

The development and progression of several complications related to T2DM are strongly associated with raised levels of glucose. There is evidence to show that early interventions to lower glucose levels can slow the progression of complications. Over time, elevated levels of blood glucose in people with T2DM can lead to life-changing complications. People with T2DM can suffer damage to their eyes, kidneys, nerves, blood vessels and heart as

a consequence of microvascular disease. People with T2DM also have an increased risk, among other health problems, of having a heart attack or a stroke. The risk of macrovascular disease in people with T2DM, according to the WHO is two-to three-fold times increased compared to a person without T2DM. Furthermore, T2DM is one of the leading causes of kidney failure and lower limb amputation (World Health Organization, 2016a, World Health Organization, 2018a, International Diabetes Federation, 2017a).

The effect of high blood glucose has been studied previously in the UK. For instance, Evans et al. (2015) studied cardiovascular mortality among adults with impaired glucose regulation in Tayside, Scotland. By using record-linked data from 2003 to 2008, the authors compared two groups of patients depending on their impaired glucose regulation (IGR) status: Non-IGR and IGR. The non-IGR group included people for whom there was a record of blood glucose testing during the studied period that was not diagnosed as IGR. The IGR group included those for whom a record of blood glucose testing during the studied period that was diagnosed as IGR. The mean age of patients was 63 years for the IGR group and 54 years for the non-IGR group. The regression analysis showed that the diagnosis of IGR was associated with an increased risk of mortality compared with people without diagnosis of IGR. The youngest group of patients had the strongest risk, thus, people <45 years in the IGR group had twice the risk than those <45 years in the non-IGR (HR: 2.20; CI: 1.12–4.33).

Moreover, Data from a Scottish Care Information – Diabetes Collaboration (SCI-Diabetes) cohort from 2001–2007 in Scotland showed that cardiovascular mortality risk was greater among people with T2DM compared to people without diabetes (Jackson et al., 2012). Further analysis of the SCI-Diabetes database have showed that T2DM conferred an excess risk of death compared to people without T2DM (Read et al., 2016). Similarly, a study conducted by Gordon-Dseagu et al. (2014) analysed UK data from the Scottish Health Survey and the Health Survey for England and reported an increased risk of mortality from all-cause and cause-specific such as CVD,

cancer, and respiratory disease among people with diabetes. However, it is important to note that the study included people with both types of diabetes.

Overall, complications of T2DM can have significant economic consequences on both health systems and individuals and their families (International Diabetes Federation, 2017a, World Health Organization, 2018a, World Health Organization, 2016a). In order to reduce the risk of complications, people with T2DM require comprehensive medical care, which should include regular monitoring of glucose levels, education about a healthy lifestyle, screening for complications as well as access to and correct use of medications (International Diabetes Federation, 2017a, World Health Organization, 2018a).

1.4 Clinical guidelines for diabetes management

According to clinical guidelines, in people who are at risk of developing T2DM, early diagnosis and optimal control of blood glucose levels, can delay the long–term complications of T2DM and reduce the related costs (American Diabetes Association, 2019c, International Diabetes Federation, 2017a). In this sub-section, I will provide an overview of clinical guidelines as well as their recommended glycaemic targets for the prevention of complications. The comparison of clinical guidelines is important because their differences could provide insight into potential variations in the approach to diabetes management.

Clinical guidelines suggest that when glycaemic targets are not achieved by lifestyle changes, pharmacological treatment should be added. Optimal treatment for people with T2DM must be based on patients' characteristics (i.e. age, HbA1c) some people may be treated with oral medication whereas others may require insulin or a combination of both oral medication and insulin (American Diabetes Association, 2019c, Inzucchi et al., 2015, World Health Organization, 2016a).

International organisations such as WHO and the International Diabetes Federation (IDF) have encouraged the development and implementation of

national measures for surveillance, prevention and control of T2DM. The development of evidence-based guidelines and protocols are important to define standards of care and to guide HCPs in the achievement of quality of care of individuals (World Health Organization, 2018a, International Diabetes Federation, 2017a). According to the WHO, worldwide 71% of countries have guidelines for diabetes care and management, which are either fully or partially implemented. These evidence-based guidelines, protocols and standards of care for diabetes are essential tools in T2DM management (World Health Organization, 2016a).

A list of guidelines which includes the global guideline developed by the IDF, and those from the US, and the UK are provided in table 1 (International Diabetes Federation, 2012, American Diabetes Association, 2019f, Garber et al., 2019, National Institute for Health and Care Excellence, 2019, Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Scottish Intercollegiate Guidelines Network (SIGN), 2017a). As can be seen in this table, all guidelines have incorporated specific aspects relating to glycaemic control. These aspects are related to glycaemic goals, recommendations on the frequency of glycaemic tests, and algorithms for glycaemic management.

Table 1. Publication date and features related to glycaemic control included in current guidelines from the IDF global guideline, the US, and the UK.

Coverage		Publisher	Year of publication/ last update	Glycaemic goals	Periodicity of glycaemic tests	Algorithm for glycaemic control
Globally		IDF	2012	✓	✓	✓
US		ADA	2019	✓	✓	✓
		AACE/ACE	2019	✓	✓	✓
UK	***England + Wales***	NICE	2019	✓	✓	✓
	Scotland	SIGN	2017	✓	✓	✓

***IDF**= International Diabetes Federation, **ADA**=American Diabetes Association, **AACE/ACE**=American Association of Clinical Endocrinologists and American College of Endocrinologists, **NICE**= The National Institute for health and care excellence, **SIGN**= The Scottish Intercollegiate Guidelines Network*

However, it is important to take into consideration that, although they cover similar aspects related to glycaemic management and control, the approach recommended by different guidelines might vary. Similarly, diversity in healthcare systems and the constant development of clinical guidelines can lead to variation in implementation and patients' outcomes across different countries (Barth et al., 2016, Chastain et al., 2014). Even within one country, the use of guidelines has been shown to vary. For instance, in the US, many physicians revealed that their decisions about glycaemic management were influenced more by medication costs than algorithms and guidelines (Grant et al., 2007). Likewise, another survey conducted in the US indicated that less than half (43%) of the physicians followed the American Association of Clinical Endocrinologists and American College of Endocrinologists (AACE/ACE) guidelines, and 13% did not use guidelines to inform their decisions (Qiu et al., 2015). According to Barth et al. (2016), guideline non-adherence is a rational process that encompasses structural, physician and patient factors where occasional deviation from clinical guidelines is considered appropriate depending on who the patient is and what their personal circumstances are.

In 2013, the IDF published a global guideline, which sought to complement their existing one published in 2012. The guideline *"managing older people with type 2 diabetes"* was released in order to improve the quality of care provided to older people, and emphasised the lack of studies on cost-effective diabetes care for older people (International Diabetes Federation, 2013). Following the IDF publication, in recent years, some guidelines have included a section on the management of T2DM for older adults. The ADA included a specific section for the management in older individuals with T2DM in their 2019 standards of care (American Diabetes Association, 2019e). Similarly, specific recommendations for older adults have been included in the NICE guideline NG28 (National Institute for Health and Care Excellence, 2019).

1.4.1 Glycaemic targets

As observed in table 2, there are slight variations in glycaemic targets depending on the guideline used. For instance, The IDF, the ADA and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines have established 53 mmol/mol (7%) HbA1c as a general goal, while the AACE/ACE has a more stringent goal. However, all agree in following an individualised approach to targets and treatments that may include lifestyle and/or pharmacological interventions (International Diabetes Federation, 2012, International Diabetes Federation, 2013, American Diabetes Association, 2019c, American Diabetes Association, 2019e, National Institute for Health and Care Excellence, 2019, Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

Table 2. HbA1c goals and recommended frequency of glycaemic test in current guidelines from the IDF global guideline, the US, and the UK.

Coverage	Publisher	HbA1c goal(s)	Frequency of glycaemic tests
Globally	IDF	• General goal of: <53 mmol/mol (7%) • Adults using multiple medications including glucose-lowering drugs: 58-64 mmol/mol (7.5-8.0%) • Functionally independent older people: 53-59 mmol/mol (7.0-7.5%) • Functionally dependent older people: 53-64 mmol/mol (7.0-8.0%) • End of life care: the goal is to avoid symptomatic hyperglycaemia • Recommends individualization	• Every 2-6 months depending on blood glucose control and changes in therapy.
US	ADA	• General goal for non-pregnant individuals: <53 mmol/mol (7%) • Patients with lifestyle or metformin only stringent goal <48 mmol/mol (6.5%) • Patients with hypoglycaemia history, with short life	• At least twice a year in patients with optimal control • 4 times a year in those with changing therapy or not

			expectancy or advanced complications less stringent goal <64 mmol/mol (8%) • Older adults with few coexisting chronic illnesses: <58 mmol/mol (7.5%) • Older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence <64-69 mmol/mol (8.0-8.5%) • Recommends individualization	meeting glycaemic goals • The frequency will largely depend on patients' clinical situation.
		AACE/ACE	• ≤48 mmol/mol (6.5%) for patients without serious comorbidities and low risk of hypoglycaemia • >48 mmol/mol (6.5%) for patients with serious comorbidities and at risk of hypoglycaemic • Recommends individualization	• Every 3 months until glycaemic levels are stable
UK		NICE	• <48 mmol/mol (6.5%) for patients with lifestyle modifications only • <53 mmol/mol (7%) for patients on drug treatment • <58 mmol/mol (7.5%) for patients on drug treatment with sub-optimal glycaemic control • Recommends individualization	• Every 3 to 6 months intervals. • 6-months interval once the HbA1c and glucose-lowering therapy are stable. • Tailored to individual needs.
	Scotland	SIGN	• <48 mmol/mol (6.5%) at diagnosis • General goal of <53 mmol/mol (7%)	• Every 3 to 6 months intervals
***IDF**= International Diabetes Federation, **ADA**=American Diabetes Association, **AACE/ACE**=American Association of Clinical Endocrinologists and American College of Endocrinologists, **NICE**= The National Institute for health and care excellence, **SIGN**= The Scottish Intercollegiate Guidelines Network*				

In Scotland, an HbA1c >86 mmol/mol (10%) is classified as sub-optimal glycaemic control, maintaining such levels of HbA1c are described as having health consequences that have been described in section 1.3.4 (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). Thus, attaining and maintaining glycaemic targets is important in the prevention of complications.

1.5 Management of T2DM

As described in the previous section, lifestyle changes, pharmacological treatment, or a combination of both are usual approaches to glycaemic management. Since it is important to understand the reasons why these are recommended and prescribed, the following section summarises current evidence about lifestyle changes and pharmacological treatment for glucose control in people with recently diagnosed T2DM. Moreover, a sub-section about other interventions is also included.

As it will be described through this section, the period after diagnosis is one of the critical points in the management of T2DM. Recent studies have shown the importance of the first years after the diagnosis of T2DM by showing that weight loss during these first years is achievable and can lead to T2DM remission (National Institute for Health Research, 2019).

1.5.1 Lifestyle management

Lifestyle interventions are a key component of management of T2DM. Recommended lifestyle changes include the adoption of a healthy diet and engagement in physical activity (Johnston et al., 2014, Kellow and Khalil, 2013). However, lifestyle management is not only limited to diet and physical activity, it also includes self-management education, diabetes self-management support, counselling for smoking cessation, and psychological care (American Diabetes Association, 2019b).The ADA has described four critical time-points for lifestyle management revision for people with T2DM. These are: at diagnosis, at annual assessments, when complicating emotional, physical or health factors arise, and when transitions in care occur (American Diabetes Association, 2019b). Similarly, the NICE guideline NG28 highlights that at and around the time of diagnosis, structured education should be offered to people with T2DM. Patient education must include individualised advice which emphasises healthy balance eating, increasing physical activity, losing weight and other aspects of lifestyle modification (National Institute for Health and Care Excellence, 2019).

The effectiveness of lifestyle management has been subject to research. For instance, the recently completed Diabetes Remission Clinical Trial (DiRECT) conducted at 49 primary care practices in Scotland and England (Tyneside region) studied the effects of intensive weight management in people with T2DM (Leslie et al., 2016). While there were no specific criteria to be met by the practices, eligible participants had to: be aged 20-65 years, diagnosed with T2DM within the previous 6 years, have a BMI of 27-45 Kg/m^2, and an HbA1c <108 mmol/mol (12.0%). Practices were randomised to provide an evidence-based weight management programme (intervention) or diabetes care by guidelines (control). People in the intervention group were asked to discontinue all oral and antihypertensive medication and follow the weight management programme with the aim of achieving and maintaining at least 15 kg weight loss induced by a low energy formula diet. This diet consisted of an 825-853 kcal/day for three months, followed by structured food reintroduction of 2-8 weeks, and an ongoing structured programme. One of the primary outcomes of the trial was remission of diabetes which was defined as HbA1c <48 mmol/mol (6.5%) after at least two months off all antidiabetic medications, from baseline to 12 months of follow-up (Leslie et al., 2016, Lean et al., 2018). After 12 months of follow-up, remission was achieved in some members of both groups, 68 (46%) in the intervention group and six (4%) in the control group. (Lean et al., 2018). At 24 months of follow-up, 53 people (36%) in the intervention group and five (3%) in the control group were in diabetes remission; OR 25.82 [95% CI 8.25–80.84, p<0.0001] adjusted for study centre, practice size list and random effect for practice. The maintenance of remission status at 24 months was associated, among other factors, with weight loss from baseline and weight change from 12 to 24 months (Lean et al., 2019).

Research on weight loss among people with newly diagnosed T2DM by non-intensive interventions has also been conducted in the UK. The ADDITION-Cambridge trial aimed to quantify the association between behaviour change and weight loss after diagnosis of T2DM, and the likelihood of remission of diabetes at 5-year follow-up. A parallel group cluster RCT was conducted

among 49 practices in England. People aged 40-69 years without a diagnosis of T2DM who had a Cambridge Diabetes Risk Score ≥0.17 were invited to attend a stepwise screening programme for T2DM. People who were identified as having T2DM by this screening programme (n=867) were randomised into either multifactorial treatment (intervention group) or routine care (control group). Multifactorial treatment consisted of more frequent consultations, 30-minutes annual review, three 10-minutes consultation with a GP and nurse, provision of educational materials and guidelines, practice-based academic detailing sessions, and encouraging earlier use of medication to improve control of risk factors. For the routine care group, practices were advised to follow current UK guidelines. Measures were taken at baseline, one- and five-year follow-up, remission was defined as an HbA1c <48 mmol/mol in the absence of any diabetes medication or bariatric surgery. At the end of the 5 years of follow-up, 84% (n=867) participants had weight and HbA1c measured and were included in the analysis. The mean age of participants was 61 ±7 years and 61% were men. At the end of the follow-up period, 55% had initiated GLMs. People who lost >10% body weight in the first year after diagnosis of T2MD were significantly more likely to achieve remission at 5 years compared with those who increased or maintained their body weight; RR:1.77, [CI: 1.32-2.38] adjusted for baseline weight, follow-up period, age, sex, ethnicity, socioeconomic group, education level, occupation, trial group, clustering of practices and date of diabetes diagnosis (Dambha-Miller et al., 2020).

Moreover, the Look AHEAD trial was conducted to examine the effects of weight loss on CVD morbidity and mortality, and to compare an intensive multi-component lifestyle intervention with diabetes support and education. Participants were randomised to receive either intensive lifestyle intervention (ILI) or diabetes support and education (DSE). ILI consisted of an intervention designed to induce weight loss by calorie-intake reduction, increased physical activity and, several individuals and group sessions. DSE consisted of annual group sessions on diet, physical activity and social support. There was not a specific criteria about duration of T2DM, 47.4% and

44.6% of people in the ILI and DSE groups, respectively, were <5 years from diagnosis of T2DM (Look AHEAD Research Group, 2014). In this trial, people with T2DM receiving lifestyle interventions experienced significant improvement in their glycaemic control and reduced their cardiovascular risk factors by reducing their blood pressure and cholesterol levels. Furthermore, high remission rates of T2DM among newly diagnosed patients, those without insulin prescription and with lower initial levels of HbA1c were observed (Johnston et al., 2014). However, it is important to take into account the large amount of support provided to patients in the ILI treatment arm.

Although research which focused on lifestyle interventions amongst people with newly diagnosed T2DM have shown promising results, in a real-life scenario lifestyle changes have shown to be very difficult to achieve. Qualitative research has provided insight into the challenges that patients may experience in adhering to lifestyle recommendations. The literature which has focused on patients' perspectives is vast, and hence only a brief overview will be provided here.

Thoolen et al. (2008) conducted a systematic review to examine how recently diagnosed patients adjust to living with T2DM during the first year of their disease and to investigate variations in patient's psychological adjustment, particularly on factors surrounding diagnosis, which could influence patients' subsequent reactions. The search was conducted in four databases, articles in English published between 1993 and 2008 which focused on T2DM and their outcomes during the first year after diagnosis were included. A total of 32 articles were included; these articles reported the findings from 24 different studies (qualitative and quantitative). Overall, the authors reported that very few people with newly diagnosed T2DM successfully achieved lifestyle changes. A major factor that seemed to influence patient's adjustments to T2DM was the presence, or absence, of symptoms and whether they experience their symptoms as such. Thus, patients who did not experience symptoms or did not feel "ill" felt that they could continue with

their unhealthy lifestyles. Moreover, the authors described that many patients did not fully understand the impact of having T2DM, however, they were interested in receiving information about changes they could integrate to their lifestyle. The authors concluded that successful adjustment in the first year after diagnosis was not necessarily related to lack of emotional distress, and emphasised the role of HCPs and the need for looking beyond emotional reactions and consider patients' perceptions of their disease and how they adapt and engage in self-care activities (Thoolen et al., 2008).

Furthermore, Frost et al. (2014) conducted a qualitative synthesis of T2DM self-management strategies for long term medical outcomes and quality of life in the UK. The synthesis included 22 articles published between 2000 and 2013 which described four different studies. After analysing the articles, the authors stated that, for people with T2DM, the emphasis of treatment on biomarkers was often perceived as unachievable and burdensome and recommended to rather place emphasis on small patient-centred goals (i.e. portion control, weight loss) that patients perceive as achievable. The authors highlighted the need to facilitate ongoing open dialogue in usual practice in order to achieve sustainable changes (Frost et al., 2014).

1.5.2 Pharmacological treatment

Non-insulin glucose-lowering drugs are the most frequent pharmaceutical treatment for T2DM and may be used as monotherapy, in combination or with insulin (Higgins et al., 2016b, Mata-Cases et al., 2016). There are several classes of medications for T2DM treatment. In this sub-section I will present the main mode of action of first-line pharmacological agents for glucose control included in the SIGN guideline 154, and which are the most frequently prescribed to people with newly diagnosed T2DM (Scottish Intercollegiate Guidelines Network (SIGN), 2017b). Furthermore, a brief account on second- and third-line drugs for glucose control will be presented.

1.5.2.1 First-line glucose lowering medication

In the UK, first-line medication for T2DM has changed in recent years, shifting from sulfonylureas to metformin (Hamada and Gulliford, 2015).

Sharma et al. (2016) reported that overall, in people with T2DM who received GLM, metformin prescription increased from 55.4% in 2000 to 83.6% in 2013 and sulfonylureas decreased from 64.8% to 41.4% in 2000 and 2013, respectively. Initial treatment in people recently diagnosed with T2DM followed a similar pattern. In 2000, 51.1% were prescribed sulfonylureas as the initial drug, and 45.1% were prescribed metformin as first-line drug therapy, whereas by 2013 91% of people with a recent diagnosis of T2DM who received drug therapy were started on metformin and 6.3% with sulfonylurea. However, the study did not consider differences in prescribing patterns according to patients' characteristics such as age or comorbidities. Moreover, treatment choices seemed to be in accordance with UK guidelines that, from 2000, recommended metformin as first-line drug treatment (Sharma et al., 2016).

1.5.2.1.1 Metformin

Metformin is one of the most effective and safe drugs and is recommended as an initial pharmacological agent when it is not contraindicated, or the patient can tolerate taking it (American Diabetes Association, 2019d, International Diabetes Federation, 2017a, Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

Metformin has been used as a GLM for approximately 60 years (it was introduced as GLM in 1959) and it is the only available biguanide currently in clinical use (White, 2014, Schernthaner and Schernthaner, 2007). The major action of metformin is to decrease hepatic glucose output by decreasing gluconeogenesis and, to a lesser extent, by increasing glucose uptake by skeletal muscles. Hence, metformin helps in reducing hepatic glucose production and gastrointestinal absorption of glucose and improves peripheral sensitivity to insulin. However, the insulin-sensitising effect is reported as smaller compared with other agents such as thiazolidinediones, which will be described below (Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Schernthaner and Schernthaner, 2007, Manolopoulos and Ragia, 2014).

In general, metformin has a high level of acceptance and relatively low cost, it does not produce weight gain, which is a benefit for overweight patients. However, there is no strong evidence about benefits for cardiovascular morbidity and mortality. The side-effects more frequently reported are gastrointestinal, such as diarrhoea and abdominal discomfort and its use is not recommended in people with renal impairment (Schernthaner and Schernthaner, 2007, Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Bianchi et al., 2018).

1.5.2.1.2 Sulfonylureas

The introduction of sulfonylureas to the market dates from the 1950s when the first-generation became available for glycaemic control (White, 2014). Currently, sulfonylureas are an alternative approach to metformin in the presence of osmotic symptoms or intolerance to metformin and should also be considered as add-on second-line treatment. First-generation sulfonylureas such as tolbutamide and chlorpropamide are now rarely used. Second-generation like glibenclamide, glipizide, gliquidone, glimepiride and gliclazide are currently used more frequently (Stingl and Schernthaner, 2007, American Diabetes Association, 2019d, Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

Sulfonylureas help to reduce blood glucose levels by increasing the endogenous release of insulin from β-cells in the pancreas. Although these drugs have high efficacy and are available at low cost, their use is associated with weight gain and hypoglycaemia. Thus, sulfonylureas should be used with caution (Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Bianchi et al., 2018).

When metformin and sulfonylureas are not tolerated, the following are also accepted by the Scottish Medicine Consortium for first-line use: sodium-glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones (Scottish Intercollegiate Guidelines Network (SIGN), 2017b). An overview of these drugs will be provided in the following sub-sections.

1.5.2.1.3 SGLT2 inhibitors

SGLT2 inhibitors are a novel and recent group of agents, these work by reducing renal glucose re-absorption from the tubular lumen in the kidney, which results in increased glucose excretion (Bailey and Krentz, 2017, White, 2014). Currently, there are three drugs licensed in this class: canagliflozin, dapagliflozin, and empagliflozin. The SIGN guideline 154 recommends SGLT2 inhibitors as monotherapy when metformin is contraindicated, not tolerated and when diet and exercise alone are not sufficient to control glucose levels, and only if a DPP-4 inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate (Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

Empagliflozin and canagliflozin have proven cardiovascular benefit, thus, in people with T2DM and CVD, the use of SGLT2 inhibitors should be considered. Moreover, the use of SGLT2 inhibitors has been associated with other benefits such as weight loss, blood pressure reduction, uric acid reduction, and low risk of hypoglycaemia. However, since SGLT2 inhibitors efficacy depends on plasma glucose levels and rate of glomerular filtration, in people with moderate renal impairment the efficacy is reduced. Moreover, some adverse-effects like genital mycotic infections, diabetes ketoacidosis, bone fracture, and lower-limb amputation have been reported (Bianchi et al., 2018, Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

1.5.2.1.4 DPP-4 inhibitors

Research into DPP-4 inhibitors began in the 1990s, however, the introduction of the specific inhibitors to the market was not until the late 2000s with the introduction of sitagliptin in 2007 (Bailey and Krentz, 2017). These drugs inhibit DPP-4 enzyme hence resulting in prolonged active incretin levels with consequent increased insulin synthesis and release, and decreased glucagon secretion. There are four DPP-4 inhibitors currently available: alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin. However, only linagliptin, sitagliptin and vildagliptin are accepted for use as monotherapy by the Scottish Medicine Consortium and should be considered for people for

whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance (Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

Overall, DPP-4 inhibitors are considered to have a good safety profile. These drugs are associated with low risk of hypoglycaemia and are also reported to be weight neutral and can be used, with a dose adjustment, in people with kidney impairment. However, their use is contraindicated in people with previous pancreatitis. Research about DPP-4 inhibitors on cardiovascular safety has shown that, with the exception of saxagliptin and alogliptin, they do not increase cardiovascular events (Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Bianchi et al., 2018).

1.5.2.1.5 Thiazolidinediones

The glucose-lowering effect of thiazolidinediones was reported in the early 1980s, the first agent troglitazone was available in the UK only for a few weeks in 1997 and was withdrawn for being associated with hepatoxicity. Two other agents, rosiglitazone and pioglitazone were introduced in Europe in 2000. However, after data indicating an increased risk of heart failure, rosiglitazone was withdrawn (Bailey and Krentz, 2017).

Thiazolidinediones increase adipose and muscle insulin sensitivity by activating nuclear receptors and promoting esterification and storage of free fatty acids in subcutaneous adipose tissue. The only drug in this class authorised in the UK is pioglitazone (Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Bianchi et al., 2018). However, the use of pioglitazone as monotherapy is restricted for people who have experienced hypoglycaemia or in whom metformin and sulfonylureas are contraindicated or not tolerated (Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

There is currently lack of evidence to draw conclusions on its effect on cardiovascular outcomes. However, the use of pioglitazone has been associated with weight gain, peripheral oedema, bone fracture, heart failure, and bladder cancer. Thus, its use should not be considered in people with

heart failure, and should be considered usually as dual or triple therapy (Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

1.5.2.2 Second-line and third-line drugs

As previously stated, guidelines vary in relation to HbA1c targets. However, all recommend that when HbA1c targets are not achieved with metformin monotherapy, HCPs should consider a combination of metformin and one of the following treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, glucagon-like peptide 1 (GLP-1) receptors agonists, or basal insulin (American Diabetes Association, 2019d, Garber et al., 2019, National Institute for Health and Care Excellence, 2019, Scottish Intercollegiate Guidelines Network (SIGN), 2017b). Furthermore, as a result of the progressive nature of the disease, it is recognised that many people with T2DM will eventually require insulin therapy (American Diabetes Association, 2019d).

1.5.3 Other interventions

Obese adults with T2DM should be offered individualised interventions to encourage weight loss such lifestyle interventions and, in some cases, bariatric surgery (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). In this sub-section I will address surgery to improve metabolic control and provide a summary on the evidence related to intensive glycaemic control.

1.5.3.1 Bariatric surgery

The weight loss after a bariatric surgery has also reported as being associated with T2DM remission. In the UK, the clinical guideline CG189 for obesity indicates that people with less than 10 years of T2DM diagnosis and with a BMI of $\geq$35 Kg/m^2 should be considered for bariatric surgery, as long as they are receiving or will receive assessment in a tier three service (specialist service) (National Institute for Health and Care Excellence, 2014).

A meta-analysis conducted by Yan et al. (2014) analysed data derived from eight studies of people with T2DM (N= 1,247) who underwent bariatric surgery. The authors reported a positively significant association between %

excess weight loss and T2DM remission (random model weighted mean differences = 9.73, 95 % CI: 4.73–14.74, p < 0.01). Remission was defined as the cessation of GLM and different glycaemic thresholds, which ranged from HbA1c of <5–6, 6.5, or 7% and FPG of <100 or <124 mg dL depending on the study. (Yan et al., 2014).

Moreover, Sheng et al. (2017) conducted a systematic review and meta-analysis with the aim to evaluate the long-term ($\geq$ 5 years) outcomes of bariatric surgery on diabetes remission, microvascular and macrovascular events, and mortality among people with T2DM. The authors reported the results from ten articles, one RCT and nine cohorts. However, the pooled estimates only included the nine cohort studies. The selection criteria included articles that either targeted or had a subgroup analysis of people with T2DM, reported at least one of the outcomes of interest, and were followed-up for at least five years. All the studies included men and women, and the comparison group consisted of people who were given non-surgical treatments for T2DM (i.e. GLM and/or lifestyle modifications). One study included only people with BMI $\leq$ 35 Kg/m^2, two studies included people with BMI <35 Kg/m^2, and six included only people with BMI $\geq$ 35 Kg/m^2. The meta-analysis showed that people in the surgery group had higher rate of diabetes remission compared with those in the non-surgical treatment group (RR = 5.90; 95% CI = 3.75–9.27). Furthermore, the authors reported no significant heterogeneity across studies (Q = 0.04, I 2 = 0%), and no publication bias as suggested by the funnel plots and Egger's test (P = 0.36). For the RCT, the authors reported that at year five the surgery group (intervention) had 50% remission rate while the non-surgical group (control) had 0%.

Thus, the evidence provided by such studies shows that weight loss has the potential to improve glycaemic control among people with T2DM. As mentioned above, bariatric surgery is available on the NHS for people with T2DM who meet certain criteria such as having a BMI $\geq$35, have attempted and struggle to lose weight with diet and exercise and agree to the long-term

follow-up after the surgery (NHS, 2017). However, bariatric surgery may have side effects such as malnutrition, gallstones, among others (NHS, 2017).

1.5.3.2 Intensive glycaemic control

This section will discuss some studies that have looked at the effects of intensive glycaemic control for people with T2DM. The definition of *intensive glycaemic control* was different depending on the study; however, it generally relates to the prescription of pharmacotherapy and the achievement and/or maintenance of HbA1c levels <42 mmol/mol (6%). I will focus on briefly describe results from ad-hoc selected RCTs conducted in people with newly diagnosed T2DM carried out to determine the effect of tight or intensive glycaemic control on β-cell function and glycaemia and/or cardiovascular risk and reduction of complications. I will also summarise the outcomes of other studies such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and describe two meta-analyses of RCTs on the effects of intensive glycaemic control effects. These did not focus on people with newly diagnosed T2DM however, results from such research are presented here because of the role that they have had in informing clinical guidelines for the management of diabetes (American Diabetes Association, 2019c, Scottish Intercollegiate Guidelines Network (SIGN), 2017a, Scottish Intercollegiate Guidelines Network (SIGN), 2017b), and to provide an overview of benefits and potential harms of an intensive approach to glycaemic control.

The KIIT trial, conducted in Korea, aimed to determine the effects of early intensive glycaemic control; with intensive insulin treatment (IIT) or initial combined oral antidiabetic drug (COAD) therapy; on long-term glycaemic control and the preservation of β-cell function in people with newly diagnosed T2DM. Participants were included if aged 25 to 70 years, diagnosed with T2DM within the previous 12 months and whose HbA1c levels were between 64mmol/mol and 108 mmol/mol. People with contraindication to insulin, oral agents, retinopathy, chronic liver disease, renal dysfunction, heart disease,

pregnant women and chronic conditions requiring long-term use of glucocorticoid treatment were excluded. A total of 112 individuals were randomised to either the IIT group or the COAD group. For a maximum of 12 weeks, participants in the IIT group had their insulin titrated every three days or two weeks based on the results of self-monitoring of blood glucose, FPG and HbA1c levels, while participants in the COAD group received standard doses of glimepiride and metformin which were titrated every two weeks based on glucose levels. After this period, participants with HbA1c $\leq$64 mmol/mol were instructed to change their treatment to lifestyle modification alone for four weeks. Then, if after these four weeks, their HbA1c was $\leq$53 mmol/mol lifestyle modifications were continued; otherwise, GLMs (COAD group schedule) was introduced. Participants' mean age and duration of T2DM were 46.9$\pm$10.1 years and 0.8$\pm$2.1 months, and 48.4$\pm$10.4 years and 0.6$\pm$1.6 months for the IIT and the COAD groups, respectively. After the intervention period, participants were followed-up for up to 104 weeks. The authors reported that 53.3% of participants in the IIT group and 18.8% in the COAD group were drug-free and considered in remission. The Cox regression analysis showed that the initial intensive treatment method was an independent attributable factor drug-free glycaemic remission. However, these results must be interpreted with caution because, in both groups, the mean BMI at baseline was relatively low, 26.9$\pm$7.3 and 25.1$\pm$3.3 Kg/m^2 for the IIT and COAD groups, respectively (Chon et al., 2018).

Similar studies have been conducted in other countries. For instance, a RCT conducted in the US aimed to assess the efficacy of early intensive diabetes therapy with either insulin plus metformin (INS) or triple oral therapy (TOT) with metformin, glyburide, and pioglitazone on glycaemic control and β-cell function. People with newly diagnosed T2DM (in the previous two months) who were drug-naïve and were aged 21 to 70 years were recruited. All participants (n=63) were randomised to either INS or TOT and followed-up for six years, completion rates were 66% and 55% for the INS and the TOT group, respectively. The mean age of participants was 44.9$\pm$10.1 years, 36% were female. At 6 years, 63.2% in the INS and 68.8% in the TOT had HbA1c

≤53 mmol/mol. β-cell function remained stable for both groups, insulin sensitivity decreased in both groups, no significant change in total cholesterol, LDL or triglycerides were reported. Moreover, the authors reported an overall low rate of mild hypoglycaemia and 24% of treatment failure (HbA1c >64 mmol/mol). The authors concluded that early intervention after diagnosis has the potential to stabilise β-cell function (Harrison et al., 2014).

The ADVANCE trial was designed to assess the effects on major vascular outcomes of lowering the HbA1c to a target of 6.5% or less in people with T2DM. The trial started in 2001 and counted with centres in Asia, Europe, North America, and Australasia. Participants were eligible if they had a diagnosis of T2DM at 30 years or older, an age of at least 55, and a history of major macrovascular or microvascular disease or at least one other risk factor for CVD. A total of 11,140 participants were randomly assigned to receive therapy with either perindopril and indapamide or matching placebo and to undergo either a strategy of intensive glycaemic control (intervention) or standard glucose control (control). Mean age for both groups was 66±6 years, mean duration of diabetes and HbA1c was 7.9±6.3 years and 7.51%, and 8±6.4 years and 7.52% for the intervention and control groups, respectively. Participants in the intervention group (n=5,571) were given gliclazide and required to discontinue any other sulfonylurea, those in the control group (n=5,569) who were using gliclazide were required to substitute it with another sulfonylurea. Follow-up was at week two, and months one, two, three, four and six, and every three months thereafter for the intervention group. For the control group follow-up was at three, four, and six months, and every six months thereafter; the median duration of follow-up was five years. After the follow-up period, the intervention group had a mean HbA1c of 6.5%, the control group a mean of 7.3%. Moreover, mean systolic blood pressure was lower in the intervention group (135.5 vs 137.9 mmHg), mean body weight was greater in the intervention group by 0.7 Kg. Major macrovascular or microvascular events were 18.1% in the intervention group and 20% in the control group; compared with the control group, there was a

statistically significant reduction of major microvascular events in the intervention group (HR: 0.86, CI: 0.77-0.97) but not in the incidence of major macrovascular events. Moreover, as compared with the control group, there was a significant reduction in renal events in the intervention group (HR:0.79; CI: 0.66-0.93) and new-onset microalbuminuria (HR:0.91; CI: 0.85-0.98). However, more people in the intervention group than in the control group were hospitalised for any cause (44.9% vs 42.8%), with some of the excess of hospitalisations due to severe hypoglycaemia (OR:1.52; CI:1.01-2.28). Severe hypoglycaemia occurred more frequently in the intervention group than in the control group (The ADVANCE Collaborative Group, 2008).

The ACCORD trial in North America studied the effects of strict and standard glycaemic control on cardiovascular events. In this study, people with T2DM were recruited if they were (a) aged 40–79 years and had CVD or if were aged 55–79 years and there was evidence of atherosclerosis, albuminuria, ventricular hypertrophy or two risk factors for CVD, (b) had HbA1c $\geq$58 mmol/mol (7.0%) and, (c) their BMI was $\leq$45 Kg/m^2. A total of 10,251 were included; mean age was 62.2 years, mean HbA1c 67 mmol/mol and mean BMI 32.2 Kg/m^2. Participants were randomised to either strict glycaemic control (intervention) with a target HbA1c of 47.5 mmol/mol (<6.5%) or a standard (control) HbA1c goal of 53-62.8 mmol/mol (7-7.9%). Those assigned to intensive glycaemic control had a greater frequency of hypoglycaemia and relative increased mortality of 22% as compared to standard therapy (The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). Post-trial analyses revealed that patients who had high HbA1c levels had higher mortality (Punthakee et al., 2014). Further analysis adjusted by selected baseline patient characteristics and treatment received showed that a greater decrease of HbA1c was associated with a lower risk of death, where 1% of HbA1c increase was associated with 22% increased risk of death (Riddle et al., 2010). Furthermore, patients who were randomised to receive strict glycaemic control and had a pre-transition (the last measure on or before treatment relaxation) HbA1c <6.5% were more likely to maintain

lower HbA1c levels after one year of treatment relaxation (Punthakee et al., 2014).

The UKPDS was a RCT conducted which aimed to determine the effect of intensive glycaemic control on the incidence of complications in people with T2DM (King et al., 1999). People with newly diagnosed T2DM (n= 3,867; 58% male) were recruited from 23 hospitals between 1977 and 1991. Participants were eligible if aged 25-65 years (mean age: 54; IQR 48-60 years) and had FPG >6 mmol/L on two mornings, 1–3 weeks apart. Mean FPG was 8.0 mmol/L (7.1–9.7), HbA1c 53.9 mmol/mol (SD $\pm$8.6). Participants were randomised to either receive conventional treatment (control) or intensive treatment (intervention). People in the control group were initially on diet only (dietician advice every three months) with the aim of maintaining FPG <15 mmol/L. However, if hyperglycaemia or symptoms occurred, people were initiated on sulfonylurea, metformin or insulin. People in the intervention group were treated with GLM (sulfonylureas or insulin) to maintain FPG <6 mmol/L and received dietary advice. After following-up the cohort for 10 years, a lower median HbA1c was reported in the intensive treatment group (treated with pharmacological treatment) than in the conventional group (initial treatment with diet). Moreover, people assigned to intensive treatment had a 25% risk reduction in microvascular disease compared to people in the conventional group. However, hypoglycaemic episodes were more frequent among people in the intensive treatment arm, particularly amongst those who received insulin therapy (UK Prospective Diabetes Study (UKPDS) Group, 1998).

Additionally, post-trial analysis of the UKPDS cohort showed beneficial effects of intensive glycaemic control. The reduction in the relative risk of microvascular disease continued during the post-trial period for patients in the sulfonylurea-insulin group. Similarly, patients in the metformin group, as compared with conventional therapy, had a reduction in the relative risk of myocardial infarction and death from any cause. This reduction was maintained throughout the post-trial follow-up period (Holman et al., 2008). It

is important to note that the diagnostic criteria for T2DM used in the UKPDS trials were different (FPG ≥7.8 mmol/L) than the criteria now used (World Health Organization, 1985). Moreover, the inclusion criteria in the UKPDS and other RCTs such as the ACCORD and ADVANCE have limited external validity as it does not reflect the contemporary British population with T2DM (Saunders et al., 2013). Saunders et al. (2013) described the proportion of people with T2DM living in Scotland who met the eligibility criteria of such RCTs. In relation to the UKPDS trial, the authors reported that a maximum of 51% of people with newly diagnosed T2DM in the Scottish population were eligible for inclusion in the trial. Patients' data in Scotland were drawn from the SCI-Diabetes – start of 2008 extract.

Further analyses of these trials and similar RCTs have been conducted in order to evaluate both treatment approaches. For instance, a meta-analysis by Hemmingsen et al. (2011) reported no significant difference between intensive and standard glycaemic therapy for all-cause and cardiovascular mortality but a reduction of non-fatal myocardial infarction, retinopathy and microvascular (as composite outcome) in the intensive therapy group. However, there was a 30% increase in relative risk of severe hypoglycaemia for the intensive therapy group compared to the standard treatment group. The length of follow-up of the studies included ranged from four months to 12 years; median follow-up time was not provided by the authors.

Likewise, Sardar et al. (2015) conducted a meta-analysis from 17 RCTs, which set out to examine regional variations in the efficacy and safety of intensive glycaemic control treatment in people with T2DM. Mean duration of follow-up was 5.1 years in North America and 4.1 years in the rest of the world. The authors reported no significant differences between intensive or standard glucose therapy for all-cause mortality and cardiovascular mortality. However, an interaction, depending on the region where the RCTs were conducted, was found. While RCTs in North America resulted in a significantly higher all-cause mortality and cardiovascular mortality for patients in the intensive than standard therapy arm, RCTs from the rest of the

world showed a non-significant difference. However, further analysis of data from the post-trial period showed significantly lower all-cause mortality for the intensive therapy patients (Sardar et al., 2015). Thus, country-specific factors may play a role in patients' outcomes following intensive glycaemic control.

Overall, RCTs studying the effects of intensive vs standard glycaemic control for people with T2DM have reported lower HbA1c levels for people receiving intensive treatment, even during the post-trial period; however, results for mortality have been inconsistent. Therefore, the benefits of intensive glycaemic control are not conclusive and may not outweigh the potential harms to patients. As a consequence, intensive glycaemic therapy to reach tight HbA1c targets in diabetes care is not supported by the evidence (American Diabetes Association, 2019c, Hemmingsen et al., 2011, Sardar et al., 2015).

1.6 Diabetes care in Scotland

As stated in section 1.4, the development of guidelines and approaches to T2DM care can differ depending on the country and may contribute to variation in diabetes outcomes (International Diabetes Federation, 2017b, Sardar et al., 2015). Therefore, in the following sub-sections, I will focus on the provision of T2DM care in Scotland, as this is the location where the data from this study originated and was collected.

People with T2DM are recommended to receive at least annual monitoring; in Scotland, this work is now mostly done outside hospitals in primary care (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). Primary care includes services provided in the community commonly by HCPs such as GPs or nurses, or allied healthcare professionals such as pharmacists, physiotherapists, midwives and occupational therapists (ISD Scotland, 2010, Scottish Government, 2018). Most care for people with T2DM is performed by GPs and nurses working in primary care. The majority of general practices are independent contractors constituted of GPs, practice-employed nurses,

that vary in size and composition of their workforce (Murrels et al., 2013, ISD Scotland, 2018b).

1.6.1 Healthcare professionals' role in diabetes care

HCPs are in regular contact with a large proportion of the population, which place them in an ideal position to provide lifestyle counselling and advice for prevention of T2DM and its complications (Geense et al., 2013, Pikala et al., 2011, Rubio-Valera et al., 2014). Every HCP contributes to the healthcare team with the relative contributions of nurses and doctors varying in different settings. Physicians are often responsible for prescribing, and traditionally their role has been recognised as a coordinator of care for people with T2DM, particularly for patients with comorbidities (Lo et al., 2016, Zenzano et al., 2011)

However, some countries, such as the UK have provided nurses with the legal authority to prescribe. The number of nurses prescribing varies considerably across health boards within the UK (Courtenay, 2018). In Scotland, the *"Primary Care Workforce Survey Scotland 2017"* reported that 12% of nurses were Nurse Practitioners who have completed additional education and have been enabled to prescribe (ISD Scotland, 2018b). Overall, nurses have had increasing participation in primary care in Scotland, whereas in 2013, it was reported that total GP consultations decreased by 1.4% while practice nurses' consultations rose by 31% compared to 2012. Furthermore, diabetes ranked as the sixth most common reason to consult a GP or a practice nurse; the majority of the consultations were with a nurse rather than a GP (National Statistics Scotland, 2013)

1.6.2 Structured education programmes

In the UK, structured education programmes for people with T2DM are available to support self-management. Currently, there are some courses available such as "Diabetes Education and Self-Management for Ongoing and Newly Diagnosed Type 2 diabetes" (DESMOND), X-PERT, Freedom 4 life, and Hypo Program. However, some programmes such as *Freedom 4 life*

are offered only in specific areas (Wiltshire) or are focused on particular aspects of diabetes, such as *Hypo Awareness Program*, which aims to improve people's knowledge of hypoglycaemia symptoms, particularly those who take insulin, sulfonylureas or glinides (Diabetes.co.uk, 2019a, Diabetes.co.uk, 2019b, Diabetes.co.uk, 2019c).

In Scotland, the SIGN guideline 116 indicates that adults with T2DM should have access to structured education programmes (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). The DESMOND programme started as a RCT in 2008 and was rolled out country-wide after achieving positive outcomes such as greater improvements in weight loss, smoking cessation and increasing understanding of diabetes in the intervention as compared to the usual care arm (Davies et al., 2008). DESMOND is available in some health boards in Scotland for people with T2DM, and usually, practices refer people with newly diagnosed T2DM directly to a DESMOND coordinator. Currently, the programme offers nine sessions monthly across Edinburgh, East, Mid and West Lothian and can be attended in either one full day or two half days (DESMOND Project, 2019).

1.6.3 Quality and Outcome Framework

As will be described in Chapter 3, the cohort analysis included data from 2004 to 2012, a period in which the Quality and Outcome Framework (QOF) was operating. Therefore, here I briefly introduce the QOF and the approach that has replaced it. The QOF was a pay-for-performance scheme introduced in April 2004 across the UK. It measured achievement of indicators, with points and payments awarded to the general practices depending on their level of achievement.

In Scotland, QOF was decommissioned in April 2016 (ISD Scotland, 2016c, Roland and Guthrie, 2016). The removal of QOF was seen as an opportunity to focus on disease prevention and increase shared decision-making and a personalised approach. Thus, increased patient involvement is sought by

focusing on their needs and preferences (Royal College of General Practitioners, 2016, Royal College of General Practitioners, 2019).

The QOF indicators covered four domains which were clinical, public health, quality and safety, and medicines management. Clinical indicators related to processes and outcomes of health conditions such as diabetes and other chronic diseases. Public health included indicators such as blood pressure and smoking. Quality and safety consisted of indicators related to outpatient referrals. Medicines management included indicators on meetings with NHS Board prescribing advisers and medication review for patients. Concerning diabetes, the last list of QOF indicators in 2015/2016 for Scotland included, among the clinical indicators, the proportion of patients on the register who had HbA1c levels under certain targets. The achievement of a range threshold for each target awarded points to practices for payment (ISD Scotland, 2016d). For HbA1c, targets were <59 mmol/mol (7.5%), <64 mmol/mol (8.0%), <75 mmol/mol (9.0%), and the corresponding points and range threshold for each were 17, 8, 10 points and 40-50%, 45-70%, and 50-90%, respectively. Likewise, practices received a maximum of 11 points if 40-90% of people with newly diagnosed diabetes had been referred to a structured education programme within nine months after entry to the register (ISD Scotland, 2016b).

In comparison to prior years, QOF's first year of implementation showed a considerable improvement in the quality of diabetes care, and in its last year, the average achievement for diabetes indicators was 98.1% (Guthrie and Tang, 2016, National Statistics Scotland, 2016). However, despite the positive changes which included diversification of nurses' role and teamwork, the incentives to adhere to guidelines was one of the major criticisms of the QOF. The financial incentives, which were calculated based on the number of points achieved by the practice, were judged as a potential drawback in person-focused care by becoming less personal, 'tick-box' medicine. (Gillam, 2010, Guthrie and Tang, 2016).

NHS Scotland's new approach to improving the quality of care after the discontinuation of QOF is by forming GP clusters. A GP cluster typically comprises five to eight GP practices, which are in similar geographical areas. The purpose of this approach is to 'encourage GPs to take part in quality improvement activity with their peers and contribute to the oversight and development of their local healthcare system' (ISD Scotland, 2016a). Thus, led by GPs, clusters of practices are meant to collaborate in order to prioritize relevant areas for planning, quality control and quality improvement (Royal College of General Practitioners, 2016, Roland and Guthrie, 2016). However, the effect of this new approach on quality of care and outcomes for people with T2DM is not clear. This change in policy, and the current variability between GPs prescribing rates; reasons for which are not yet clear (Royal College of General Practitioners, 2016); offer opportunities for research to describe and explore the effect diabetes management and treatment decisions both before and after the new policy was introduced.

1.7 Summary

Sub-optimal glycaemic control leads to an increased risk of microvascular and macrovascular complications. Although optimal glycaemic control helps reduce the risk of complications, intensive glycaemic control can be unsafe for some people and targets should be tailored to each patient (International Diabetes Federation, 2012).

As indicated in section 1.5, the time of diagnosis and of the annual assessments have been recognised by the ADA as two of four critical time points for optimal management of T2DM; the other two time points being when new complications develop, and when transitions in care occur. At diagnosis, people with T2DM usually experience the challenge of integrating diabetes management into their daily lives. Thus, this time point provides an opportunity for HCPs to assess barriers to treatment and to establish glycaemic targets; although these targets must be individualised (American Diabetes Association, 2019b, American Diabetes Association, 2019c, Thoolen et al., 2008, Frost et al., 2014).

After diagnosis of T2DM, guidelines recommend that lifestyle modifications should be the first step to take for glycaemic management and treatment modifications such as drug treatment initiation or intensification should be based on HbA1c levels (International Diabetes Federation, 2012). Currently, clinical guidelines recommend a higher HbA1c target for certain clinical groups and older people with T2DM. Most guidelines, including the Scottish SIGN guidelines, have established a general HbA1c goal of 53 mmol/mol (7%) (International Diabetes Federation, 2017b, Inzucchi et al., 2015, Scottish Intercollegiate Guidelines Network (SIGN), 2017b)

In Scotland, most of diabetes care is done in primary care by HCPs such as GPs or nurses (Murrels et al., 2013, ISD Scotland, 2018b). Nurses' participation in diabetes care in primary care has increased over the years, the activities that nurses currently perform range from provision of education to prescription of pharmacological therapy (National Statistics Scotland, 2013). Furthermore, in Scotland, some people with T2DM have the opportunity to receive additional education via structured education programmes such as DESMOND (DESMOND Project, 2019).

From 2004 to 2016, the QOF operated in Scotland. During this, practices were financially rewarded, in a point-system scheme, for the achievement of clinical indicators (ISD Scotland, 2016d). One of the major criticism of the QOF was the perceived lack of person-centred care (Guthrie and Tang, 2016, Roland and Guthrie, 2016). After QOF's decommission, "GP clusters" are responsible for reviewing and improving quality of care in Scotland (ISD Scotland, 2016a).

The study of people with T2DM represents an opportunity to improve T2DM management and inform practice using real-world data (RWD), which is defined as data generated during routine clinical practice rather than collected in the context of a RCT (Berger et al., 2017). The use of RWD, which generates real-world evidence, has been recognised as playing an important role in the evaluation of epidemiology, treatment patterns, compliance, and health outcomes of different treatments (Mahajan R., 2015,

Berger et al., 2017, McDonald et al., 2017). Studies using RWD may have a wide range of outcomes. However, the evidence generated by RWD traditionally comprise clinical and demographic information which lack the perspectives and experiences of patients and HCPs (McDonald et al., 2019).

Thus, in the next chapter, I will describe the findings from my review of the literature, which included quantitative and qualitative studies, and focused on two main broad areas: (1) prescription patterns of GLM and time to drug treatment initiation in people recently diagnosed with T2DM, and (2) HCPs' perspectives and experiences in providing care to people with T2DM, particularly about factors influencing clinical decision-making. The decision to focus the literature search on GLM initiation in people with newly diagnosed T2DM was based on the sensitive period that the time after diagnosis represents in patients' lives and the future of their treatment. As described in this chapter, the period soon after diagnosis is recognised as crucial for optimal management of T2DM. Actions taken at this point may affect the person's quality of life in the long-term, and attempts at improving the glycaemic control of people with T2DM must be prioritised (International Diabetes Federation, 2017b, American Diabetes Association, 2019c).

Chapter 2 Literature Review: management of T2DM

2.1 Introduction

In this chapter, I will present the findings of a literature review focused on the management of T2DM with a particular focus on GLM initiation in people with T2DM. As described in the previous chapter, the first approach to managing T2DM varies between guidelines, and there is no international consensus on whether to start management of T2DM with lifestyle changes alone or in combination with GLM.

However, clinical guidelines highlight that the adoption of a healthy lifestyle is central to effective diabetes management and should be emphasised in the initial comprehensive medical evaluation after diagnosis. Attaining and maintaining clinically recommended levels of blood glucose at an early stage is crucial for the prevention of T2DM complications. Moreover, clinical guidelines recommend that targets and therapies should be adapted to meet patients' circumstances and needs (International Diabetes Federation, 2017b, American Diabetes Association, 2019b).

2.1.1 Aims

The purpose of this literature review is to identify, critically appraise and synthesise the relevant published quantitative and qualitative research relevant to GLM initiation in people with T2DM. The specific aims are as follows:

1. To describe glucose-lowering prescriptions patterns, identify factors associated with glucose-lowering treatment initiation in people with T2DM, and describe clinical inertia in the context of T2DM.
2. To explore and describe HCPs' reasons for their choice of treatment (lifestyle interventions and/or pharmacological therapy) following the diagnosis of T2DM.

These aims cover broad themes that are important to understand GLM initiation in people with T2DM. However, the reason for having such broad aims is because the initial scoping review showed insufficient literature focusing on glucose-lowering initiation in people recently diagnosed with T2DM and studies focused on reasons for initiating GLM in those newly diagnosed.

2.1.2 Overview of methods

At my first-year PhD review, after discussion with the panel and supervisors and, considering the scope and timescale of the PhD research, I decided to conduct a systematic search and literature review instead of a systematic review in recognition that I would not be able to draw upon time and human resources (a second reviewer) to conduct two full systematic reviews.

Grant and Booth (2009) have identified and characterised 14 different types of reviews commonly used. The authors indicate that although both *systematic reviews* and *systematic search and reviews* aim for an exhaustive comprehensive searching, there are some differences between them. Therefore, before moving onto the two main sections of this chapter it is important to address these differences.

In a *systematic review*, research evidence is systematically searched for, appraised and synthesised, it often adheres to guidelines on the conduct of a review and includes a quality assessment which determines the inclusion and exclusion of articles. A *systematic search and review* usually addresses broad questions and seeks to identify the most significant items in the field, and although it demonstrates an extensively researched literature, it may or may not include quality assessment. The strengths of this latter type of review are the incorporation of multiple study types to provide a more complete picture of the research topic. However, the major limitation or criticism of this type of review is related to the fact that the articles included

are assessed and valued without a standardised tool or checklist (Grant and Booth, 2009).

The process of conducting a *systematic search and review* commenced in 2016 and was updated in 2019. Given the different nature and scope of the literature aims (one quantitative and one qualitative) two different search strategies were built. Thus, to respond to aim one, the methods followed are presented in sub-section 2.2.1, and to respond to aim two, in sub-section 2.3.1.

Findings from the reviews are presented in a narrative form in two main sections; sub-sections were organised according to the themes identified after reading the articles retrieved during the search. The first section relates to the first aim and focuses on quantitative research. It covers aspects related to prescription patterns and time to treatment initiation and clinical inertia. The second part aims to describe clinical decision-making from HCPs' perspective, which included qualitative studies. Although tables with a summary of the articles are presented in each section, a narrative or textual approach of the findings from the studies included was adopted because it offers an effective way of synthesising findings from multiple studies designs, such as qualitative and quantitative (Popay et al., 2006).

2.2 Section 1: prescription patterns and time to drug initiation in people with T2DM

The aim of this component of the literature review was to describe prescription patterns of first-line GLM in people with T2DM, the characteristics of those receiving such prescriptions and time to GLM initiation to understand how T2DM is managed in real-world practice. The existing literature on treatment patterns is extensive and has been the focus of study in several countries. However, there is a relatively small body of literature about time to initial drug initiation and predictors of treatment

initiation. A detailed account of these studies is presented in the following sub-sections.

First, I will describe the methods utilised. Then, I will present the results of the database search and screening process. Next, I will move onto the first sub-section (2.2.2.1), in which I will describe the changing patterns of GLM in the US, Europe and the UK. The introduction of new medications and the constant monitoring of their secondary effects shape prescription patterns. For instance, an early study on the use of metformin for glucose control by Gottlieb and Auld (1962) described its benefits, particularly when a patient was intolerant to sulfonylureas and tolbutamide. However, its use did not increase until decades later. Similarly, in 2010, ten years after its approval, the drug rosiglitazone was suspended and withdrawn from the market. This was the result of research indicating that it may increase the risk of myocardial infarction (Cohen, 2010). As it will be described in section 2.2.2.1, trends in the use of GLM have changed over time.

Next, in sub-section 2.2.2.2 I will introduce the concept of “clinical inertia”. In the study of pharmacological therapies, when healthcare providers are considered to not initiate or intensify treatment for diagnosed patients appropriately, such behaviour is termed “clinical inertia”. The term was first coined by Philips et al., who identified this behaviour in the management for hypertension, dyslipidaemia, and diabetes (Phillips et al., 2001).

Finally, in sub-section 2.2.2.2 I will present the outcomes of the studies, which specifically focused on time to treatment initiation and predictors of GLM prescription.

2.2.1 Methods

A priori eligibility criteria were established. These criteria were determined after an initial review which was conducted to explore the evidence on the research topic.

2.2.1.1 Eligibility criteria

2.2.1.1.1 Inclusion criteria

1. Observational studies (cross-sectional, cohort, survey, or case-control). Since the aim is to describe real-world practice, RCTs were not considered.
2. Articles reporting proportions of patients with and without pharmacological treatment after T2DM diagnosis and/or prescribing patterns after diagnosis in the US and Europe. This criterion was established after the initial scoping review showed a sheer number of articles describing patterns worldwide. Although with some differences[2], GLMs for T2DM available in the US and Europe are similar (Davies et al., 2018).
3. Articles describing clinical inertia in people with T2DM in the UK.
4. Articles reporting time to drug treatment initiation in people with newly diagnosed T2DM, no geographical limitations.
5. Only articles published in English and available as full-text (if the same results were published in more than one article, only the most recent and complete was included).

2.2.1.1.2 Exclusion Criteria

1. Studies that do not provide new empirical data such as reviews, editorial letters or others will be excluded, as well as those not available as full text.
2. Articles focused only on hypothetical reasons for treatment choice were excluded.
3. Articles describing prescription patterns in newly diagnosed not in Europe nor the US were excluded.
4. Articles describing clinical inertia outside the UK were not included.

[2] Not licensed in the US: vildagliptin, gliclazide. Not licensed in Europe: rosiglitazone, colesvelam, quick-release bromocriptine, human insulin inhalation powder, pramlintide DAVIES, M. J., D'ALESSIO, D. A., FRADKIN, J., KERNAN, W. N., MATHIEU, C., MINGRONE, G., ROSSING, P., TSAPAS, A., WEXLER, D. J. & BUSE, J. B. 2018. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care,* 41**,** 2669..

5. Articles focused on describing patterns of use of specific medications (i.e. metformin only) were not considered.
6. Studies describing time to drug treatment initiation not focused on newly diagnosed patients or which data are not stratified and therefore not possible to analyse, were excluded.

2.2.1.2 Information sources and search strategy

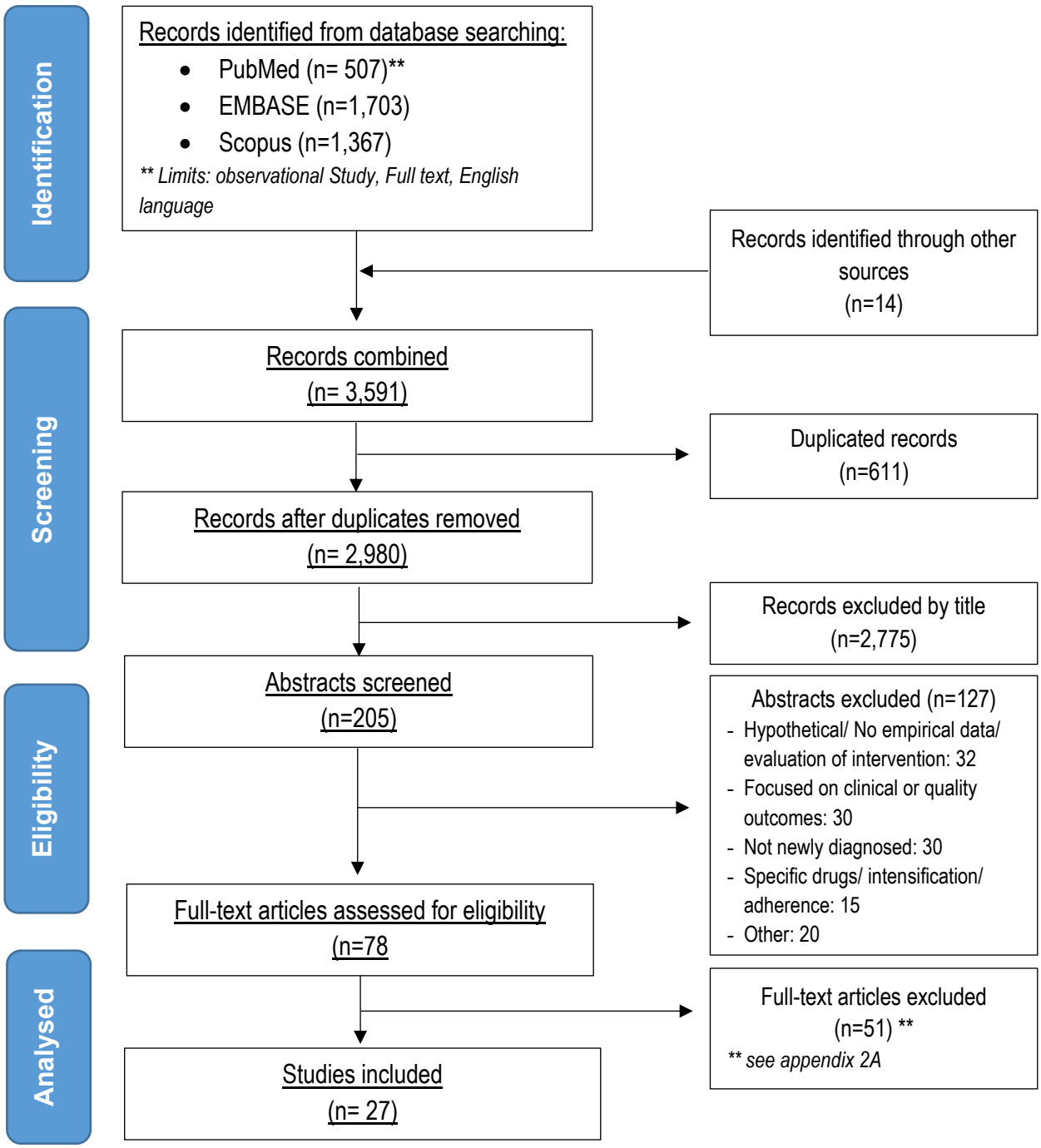
The literature search was conducted in three electronic databases: Excerpta Medica Database (EMBASE), Medline via PubMed and Scopus. The complete list of the search terms employed for each database is available in appendix 1A.

2.2.1.3 Selection process

The software EndNote X9 was used to manage records and identify duplicate studies. The selection process was performed, according to the a priori inclusion and exclusion criteria, in three main stages: 1) all retrieved articles were screened by their study title. 2) abstracts from all selected articles in the first stage were read to determine their relevance. 3) full-text of all those articles considered potentially eligible were read to determine their relevance according to the inclusion criteria. Moreover, references from selected studies were manually scanned for additional relevant studies.

In figure 1 is presented the review process concerning this section of the literature review. Specific details of full-text articles which were evaluated and not considered for this review are presented in appendix 2A.

Figure 1. Overview of the literature review process (database search) of section 1.



2.2.2 Results

A total of 27 articles were included in this section of the literature review. Articles were concerned with prescription patterns, clinical inertia, and time to treatment initiation in people with newly diagnosed T2DM. The narrative review of the articles included is presented as follows:

- Sub-section 2.2.2.1 presents studies that described prescription patterns of glucose-lowering medication, which includes those for the US, mainland Europe and the UK.
- Sub-section 2.2.2.2 is concerned with studies focused on clinical inertia in the UK, and
- Sub-section 2.2.2.3 presents the articles focused on time to treatment initiation in people with newly diagnosed T2DM.

Assessment of study quality

Although this type of review does not strictly require a quality assessment of the studies included (Grant and Booth, 2009), the appraisal was conducted in order to give the reader a context of the overall quality of the literature presented. Quality of the included studies was assessed using the Newcastle – Ottawa quality assessment scale (NOS) (Wells et al.) for cohort studies and the Joanna Briggs Institute (JBI) (Moola et al., 2017) critical appraisal checklist for analytical cross-sectional studies. The NOS assesses three perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. The scale includes eight questions (see appendix 3), each question can be awarded a maximum of one star with exception of question five which is concerned with comparability and can be awarded a maximum of two stars. Thus, the maximum score for this scale is nine (Wells et al.). The JNB includes eight questions (see appendix 3), where the answer for each one can be either yes, no, unclear and, not applicable. In the current study, articles assessed using the JBI were given a star if the answer was yes or

not applicable, otherwise if the answer was no or unclear the field was left empty. Hence, articles assessed using the JBI could have a maximum of eight stars (Moola et al., 2017).

Currently, official threshold scores for the assessment tools used have not been determined (Wells et al.). However, in order to provide an overview of the quality of the studies included in the review, discretionary cut-off points were created to classify articles as high, medium or low quality; high-quality articles were those with at least 8 stars, medium those with 5–7, and low quality those with ≤4 stars. Below, table 3 presents a summary of the assessment, the table includes the scale used and the score of each article. Overall, 37% of the articles were of high-quality and the remaining 63% of medium quality.

Table 3. Quality appraisal summary

No.	First author	Year	Scale	Score	Quality
1	Boyc	2007	NOS	7/9	Medium
2	Brown	1999	NOS	7/9	Medium
3	Chung	2015	NOS	9/9	High
4	Desai	2012	NOS	7/9	Medium
5	Fillion	2009	NOS	8/9	High
6	Grimes	2014	NOS	8/9	High
7	Hamada	2015	NOS	8/9	High
8	Hamada	2016	NOS	7/9	Medium
9	Hazel-Fernandez	2015	NOS	8/9	High
10	Heald	2018	NOS	8/9	High
11	Hippisley-cox	2004	JBI	7/8	Medium
12	Kennedy	1988	NOS	5/9	Medium
13	Khunti	2013	NOS	7/9	Medium
14	Khunti	2016	NOS	7/9	Medium
15	Kostev	2018	JBI	6/8	Medium
16	Lopez-Sepulveda	2017	NOS	7/9	Medium
17	Lunger	2017	NOS	6/9	Medium

18	Mauricio	2017	NOS	8/9	High
19	Mor	2015	NOS	9/9	Medium
20	Pani	2008	NOS	7/9	Medium
21	Sharma	2016	JBI	7/8	Medium
22	Sinclair	2012	NOS	8/9	High
23	Spoelstra	2004	NOS	9/9	High
24	Sun	2013	NOS	7/9	Medium
25	Wysowski	2003	JBI	6/8	Medium
26	Zhang	2012	NOS	8/9	High
27	Zografou	2014	NOS	7/9	Medium

2.2.2.1 Prescription patterns of glucose-lowering medication

In this sub-section, I will present evidence from the US and Europe; then, I will focus on what is currently known from data in the UK. In table 4 is presented a summary of the articles found in the search which were included in this section.

Table 4. Articles focused on prescription patterns of glucose-lowering medications found in the search

First author, Year Country	Population of study	Main outcome of interest
Boyc 2007 France	Data obtained from the IMS Disease Analyzer–Mediplus France Database. Includes approximately 840 practices. N= 14,281 participants (2001 cohort: 4,672, 2002 cohort: 8,060, 2003 cohort: 10,724)	Mean age was 64.14 years (2001), 64.09 years (2002), and 64.24 years (2003). Metformin monotherapy 2001:17.38%, 2002: 19.51%, 2003: 21.31% Sulfonylurea monotherapy: 2001: 34.98%, 2002: 33.10%, 2003: 29.47%
Brown, 1999 US	Participants were drawn from a diabetes registry which covered 20% of the population in Portland, Oregon. N= 6,318 of incident T2DM cases.	79.2% were prescribed sulfonylurea monotherapy in 1988, the proportion dropped to 20.5% in 1997. Metformin monotherapy was introduced in 1995. In 1996 accounted for 7% of prescriptions and in 1997 increased to 9.8%. No drug therapy (diet and exercise) declined, from 37.2% in 1989 to 16.1% in 1997.
Desai, 2012 US	Data were obtained from claims data from a pharmacy benefit manager. People were included in the analysis if aged 18 to 100 years,	Participants mean age was 58 years. In 2006: 51% were started on metformin, 26.2% were started on a sulfonylurea, 20.1% were started on a

	newly initiated on GLM between 2006 and 2008. N= 254,973 patients.	thiazolidinedione. In 2008: 65% were started on metformin, 18.1% were started on a sulfonylurea, 8.3% were started on a thiazolidinedione.
Fillion, 2009 UK	Data were drawn from GPRD which links over 400 practices. The cohort consisted of patients (N=67,981) with T2DM from 2000 to 2006.	Prescription rates per patient-year were 9.6 in 2000 and 14.8 in 2006. Metformin prescription increased across the years, and in 2002 surpassed sulfonylureas as the most prescribed. Sulfonylureas use decreased modestly over time (proportions not presented).
Grimes, 2014 Ireland	The cohort (N=20,947) was drawn from two primary care reimbursement services pharmacy claims database (the general medical services scheme and the long-term illness scheme) and included people with newly treated (initiated on monotherapy, excepting insulin) T2DM aged 40 years or older from 2008 to 2009.	The majority of the cohort were male (57.9%). Overall, 76% were initiated on metformin, 22% on sulfonylureas, and 2% on other drugs.
Hamada, 2015 UK	Population-based cohort (N=12,881) from the UKCPRD database. People were included if: diagnosed with T2DM between 1990 and 2013, aged 80 years or older, were prescribed GLM.	Mean age at diagnosis for the cohort was 83 years. The majority were female (61%). Prescription of sulfonylureas changed from 94% in the early 1990s to 29% in 2010s. Prescription of metformin changed from 22% in the 1990s to 86% in 2010s.
Hamada, 2016 UK	Cohort (N=5,324) from the UKCPRD database. People with T2DM who died between 2011 and 2013 were sampled.	The median age was 86 years, 50% female. Most patients (78%) received GLM during the last year of their life. Metformin and sulfonylureas were the drugs most prescribed.
Hazel-Fernandez, 2012 US	Cohort (N=17,527) from Medicare Advantage Prescription Drug plan members of Humana Inc. health insurance plan. Pharmacy claims data of metformin from 2007 to 2012 of people aged 18-89 years who were diagnosed with T2DM were used.	Mean age was 69.6 years, 51% were female. Most patients (59.4%) had not changed in their treatment in 12 months after initiating with metformin. One third (33.3%) discontinued, 4.9% added and 2.3% switched to another drug.
Heald, 2018 UK	Analysis at GP practice level. Data were drawn from the National Diabetes Audit and QOF.	Overall, the use of metformin increased by 4.4% from 2015/2016 to 2016/2017. Use of sulfonylureas declined 2% for the same period but remained the most common treatment (overall) with 62% people with T2DM being prescribed this drug.
Kennedy, 1988 US	GLM data were drawn from three databases from IMS America: 1) the National Prescription Audit, 2) the National Disease and Therapeutic Index, and 3) the U.S. Pharmaceutical Market-Drugstores.	Tolbutamide: in 1964 accounted for 75% of the market. In 1986 10%. Chlorpropamide: in 1986 accounted for 33% Glyburide: in 1986 29% of prescriptions Glipizide: in 1986 21% of prescriptions.
Kostev, 2018 Germany	Data from the Disease Analyzer database (QuintilesIMS). Patients with an initial diagnosis of T2DM and available HbA1c values between 2011 and 2015 were included. N= 9,850	Mean age was 80.7 years, 31.2% were men. Prescription patterns differed significantly between nursing home and home care settings for metformin (46.6% vs 60.5%), insulin (57.9% vs 41.1%), sulfonylurea (24.9% vs 34.2%), DPP4 inhibitors (13.4% vs 19.8%), and other antihyperglycemic drugs (7.8% vs 12.1%).

Lopez-Sepulveda, 2017 Spain	Data of drug utilisation was obtained from public healthcare system databases for the period 2001-2014.	Overall, the use of GLM increased by 20.1% in the study period. Sulfonylureas use decreased by 45.5%. The use of metformin increased and in 2014 represented 45% of drugs used.
Lunger, 2017 Austria	Cohort (N=7,760) from the diabetes registry Tyrol. People were analysed if they attended one visit (outpatient or inpatient) between 2012 and 2015.	Mean age was 65.2 years, 58% were female. Metformin was the drug most prescribed; monotherapy was used in 16.6% of all patients. However, proportions varied according to age. People over 60 years of age had fewer prescriptions for metformin than those under 60 years.
Sharma, 2016 UK	Data obtained from THIN database which includes data from 550 practices throughout the UK. Overall, 406 344 people with T2DM were included; 203,639 of these were newly diagnosed between 2000 and 2013.	62.6% of people with newly diagnosed T2DM were prescribed GLM. Prescription of metformin increased from 45.1% in 2000 to 91% in 2013. Use of sulfonylureas decreased from 51.1% in 2000 to <10% in 2013.
Wysowski, 2003 US	Data about oral antidiabetic drugs from 1990 to 2001 derived from two pharmaceutical marketing research databases from IMS Health and National Disease and Therapeutic Index.	Dispensed outpatient prescriptions changed over time. Metformin was marketed in 1995 and in 2001 accounted for 32.7% of prescriptions. Sulfonylureas dominated the market in 1990, glipizide and glyburide accounted for 77% of prescriptions, and by 2001 these accounted for 35.5% of prescriptions.

2.2.2.1.1 Research in the US

In the US, the study of prescription patterns dates from the 1960s. In that decade, tolbutamide was the most frequent medication used. By the 1970s, its use had decreased, and in 1986, it accounted for 10% of prescriptions while chlorpropamide (a first-generation sulfonylurea) was reported as the most frequently used drug for treating what was known as non-insulin dependent diabetes at the time. However, the use of second-generation sulfonylureas (glyburide and glipizide) was increasing, and by 1990s these were the most commonly prescribed medications for glucose control for people with T2DM in the US (Kennedy et al., 1988, Wysowski et al., 2003).

However, it was not until mid-1990s that metformin's use started to make an important contribution to the treatment of T2DM in the US (Brown et al., 1999), and by 2001 it was estimated to account for almost 33% of prescriptions, forming only a slightly smaller proportion than second-

generation sulfonylureas which had 35.5% of the market (Wysowski et al., 2003).

More recent studies have also looked at treatment patterns for people with T2DM. Desai et al. (2012) evaluated the use of specific drugs for the initial management of T2DM in a cohort of 254,973 patients (of 18 to 100 years of age) who initiated oral hypoglycaemic monotherapy between 2006 and 2008. They reported that metformin was the most prescribed drug during the study period, accounting for 51% to 56% of initial prescriptions in 2006 and 2008 respectively. However, as they relied on pharmacy claims, it is not possible to know why specific medications were prescribed to individual patients.

Hazel-Fernandez et al. (2015) conducted a historical cohort analysis among people aged 18-89 years covered by the US government-sponsored health insurance Medicare who were diagnosed with T2DM and initiating metformin between 2008 and 2011. A total of 17,527 people were included, the majority (59.4%) remained without changes in their drug prescription after 12 months of follow-up, it was also reported that increased age, Black race[3], and pill burden were associated with a decreased hazard of addition of a further diabetes treatment. Furthermore, after analysing by prescriber, it was found that people were more frequently prescribed metformin in primary care or by an internal medicine physician than by an endocrinologist; however, no more information about prescribers' characteristics was provided.

2.2.2.1.2 Research in Europe

In Europe, trends in medication use have been studied in countries such as Spain, Germany, France, Ireland, and Austria. Here, I will present a summary of the main findings of such studies.

[3] People who participated in Hazel-Fernandez et al's study were categorised in White, Black and Hispanic race. The term "Black race" is used here in accordance with what was reported by the authors.

Boyc et al. (2007) examined prescribing trends for GLM from 2001 to 2003 using a database from the IMS Diseases Analyzer-Mediplus, which contains information about patient characteristics, diagnoses, and prescribed medication in France. People were included if they were categorised as having T2DM, were ≥ 20 years old, and had received at least two prescriptions for an oral GLM, a total of 14,281 unique individuals were analysed. There was a prescribing trend shifting from sulfonylureas (34.9% to 29.4%) to metformin monotherapy (17.3% to 21.3%). However, older individuals were more likely to receive sulfonylurea monotherapy instead of metformin monotherapy.

Similarly, a retrospective cohort study conducted in Ireland sought to describe the utilisation patterns of GLM in people receiving their first medication for T2DM; however, no data about disease duration was presented. It was reported that 76% started treatment with metformin, and 22% with a sulfonylurea. Older age was associated with a higher likelihood of being prescribed sulfonylurea (Grimes et al., 2014). Lunger et al. (2017) reported similar trends in Tyrol, Austria. They described that 85% of people with T2DM between 2012 and 2015 received at least one GLM. In general, metformin was the most commonly prescribed medication, except for older patients (≥ 60 years). Likewise, a study conducted in the Andalusian region in Spain showed that, during 2001-2014, the use of sulfonylureas decreased while metformin usage increased (López-Sepúlveda et al., 2017).

In Germany, Kostev et al. (2018) analysed prescription patterns in people with T2DM living in nursing homes and home care settings. Hence, the participants were older adults, mean age was 80.7 and 74.8 years old in a nursing home and home care, respectively. They reported that, although there was no significant difference in the proportions of people with HbA1c >58 mmol/mol (7.0%), prescription patterns differed significantly between settings. In nursing home settings, insulin was the most common therapy (57.9%) while in people living at home, metformin formed the most common

treatment (60.5%). Thus, these findings suggest that factors other than HbA1c may influence treatment decisions.

2.2.2.1.3 Studies in the UK

In the UK, first-line T2DM drug treatment choices have changed over time. Similar to what has been reported in the US and other European countries, there has been an overall shift from sulfonylureas to metformin. Filion et al. (2009) analysed trends in the prescription of GLM among people with T2DM. They analysed data for people with T2DM from 2000 to 2006 from the General Practice Research Database (GPRD), which was linked to around 400 general practices in the UK. They selected people with a diagnosis of T2DM who were at least 30 years of age at diagnosis; their cohort included 30,234 people. In general, it was reported that from the year 2000 to 2006 prescription rates of GLM increased from 9.6 prescriptions/patient-year to 14.8 prescriptions/patient-year. The absolute increase was greatest for the prescription of metformin, which in 2002 surpassed sulfonylureas and became the most commonly prescribed GLM.

A similar study was conducted by Sharma et al. (2016), who investigated trends in incident and prevalent diagnoses of T2DM and its pharmacological treatment between 2000 and 2013. The cohort consisted of 406,344 people with T2DM ($\geq$ 35 years at the time of diagnosis); data were obtained from The Health Improvement Network (THIN) primary care database. The THIN database contains medical records from more than 550 general practices in the UK. The overall proportion of people receiving a prescription for metformin increased markedly from 55.4% in 2000 to 83.6% in 2013, whereas the proportion of people receiving a prescription for sulfonylureas decreased from 64.8% to 41.4% in 2000 and 2013, respectively. Moreover, a sub-cohort analysis, which included 203,639 people with newly diagnosed T2DM, showed that the use of metformin increased annually, and in 2013, 91% of newly diagnosed patients were prescribed metformin as first-line treatment. The rapid increase in the prescription of metformin was attributed

to HCPs' adherence to clinical guidelines, although information about choice of treatment was not available; likewise, there was no information about whether treatment patterns differed between subgroups of patients.

A more recent study, which looked at the pattern of prescribing of GLMs for T2DM in England in 2016/2017, showed that metformin was taken by 51% of people with T2DM. The analysis also demonstrated that, as monotherapy or combined with other drugs, the proportion of metformin users grew by 4.4% compared with 2015/2016. Heald et al. (2018) also noted that the use of sulfonylureas declined by 2% between these years. Furthermore, the proportions of people prescribed other agents such as SGLT-2 inhibitors and the Degludec/Liraglutide combination grew strongly at 70% and 80% per annum, respectively. Notably, some older medications such as tolbutamide and glibenclamide were still being prescribed in some practices. However, no potential explanations for these patterns were provided by the authors (Heald et al., 2018).

So far, these studies have provided insight into prescribing pattens in the UK. However, it is worth to note that the duration of T2DM has not been considered in the analysis. Hence, it is not possible to know if patterns differ among people with newly diagnosed T2DM.

2.2.2.1.4 Glucose lowering medication for older people with T2DM

Two studies of GLM prescription, which focused exclusively on older people with T2DM, in the UK, were found. Both studies reported the lack of studies which could inform treatment decisions for elderly people with T2DM. In 2015, a population-based cohort was conducted using the UK Clinical Practice Research Datalink (CPRD) with the aim to evaluate trends in GLM utilisation for people with T2DM diagnosed over 80 years of age. Overall, 26,230 people with T2DM aged 80 years or older at diagnosis were identified between 1990 and 2013. It was reported that 51% did not receive a GLM prescription and that people who remained without medication were slightly

older than those who received a prescription (median age 84 vs 83 years). Moreover, there was a higher proportion of patients with coronary heart disease among those who remained without drug prescription than among those who received a prescription (32% vs 28%, P<0.001). Among people who received GLM prescription from 1990 to 2013, the main drug therapy changed from sulfonylureas (94% in the early 1990s to 29% in 2010) to metformin (22% to 86%). However, sulfonylureas were more likely to be prescribed than metformin to people over 90 years of age. While data for the group who did not receive GLM were not analysed, the authors recognised that important insights could be obtained from a comparison of people who received GLM prescription and those who did not (Hamada and Gulliford, 2015).

A UK CPRD study evaluated primary care drug utilisation by people with T2DM (≥80 years), in their last year of their life, who died between 2011 and 2013. The selection criteria included people with T2DM who visited their GP at least once every three months in the last year of their life. A total of 5,324 patients were included, with a median age of 86 years and median T2DM duration of 10 years. The majority (78%) of people were treated with GLM during the last year of their life. Overall, metformin and sulfonylureas were the drugs most commonly prescribed. However, in people with decreased renal function, metformin was less frequently prescribed. Large proportions of people were receiving other drugs such as antihypertensives (76%), and statins (62%). This study showed that during their last year of life, older people with T2DM received intense pharmacological treatment. However, the authors believed that their care might not have been considered as being for the end-of-life and acknowledged the need for more research in this field (Hamada and Gulliford, 2017).

The previous sections reviewed prescription patterns and showed that non-insulin GLM are the most frequent pharmaceutical treatment for diabetes, as monotherapy, or in combination alone or with insulin (Boyc et al., 2007,

Sharma et al., 2016, Heald et al., 2018). Moreover, it showed that among the elderly, who also often have other health conditions, prescription patterns might slightly differ from the ones for younger people with T2DM (Hamada and Gulliford, 2015, Hamada and Gulliford, 2017, Kostev et al., 2018). As indicated in the aims section of this chapter, due to the lack of research on initiation of GLM in people with newly diagnosed T2DM, I broadened the search and found an increasing body of literature focusing on clinical inertia. This topic, which I present in the following section, provides insights into the timing of GLM initiation and factors related to it.

2.2.2.2 Clinical Inertia

In recent years, there has been increased interest in clinical inertia in relation to T2DM. In the context of T2DM, Strain et al. (2014) defined it as: *"a failure to initiate or intensify treatment in a timely manner in people with diabetes whose health is likely to improve with this intensification"*. Thus, clinical inertia can occur in people with a recent diagnosis of T2DM due to failure to start pharmacological treatment at an appropriate time. For those already receiving pharmacological treatment the term relates to lack of treatment escalation, either by increasing doses or addition of further drugs (tablets and/or insulin) (Strain et al., 2014). However, Khunti and Davies (2017) have recently argued that inertia can relate not only to initiating or increasing treatment but also to decreasing or halting pharmacological treatment when it would be appropriate to do so. They have suggested that clinical inertia should be reserved for the lack of adherence to guidelines and introduced a new term "therapeutic inertia", which should be used to describe *"failure to advance therapy or to de-intensify therapy when appropriate to do so"*.

Most of the studies on clinical inertia in relation to T2DM, both quantitative and qualitative, have focused on treatment intensification or initiation of insulin for people with T2DM who are already receiving GLM rather than initiation among people with recently diagnosed diabetes. Furthermore, it is worth noting that many of the studies on clinical inertia have been funded by

large pharmaceuticals companies (McEwen et al., 2009, Ruiz-Negrón et al., 2019, Zhang et al., 2011, Patel et al., 2012, Sinclair et al., 2012, Strain et al., 2014, Qiu et al., 2015) and that the main focus of such studies are reasons and barriers to drug prescription or treatment intensification. Thus, there is a lack of evidence about initiation of first-line GLM in newly diagnosed people with T2DM. Only four studies were found which focused on clinical inertia in the UK, these are presented in table 5.

Table 5. Articles focused on clinical inertia in the UK found in the search

No.	First author, year	Population of study	Definitions and Endpoint	Main outcome of interest
1	Khunti, 2013	Cohort (N=81,753) analysis from the CPRD database covering the period from 2004 to 2006 with follow up to 2011 (maximum follow up time was 7.3 years). People with T1DM, treated with diet only, or insulin only were omitted from the analysis	Poor glycaemic control cut-off points: 1) HbA1c > 53mmol/mol 2) HbA1c > 58 mmol/mol, 3) HbA1c >64 mmol/mol. Endpoint: Time between being in poor control and treatment intensification	Mean baseline HbA1c was 68 mmol/mol, 73 mmol/mol, and 75 mmol/mol in people taking one, two, or three GLMs, respectively. Mean age at diagnosis was 62.6 years, 61.5 years and 59 years for people taking one, two, or three GLMs, respectively. In people with HbA1c >53 mmol/mol taking one agent, median time to intensification with an additional oral agent was 2.9 years, median time to intensification with insulin was .7.2 years. Median time to insulin intensification in people with HbA1c >53 mmol/mol taking two or three OADs was 7.2 and .7.1 years, respectively
2	Khunti, 2016	Cohort (N=11,696) of people ≥18 years with T2DM. data were extracted from the UKCPRD. Participants were included if they had started basal insulin between 2004 and 2011, with follow up on 2013.	Poor glycaemic control was defined as a recording of HbA1c ≥58 mmol/mol taken >6 months after starting basal insulin. Endpoint: the likelihood of intensification and time spent in poor glycaemic control before intensifying treatment	Mean age was 65.5 years, 55.7% were men. Mean duration of T2DM was 8.2 years. For those who received treatment intensification mean age was 61.3 years, mean duration of diabetes 7.7 years. From all patients, 36.5% had their treatment intensified. Median time from initiation of basal insulin to intensification with either bolus or premix insulin or GLP-1 was 4.3 years regardless of HbA1c. Increasing age and duration of T2DM were associated with longer time to intensification. Increasing BMI was associated with shorter time to intensification. 30.9% of people with poor glycaemic control had their treatment intensified. The median time was 3.7 years.

3	Mauricio, 2016	Data from the Cegedim Strategic Data patient database (included data from the UK, France, Germany, Italy, Spain, and the US). Data of people with T2DM (N=40,627) initiating basal insulin with or without oral GLM from 2008 to 2012, aged 30 years or older were included in the analysis	Target achievement was defined as HbA1c ≤53 mmol/mol. Endpoint: predictors of longer achievement of glycaemic control and risk of hypoglycaemia.	Mean age was 63.3 years. More than half (62.9%) of patients in the UK initiated basal insulin with very high HbA1c (>75 mmol/mol). Overall, compared with those who achieved an HbA1c ≤53 mmol/mol three months after starting basal insulin, people with HbA1c >53 mmol/mol three months after basal insulin initiation were more likely to not reach the HbA1c target at 24 months (OR 3.70; CI 3.41-4.00).
4	Zografou, 2014	People with T2DM (N=509) who received insulin prescription between 2002 and 2011. Data derived from SCI-diabetes.	Poor glycaemic control by three cut-off points: >7%, >8% and >9% HbA1c. Endpoint: time from diagnosis to insulin prescription and time with poor glycaemic control.	Median age at time of insulin prescription was 63 years. Median time to insulin prescription was 73 months after diagnosis, HbA1c at prescription was 10%. Moreover, median time until insulin prescription with sub-optimal HbA1c was: 49 months for HbA1c >7%, 25 months for HbA1c >8%, and 10 months for HbA1c >9%.

Overall, studies focusing on treatment intensification or escalation have reported evidence of delays in treatment intensification for people with T2DM with sub-optimal glycaemic control (Khunti et al., 2013, Mauricio et al., 2016, Zografou et al., 2014, Khunti et al., 2016). Mauricio et al. (2016) analysed electronic medical records in France, Germany, Italy, Spain, the UK, and the US in insulin naïve people >30 years of age with T2DM initiating basal insulin analogues (insulin preparation that mimics physiological insulin) with or without oral glucose-lowering drugs. They reported that most patients started basal insulin when they had very high HbA1c levels >75 mmol/mol (9%). Mean HbA1c at the time of basal insulin initiation range from 69 mmol/mol in Germany to 85 mmol/mol (9.9%) in the UK (Mauricio et al., 2016).

Similarly, research conducted in the UK by Khunti et al. (2013) showed a delay in treatment intensification in people with T2DM with sub-optimal glycaemic control. Patients who received treatment intensification, by addition of further oral antidiabetic drugs or insulin initiation, had a mean HbA1c of 9.4 ±2.3%. However, it is important to note that this study did not take patients' clinical characteristics into account and based their analysis mainly on HbA1c levels. Hence, the analysis carried out did not include important covariates such as age, BMI or comorbidities that may have influenced decisions about treatment intensification (Khunti et al., 2013).

Although treatment intensification is out of the scope of this PhD, the literature about clinical and therapeutic inertia provided insight about aspects related to prescription of GLM in people with T2DM, and highlighted the need for considering variables other than HbA1c.

2.2.2.3 **Management for newly diagnosed people with T2DM**

As previously mentioned, a large proportion of research identified from the literature search has focused mainly on treatment trends and intensification of treatment among people already receiving monotherapy for the treatment of T2DM. However, some studies (see table 6) have been carried out which have looked at treatment initiation in people with newly diagnosed T2DM. These studies will be summarised in this sub-section.

Table 6. Articles found in the search which focused on newly diagnosed T2DM – time to GLM initiation.

No.	First author, year and Country	Population of study	Main outcome of interest
1	Chung, 2015 US	Data extracted from EpicCare group practice with approximately 100 physicians in northern California. People (N=2,258) were included in the analysis if were diagnosed with T2DM, aged 35 years or older, not having a record of being diagnosed as T1DM, not pregnant during 2007-2010. People	Mean age was 56.9 years, 57% were male. Mean baseline HbA1c was 7.3%. 55% of patients were treated with either GLM or education/counselling during the first year of follow up. Amongst those who initiated treatment, 46% did it in the first week, 68% in the first month of diagnosis.

		without a diagnosis but who had evidence of having received GLM were not included as well as those with active cancer of serious kidney or liver disease.	Metformin was prescribed to 87% of those who received GLM prescription. Compared with people who did not receive treatment, those who did were more likely to be young, obese, have higher levels of glucose, triglycerides, and LDL cholesterol.
2	Hippisley-Cox, 2004 UK	Cross-sectional study of 7,870 people with diabetes in 2003 across 42 practices in the Trent region.	65.7% were treated with GLM, and 34.3% (2,700) did not have recorded drug prescription. Compared with those who received a prescription, people treated by diet only were significantly less likely to have as many records of measurements of HbA1c, cholesterol, blood pressure, BMI, and other clinical care data.
3	Mor, 2015 Denmark	Cohort of people with newly diagnosed T2DM (N=1,158) between 2009 and 2014 and who were followed up for 365 days. Data extracted from a nationwide DD2 cohort.	Overall, 57% were men, 66% enrolled from hospital outpatient clinics. 26% did not receive GLM during the first year after diagnosis, 62% received monotherapy, and 12% combination therapy. People who did not receive medication were older.
4	Pani, 2008 US	Participants data (N=5,804) were obtained from 12 outpatient practices in Massachusetts from the period between 2005 and 2006	Disease progression was defined as HbA1c ≥7% or treatment initiation. The multivariate analysis showed that baseline HbA1c and younger age were the major independent predictors of disease progression. Each decade of age reduced the risk of progression by 15% (OR 0.85; CI: 73–0.99).
5	Sinclair, 2012 UK	The cohort was drawn from the IMS MediPlus database. People ≥30 years with newly diagnosed T2DM during the period of 2003 to 2005 and who were followed up for at least two years were included in the analysis.	Mean age was 62.4 years, 54% were men. 36%, 42%, and 51% of participants initiated GLM within 180 days, one year, and 2 years of diagnosis.
6	Spoelstra, 2004 The Netherlands	Data were drawn from 17 GP practices in a middle-sized town. People with newly diagnosed T2DM from 1994 to 2000 were included in the analysis (N=603).	Mean age was 62 years, 43.4% were men. Overall, 53% started GLM in the first month after diagnosis. Three years after diagnosis 81% had received GLM prescription.
7	Sun, 2013 US	Cohort study used the GE Healthcare's Clinical Data Services electronic medical record dataset. People with newly diagnosed T2DM between 2004 and 2005 were included in the analysis (N=2,254)	Mean age was 58 years, 58% were men. Over two years of follow up, 66.1% initiated oral GLM. The median time to treatment initiation was three months. 73.6% of people with baseline HbA1c of ≥9% received GLM.
8	Zhang, 2012 US	The cohort was drawn from the GE Healthcare's Clinical Data Services electronic medical record.	Mean age at diagnosis was 52 years for people <65 years, and 73 for those ≥65 years of age.

	People with newly diagnosed T2DM between 2003 and 2005, of at least 30 years of age, whose data was available two years before and after diagnosis were included in the study (N=10,743).	Time to treatment initiation was longer for older patients compared with younger patients (HR: 0.82; CI: 0.75-0.90).

A study conducted in The Netherlands by Spoelstra et al. (2004) aimed to investigate which factors determined the initiation of GLM in people with T2DM in general practice. In total, 603 people with T2DM diagnosed from 1994 to 2000 were included in the analysis, 53% were prescribed GLM at diagnosis; after three years of follow-up, 81% had received drug prescription. The Kaplan-Meier curves showed a tendency for men to start treatment sooner after diagnosis than women; however, this difference was not statistically significant. The initiation of GLM was strongly related to baseline glucose levels. However, this study has the limitation that only 66% of participants had recorded blood glucose values. Furthermore, the authors stated that GPs' reasons for prescribing or following guidelines is unclear (Spoelstra et al., 2004), which highlights the need for research to focus on clinical decision-making.

In Denmark, Mor et al. (2015) conducted a cohort study with the aim to examine prescribing practices and predictors of glucose-lowering therapy within the first year following diagnosis of T2DM. Participants were selected if they had been recently diagnosed with T2DM and followed up for 365 days. Data from 1,158 people recently diagnosed with T2DM were included. Overall, 57% (659) of the patients were men. During the first year of diagnosis, 26% (302) did not receive GLM, 62% (723) received monotherapy and 12% (133) received combination therapy. The likelihood of receiving GLM was higher for people <40 years old (adjusted RR: 1.29; CI:1.16-1.44) and those aged 40-59 years old (adjusted RR: 1.16; CI:1.08-1.24) compared with those ≥60 years. Similarly, patients who had a high baseline blood glucose were more likely to receive GLM (≥59 mmol/mol, adjusted RR: 1.25; CI: 1.10-1.42), compared with those ≤48 mmol/mol. An important observation

is that 66% of participants had been enrolled from hospital outpatient clinics which may indicate more advanced T2DM.

A similar study was conducted in the UK by Hippisley-Cox and Pringle (2004). In 2003, a cross-sectional study was conducted in order to establish the proportion of patients with T2DM treated by diet only and the inter-practice variation in the use of medications. Data were provided by 42 practices in the Trent region. People registered as having T2DM and who were at least 35 years old were included in the study. Overall, 7,870 patients with T2DM were identified, 65.7% (5,170) were treated with GLM, and 34.3% (2,700) who did not have recorded drug prescription were assumed to be treated with “diet only”. Compared to those receiving medication, people treated by diet only were reported to be significantly less likely to have as many records of measurements of HbA1c, cholesterol, blood pressure, BMI, and other clinical care data. These results remained significant after adjustment for age, sex, deprivation, and the general practice where they were registered. Similarly, people treated with diet only were less likely to be referred to a dietician, a podiatrist or chiropodist than those who received a drug prescription (Hippisley-Cox and Pringle, 2004). The authors concluded that there was substantial variation between practices in the management of T2DM and that routine surveillance could be improved. The author’s emphasis on variation between clinicians is in line with Spoelstra et al’s conclusion, thus this study also emphasises the need for studying clinical decision-making. However, it must be considered that this study was conducted before the implementation of QOF, which sought to improve the quality of diabetes care and that prescribing patterns may have changed after the study was conducted.

In order to assess the association between patient age and initiation of GLM initiation following the diagnosis of T2DM, Sinclair et al. (2012) conducted a cohort analysis using the Intercontinental Medical Statistics MediPlus database in the UK. Participants were included if they were newly diagnosed

and at least 30 years old. The status of “newly diagnosed” was defined as no prior diagnosis of T2DM, no prescription for GLM in the previous 12 months before diagnosis and follow-up for two years after diagnosis. Between 2003 and 2005, 11,543 people were identified as newly diagnosed with T2DM, mean age was 62.4 years, and 54% were male. Overall, 36%, 42%, and 51% of participants initiated GLM within 180 days, one year, and 2 years of diagnosis. Metformin was the drug most commonly prescribed as first treatment (76%), followed by sulfonylureas (19%), and insulin (4%). In addition, differences were found in time to drug treatment initiation and the choice of the first-line drug. In this instance, the use of metformin decreased with increasing age, and the use of sulfonylureas increased with a patient’s age. Similarly, the proportion of people with GLM prescription was lower among older than younger people, though, the effect of age was reduced in people with higher baseline HbA1c. However, it is worth noting that HbA1c measurements were only available for 55% of the cohort and that further patients’ characteristics such as BMI and socioeconomic data were not included in the analysis (Sinclair et al., 2012). Similar to previous studies in this section, the need to conduct further research to better understand the differences in prescription patterns, particularly among young and old people with newly diagnosed T2DM, was identified.

Some similar studies have been conducted in the US. A cohort analysis, including people diagnosed with T2DM in 2004/2005 who were at least 18 years old, and who were followed-up for one year reported clinical predictors of GLM initiation after one year. After adjusting for race, sex, and weight change, the likelihood of drug initiation decreased by 40% with every decade of age (Pani et al., 2008). Likewise, Sun et al. (2013) carried out a cohort analysis of people with T2DM diagnosed in 2004-2005 who were followed-up for at least 2 years and who were eligible for statin therapy based on ADA recommendations in 2008. Data for 2,254 patients were analysed; after two years, 66.1% were initiated on GLM, the median time to drug treatment

initiation was three months (Sun et al., 2013). Similarly, results from Zhang et al. (2012) who conducted a retrospective cohort study of people with newly diagnosed T2DM of at least 30 years of age, and who were followed-up for at least two years, revealed variations in time to drug prescription. Overall, 10,743 people were included; however, data on baseline HbA1c were available for only 5,600 (52.1%). Older patients had longer time to GLM initiation than younger patients did. Moreover, at diagnosis, 25% of patients <65 years initiated drug treatment while only 15% of people $\geq$ 65 years did. In general, the proportions of people initiating GLM increased as HbA1c increased, other factors associated with increased likelihood of initiating drug therapy included higher BMI, and the use of lipid-lowering medication. Moreover, the authors explained that reasons for not prescribing were not included in their database (Zhang et al., 2012).

In addition, Chung et al. (2015) examined patterns and predictors of initiation of treatment for incident diabetes in an ambulatory care setting in the US from 2007 to 2010. Data from 2,258 people of at least 35 years old, with newly diagnosed T2DM were analysed. Mean age was 56.9 years and 57% were male. Most patients (55.1%, n=1,244) had recorded treatment in the first 12 months of diagnosis; 20% received medication only, 19.8% received medication and education/ counselling and 15.3% received education/ counselling only. The Kaplan-Meier cumulative hazard estimates showed that among those who received treatment of any kind, it occurred quickly. Amongst those who received treatment 46% (570) did so in the first week, and within the first month, 68% (840) had already initiated treatment. Moreover, the majority of those who received medication, the prescription was metformin (87%). The bivariate analysis of people with and without treatment showed that those who received treatment of any kind were younger (53.9+12.2 years vs, 60.6+15.0 years, p <0.001), less likely to be female (39.6% vs 47.5), more likely to be categorised as obese (45% vs 33.3%, p <0.001), more likely to have higher HbA1c levels (7.9% +2.0 vs.

6.4% +0.6, p <0.001). An important aspect to take into consideration is that people were considered to have received education/counselling based on attendance data and not solely on physician referral thus data may not reflect the real proportions of counselling/education prescriptions (Chung et al., 2015).

2.2.3 Section summary

This sub-section has provided a summary of the literature relating to glucose-lowering prescriptions patterns and the factors associated with glucose-lowering treatment initiation in people with T2DM. Sub-section 2.2.2.1 has shown that over the years, there has been a general shift from sulfonylureas to metformin as first-line GLM in both older and younger populations. The studies presented provided interesting findings; however, few studies investigated patient characteristics that may influence prescription patterns. Sub-section 2.2.2.2 presented two relatively new concepts, clinical inertia and therapeutic inertia, both of which relate to pharmacological management. The studies have found that overall, there is a delay in treatment intensification; however, treatment initiation and the analysis of clinical variables other than HbA1c need to be considered. Sub-section, 2.2.2.3, provided insights about disease management in people with newly diagnosed T2DM. The studies presented in this sub-section demonstrated that although HbA1c was an important factor for the initiation of GLM, other aspects such as age played a role. However, it is important to consider that most of the studies reported high proportions of missing data and the need for studying clinical decision-making in people with newly diagnosed T2DM.

Thus, metformin is currently the medication most commonly prescribed as fist-line agent and, time to prescription differs according to patients' characteristics. In the UK, the study which most recently looked at time to drug prescription used the period of 2003 to 2005 (Sinclair et al., 2012); it is not clear whether the introduction of QOF may have influenced time to first GLM after diagnosis of T2DM. Moreover, as reported by the studies

presented in the last sub-section, HCPs reasons when deciding when to prescribe and the factors that they consider when prescribing remain unclear. Hence, I conducted a literature review of studies of early treatment of T2DM from the HCPs' perspectives. However, due to the dearth of qualitative literature on initiation of GLM I will provide a broader review of the literature. A summary of the studies identified is presented in the following sections.

2.3 Section 2: HCPs' perspectives and experiences in the management of T2DM and clinical decision-making.

By conducting an additional search, I sought to gather information about qualitative research, which had looked at HCPs' experiences, views and attitudes with regards to diabetes care, particularly on clinical decision-making regarding the initiation of GLM in people with T2DM. However, there was no qualitative literature which specifically focused on this topic. Therefore, I broadened the search to include literature that looked at treatment decision-making amongst HCPs in primary care for people with T2DM more generally.

Hence, the qualitative literature review included aspects that HCPs' consider and take into account to inform their decisions; for instance, their perceptions about patients, organisational factors such as workforce, time constraints, and HCPs' experiences and views on clinical guidelines. These aspects led me to include a sub-section on patient-centred care because, as I will describe later, HCPs' sometimes perceived that organisational factors conflicted with tailored care. Furthermore, this review also helped me to develop a topic guide and refine the research questions for this PhD.

2.3.1 Methods

In a similar way to the previous section 2.2, a priori eligibility criteria were established, these criteria were determined after an initial review which explored the topic.

2.3.1.1 Eligibility criteria

2.3.1.1.1 Inclusion criteria

1. Qualitative articles which focused on the management of T2DM from HCPs' perspectives, no geographical limitation.
2. Qualitative articles focused on HCPs' views on clinical guidelines for T2DM, or on guidelines in a general way (not focused on any disease or condition).

2.3.1.1.2 Exclusion Criteria

1. Quantitative studies that surveyed HCPs on hypothetical cases.
2. Articles that focused on medication adherence and compliance.
3. Articles that focused on guidelines for specific diseases other than T2DM.
4. Articles not available full-text
5. Articles not published in English.

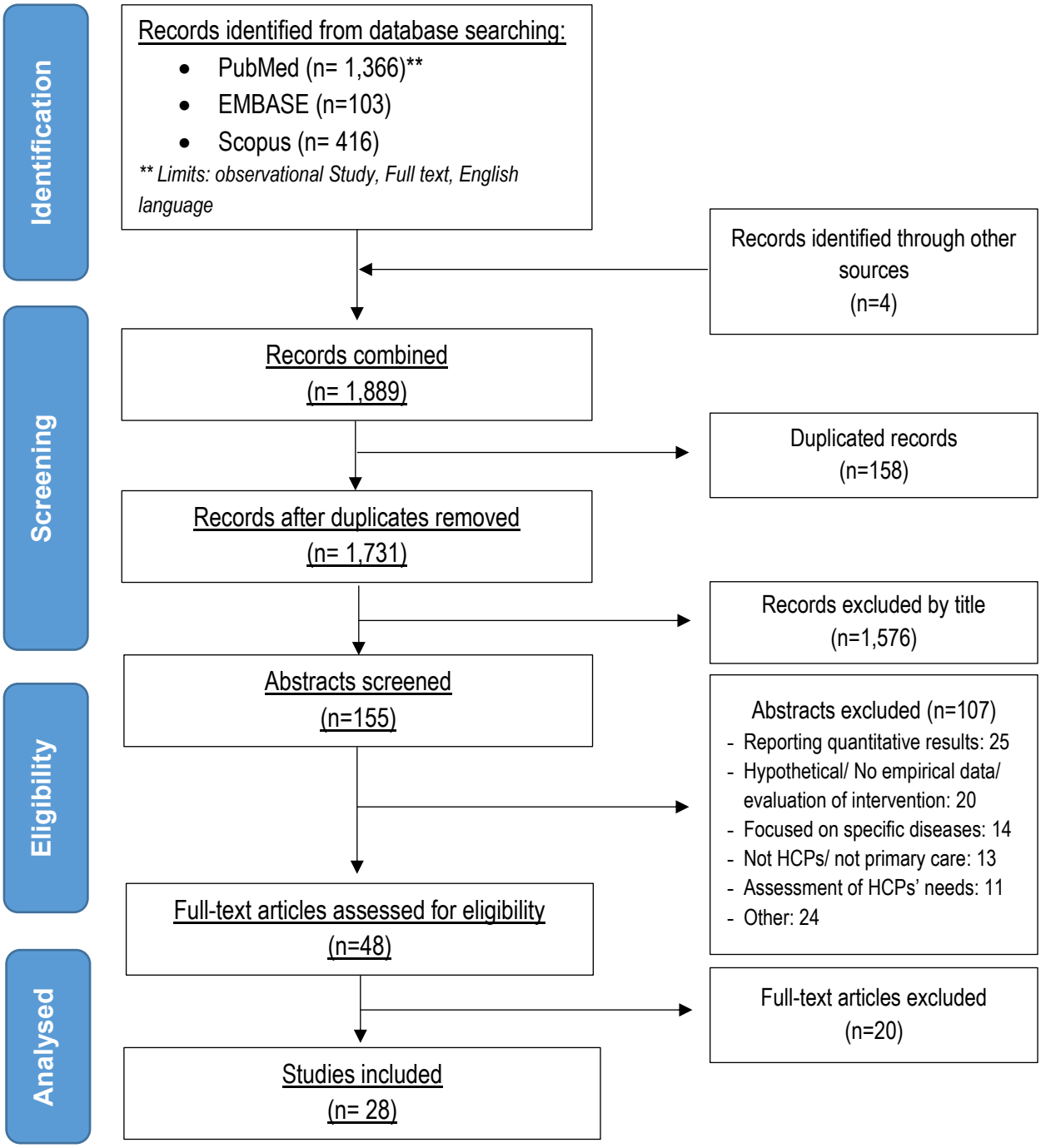
2.3.1.2 Information sources and search strategy

The literature search was conducted in three electronic databases: Excerpta Medica Database (EMBASE), Medline via PubMed and Scopus. The complete list of the search terms employed for each database is available in appendix 1B.

2.3.1.3 Selection process

The software EndNote X9 was used to manage records and identify duplicate studies. The selection process was performed, according to the a priori inclusion and exclusion criteria, in three main stages: 1) all retrieved articles were screened by their study title. 2) abstracts from all selected articles in the first stage were read to determine their relevance. 3) full-text of all those articles considered potentially eligible were read to determine their relevance according to the inclusion criteria. In figure 2 is presented the review process concerning this section of the literature review. Specific details of full-text articles which were evaluated and not considered for this review are presented in appendix 2B.

Figure 2. Overview of the literature review process (database search) of section 2.



2.3.2 Findings

A total of 28 articles were included in this section of the literature review. The narrative review of the articles included is presented as follows:

- Sub-section 2.3.2.1 Management of type 2 diabetes in primary care: HCPS' perspectives
- Sub-section 2.3.2.2 Attitudes, experiences and views on clinical guidelines which include patient-centred care which and pay for performance schemes.

All the above themes were intertwined and many of the articles found covered various sub-themes. Contrary to the quantitative review where a summary of the studies included was presented in a table format, the qualitative review will only provide, through the two main sub-sections, a narrative summary of the papers.

Assessment of study quality

Even when studies are not to be excluded based on quality, assessment of the methodological strengths and limitations is important. For qualitative studies, the focus of the appraisal should be the study methodological rigour rather than the risk of bias (Noyes et al., 2019). The Cochrane handbook states that more than 100 appraisal tools for qualitative studies are available (Noyes et al., 2019). However, it recognises that many do not focus on the study rigour. One tool that it is recognised and recommended is the CASP tool for qualitative research (Noyes et al., 2019, Critical Appraisal Skills Programme, 2018). Therefore, articles selected were appraised using the CASP checklist for qualitative research. This tool includes 10 questions (see appendix 3B); however, the first two questions are considered screening questions which, if answered yes to both, indicate that it is worth proceeding with the remaining eight. Each question can be answered with a 'yes', 'no', or 'can't tell', for this review, if the answer to a question was 'yes' one point was added to their score; thus, 10 is the maximum score possible for any article.

Below, table 7 presents a summary of the score of each article included in the qualitative review.

Table 7. Summary of quality appraisal of qualitative studies

No	First author	Year	Score	No	First author	Year	Score
1	Al-Alawi	2019	9/10	**15**	Luijks	2015	8/10
2	Alexander	2016	8/10	**16**	Mayer	1999	7/10
3	Aujoulat	2015	8/10	**17**	McDonald	2008	10/10
4	Baynouna	2018	6/10	**18**	McDonald	2007	9/10
5	Brown	2002	5/10	**19**	Milos	2014	8/10
6	Carlsen	2008	8/10	**20**	Noor Abdulhadi	2013	9/10
7	Daniels	2001	5/10	**21**	Patel	2012	8/10
8	Gabbay and May	2004	9/10	**22**	Pather	2019	9/10
9	Hunt	2012	7/10	**23**	Pooley	2001	7/10
10	Ingemansson	2014	7/10	**24**	Proser and Walley	2007	8/10
11	Kinnuen-Amoroso	2013	7/10	**25**	Radwan	2018	9/10
12	Lawton	2016	9/10	**26**	Sola	2014	8/10
13	Le	2015	8/10	**27**	Tracy	2003	7/10
14	Lee	2012	9/10	**28**	Zafar	2015	8/10

2.3.2.1 Management of type 2 diabetes in primary care: HCPS' perspectives

As described in the previous chapter, most T2DM care and management in Scotland and the rest of the UK is now done in primary care. Therefore, HCPs working in these settings play an important role in T2DM management; they are responsible for pharmacological treatment choices and time to initiation for most people with T2DM (Saudek, 2002). However, as I will describe in this section which explores HCPs' views about and experiences of managing people with T2DM, clinical decision-making is the result of at least three interrelated or intertwined dimensions: patients, HCPs and the healthcare system itself.

2.3.2.1.1 HCPs' perspectives on the influence of patient-related factors on treatment choices

Based on 26 semi-structured interviews, which explored the experiences of doctors and nurses, who worked in diabetes care at primary healthcare centres in Oman, of their encounters with patients with T2DM, Noor Abdulhadi et al. (2013) argued that patients' attitudes and characteristics appeared to have an important influence on treatment approaches and outcomes. The HCPs who participated in this study regarded the elderly and people with low educational levels as amongst the most "difficult" patients. In general, these patients were perceived as having generalised difficulty in modifying lifestyle habits. Likewise, religious patients who believed that diseases came from God who decided their fate were perceived to be less likely to want or be able to change their lifestyle and follow medical advice and thus, were considered less likely to manage their disease effectively. Barriers to optimal diabetes care, from the HCPs' perspectives, were mostly related to attitudes generated by patients' behaviour. HCPs expressed frustration due to unsuccessful efforts to improve patients' health, discussions with some patients were considered useless, and thus they preferred to only focus on the disease by acting as disease-oriented doctors and avoiding asking personal details *"No, I did not ask about any personal details, what is the use of that. She never follows any instructions. I focused only on her medical condition and that it is."(Noor Abdulhadi et al., 2013, p. 263).* However, the authors also found that some HCPs could not speak Arabic, which is the language most commonly spoken by their patients who often cannot speak English. HCPs' inability to speak their patients' language made necessary the assistance of other HCP or family members. This situation led HCPs to focus only on their medical condition and clinical information and to avoid deep discussions with their patients (Noor Abdulhadi et al., 2013).

Similarly, Al-Alawi et al. (2019) conducted semi-structured interviews with HCPs responsible for providing diabetes care at primary healthcare centres

in Oman. HCPs perceived the cultural beliefs and traditions of people with T2DM as influencing their behaviour regarding T2DM management. For instance, HCPs suggested that their patients followed other people's advice, such as family and friends, instead of their own. This situation was described as causing patients to not attend their appointments to monitor their diabetes and generating disbelief about the information HCPs provided. Likewise, Brown et al. (2002) conducted focus groups with 36 physicians in Canada to explore issues and perceptions regarding the management of people with T2DM. The authors reported that patient's attitudes such as passivity or unrealistic perspectives were seen as barriers to optimal T2DM management. Conversely, the ability to assume responsibility for their diabetes was described as a facilitator. However, it was pointed out that sometimes the motivation to change was frequently triggered by major health events such as the fear of receiving insulin.

Furthermore, Pooley et al. (2001) interviewed people with T2DM and HCPs who delivered diabetes care in England to explore the issues they perceived as central to effective management of diabetes in primary care. The authors reported that, although in general patients' and HCPs' concerns were similar, HCPs who participated in their study were more concerned about patients' compliance with recommendations than with establishing a management plan in collaboration with the patient. However, HCPs identified time constraints as a barrier to delivering patient-centred consultations, particularly when they were not familiar with the patient due to lack of continuity of care. Nevertheless, it is important to consider that this study was conducted several years ago and since then changes in the healthcare system have occurred.

Aujoulat et al. (2015), who conducted group interviews with GPs in Belgium to elucidate beliefs about clinical inertia and to identify modifiable provider-related factors associated with clinical inertia, reported that from the HCPs' perspective, patients' attitudes such as perceived aggressiveness, poor

adherence to treatment recommendations, refusal of pharmacological treatment (i.e. insulin) or denying their medical needs created a general feeling of dissatisfaction and powerlessness amongst them. These perceived feelings were reported by the authors as being related to the delay of pharmacological treatment initiation and clinical inertia (Aujoulat et al., 2015). While the study focused on experiences with insulin, these findings highlight the fact that HCPs' perceptions of patients' attitudes may influence their decisions about T2DM management. However, it must be acknowledged that no individual interviews were conducted, thus, the results reported might not fully reflect the experiences of all GPs who participated in the study.

As mentioned above, no studies were identified that focused on treatment initiation in people with newly diagnosed T2DM. In contrast, insulin initiation has received more attention. However, since insulin initiation relates to clinical decision-making, the most relevant literature is presented in this section. In this respect, HCPs have generally expressed the view that decisions about insulin initiation are strongly influenced by patient-related factors. For instance, Lee et al. (2012) conducted semi-structured interviews and focus groups with HCPs who provided diabetes care in Malaysia with the aim of identifying barriers to insulin initiation from HCPs' perspectives. HCPs reported that a common perception among patients was that insulin is the cause of severe complications, and some patients considered insulin initiation as a punishment, which increased patients' fear of starting on insulin. Thus, HCPs' perceptions of patients' beliefs may hinder optimal diabetes treatment; in this instance, by delaying timely initiation of insulin therapy.

Similar findings were reported in a qualitative study carried out in the UK by Patel et al. (2012). The authors sought to explore barriers to prescribing of insulin, particularly delays to initiation, from the perspective of HCPs involved in managing T2DM in a multi-ethnic setting. Semi-structured interviews were conducted with HCPs from primary and secondary care. Overall, most

barriers were attributed to patients, with “psychological insulin resistance” being regarded as very common, regardless of ethnicity. Moreover, there was a perception that South Asian patients were more likely to be negatively influenced and feel stigmatised of having diabetes by other people’s comments. The stigma of having T2DM usually led patients to avoid or wish to discontinue certain treatments such as insulin therapy *“One person’s neighbour comes: ‘Oh why are you taking insulin, I’m fine with my tablets, my doctor gave me new tablets’. They’ll come back: ‘Doctor, I don’t want insulin, my neighbour is taking this’. There are a lot of such issues”*. (Patel et al., 2012, p1313). However, the study was conducted in an area in the UK with a high number of people from South Asia, hence the findings might not reflect the experience of HCPs in Scotland.

In general, these studies recognise the complexity of treatment decision-making in people with T2DM. For instance, Pooley et al. (2001) highlighted that patients’ attitudes and behaviour influence HCPs’ decisions and may delay treatment initiation. Similarly, Noor Abdulhadi et al. (2013) observed that other patient-related aspects, such as the perceptions of patients’ health literacy may influence HCPs decisions about treatment decision-making as such patients were often perceived as less likely to follow medical advice. Moreover, HCPs recognised the need for a patient-centred holistic approach, however, they acknowledged that such approach requires extensive communication and time (Al-Alawi et al., 2019, Pooley et al., 2001, Noor Abdulhadi et al., 2013).

The aspects reported so far, related to patients, are not the only ones reported as influencing clinical decision-making, as I will describe in the following sections, HCPs-related and organisational factors were perceived as also influencing HCPs clinical decision-making about treatment for T2DM.

2.3.2.1.2 Healthcare professional-related factors

HCPs in the study by Noor Abdulhadi et al. (2013) indicated that sometimes their own attitudes could influence patients' views and feelings about medication to control their diabetes. For instance, some HCPs acknowledged aggression towards non-adherent patients and referred to, sometimes having attempted to frighten them with the threat of potential complications if they continued to be non-adherent. However, some mentioned that using a friendly approach with patients was a better strategy as it helped create trust and confidence. Therefore, a lack of good communication skills was seen by HCPs as a barrier to optimal diabetes care. In addition, some HCPs reported that avoiding deep discussions or social talk with patients and focusing only on the current medical condition was a result of the lack of good communication skills (Noor Abdulhadi et al., 2013). Likewise, additional research conducted in Oman by Al-Alawi et al. (2019) described different perspectives and experiences from HCPs in relation to the challenges and opportunities for service improvement in diabetes care in primary care. The study included observations of their daily practice and interviews with physicians, nurses, dieticians, health educators, pharmacists, a psychologist and a medical orderly. While these HCPs also described being frustrated by their patients' attitudes and behaviours, they indicated that good communication with patients is necessary to achieve optimal care (Al-Alawi et al., 2019).

Similarly, Lee et al. (2012), interviewed HCPs working in government clinics, university-based primary care clinics and hospital and private GP clinics and hospitals in Malaysia, and reported HCP-related barriers to insulin initiation. These barriers included HCPs' perceptions of patients' negative attitudes and their perceived lack of motivation. However, according to participants, these negative attitudes were the result of patients' unwillingness to modify their habits or adhere to treatment. Furthermore, lack of confidence was mentioned by some HCPs who considered themselves to be unfamiliar with some aspects of insulin treatment and who considered that insulin initiation

should be done in hospitals or specialised clinics. Likewise, HCPs in Brown et al. (2002) study pointed out the need for ongoing medical education in order to develop the skillset that would allow them to manage people T2DM comfortably.

The non-specialist role of HCPs was also pointed out by Zafar et al. (2015), who interviewed HCPs (19 GPs and one nurse) working in primary care in the UK. All interviewees were reported as having a leading role in diabetes management at their practices. Some of the HCPs interviewed reported that their limited expertise in T2DM management could contribute to clinical inertia. HCPs' suggested that the lack of expertise was caused by the shift in diabetes management from secondary to primary care (Zafar et al., 2015). This leads us to the next important component influencing treatment decision-making: organisational factors.

2.3.2.1.3 Organisational factors

These factors relate to the healthcare system and the organisation of healthcare; primarily to time constraints and the nature of the workforce. In the study conducted by Noor Abdulhadi et al. (2013), which was described above, HCPs (doctors and nurses) considered counselling patients to be a fundamental but time-consuming task, which HCPs often reported to be hindered by their high workload and lack of time. For instance, some HCPs suggested that their workload was a barrier to providing optimal diabetes care and that short consultation length affected their interactions with patients. Furthermore, some HCPs believed that a shortage of well-trained or qualified personnel increased their already high workloads (Noor Abdulhadi et al., 2013).

Pooley et al. (2001) reported that a common view held by HCPs working in primary care in England was that lack of time underpinned many issues. For instance, lack of time during consultations was perceived as limiting the exchange of complex information, and the delivery of a patient-centred

approach *"Diabetic patients do need time, and that's the hard thing really-fitting them in anywhere… people don't understand how much time we actually spend with patients."(Pooley et al., 2001, p.321).* Since the experience of living with diabetes is highly variable for each patient, HCPs recognised the need for tailored care; however, lack of time and resources was described as restricting them from doing this. Likewise, high-quality consultations were seen as difficult to achieve due to time constraints, which challenged good communication with patients, as HCPs lacked time to give information to patients or to answer their questions. Many HCPs identified a constant conflict between the service they would like to be able to provide and the care that was possible to give. Hence, a patient-centred approach was considered the area most difficult to deliver as it required lengthy and repeated consultations (Pooley et al., 2001).

Alongside consultation length, lack of staff continuity has been highlighted by HCPs as a barrier to good communication with patients which may lead to inadequate consultations with HCPs feeling unable to address patients' needs. Lack of continuity has been reported by HCPs as potentially affecting the initiation of certain treatments, such as insulin, because they perceive that not being able to maintain follow-up of their patients makes more difficult for them to assess effectively patients' needs, concerns and circumstances (Lee et al., 2012, Pooley et al., 2001). Lack of continuity of care was also described as creating communication problems as it becomes difficult to be familiar with patients' circumstances and to deal with patients' concerns effectively (Pooley et al., 2001). Equally, Lee et al. (2012) reported that physicians in their study believed that they were unable to maintain the follow-up of their patients due to lack of continuity of care. However, HCPs also described that sometimes the inability to provide continuity of care relates to other healthcare system-related barriers, such as lack of personnel (Lee et al., 2012).

In addition, limited availability of educational materials, and language barriers among people from different ethnic and linguistic backgrounds have been described as factors affecting effective communication with patients and optimal disease management (Daniels et al., 2001, Lee et al., 2012, Al-Alawi et al., 2019). Milos et al. (2014) conducted focus groups with GPs in primary care in Sweden and reported that some GPs considered that educational materials with patient-adapted information about guidelines would benefit the patient-doctor relationship by creating a dialogue about the treatment approach. Thus, evidence-based information written in a way that is easily understandable by patients was believed to be a good alternative that could help patients to better understand HCPs' suggestions and approach to treatment, and foster discussion.

2.3.2.2 Attitudes, experiences and views on clinical guidelines

In this sub-section, I will draw upon HCPs' attitudes and experiences in relation to evidence-based clinical guidelines. Studies that have looked at HCPs' experiences of clinical guidelines for the management of T2DM were scarce. Hence, in order to better understand how HCPs use clinical guidelines to inform their decisions, I reviewed a broader literature and included studies that looked at clinical guidelines in a more general way. Therefore, this sub-section is not included under the organisational factors.

Some studies have shown that clinical outcomes improve when HCPs adhere to clinical guidelines recommendations. However, quantitative studies have reported a generalised lack of adherence to guidelines (Barth et al., 2016, Qiu et al., 2015). For the management of T2DM, guidelines are considered essential tools for the improvement and standardisation of patient care (Barth et al., 2016). As described in chapter 1, guidelines have included algorithms to help health professionals decide on when to start GLM. In this section, I will discuss HCPs' attitudes towards guidelines, the ways in which HCPs such as GPs and nurses follow them, and the possible reasons behind differences in how they approach and implement these guidelines.

Healthcare professionals' perceived quality and usefulness of clinical guidelines.

Overall, studies which have explored HCPs' perceptions and attitudes have found that guidelines are seen as useful tools, which help support evidence-based decision-making and improve quality in the general practice by standardising healthcare and guiding practice to optimal care (Alexander et al., 2016, Hunt et al., 2012, Ingemansson et al., 2014, Luijks et al., 2015, Solà et al., 2014). However, some studies have also reported ambivalent feelings amongst some HCPs. In a study conducted by Radwan et al. (2018), who interviewed 20 senior doctors and nurses managing chronic diseases in Palestine, HCPs praised the existence of clinical guidelines; however, some revealed that they questioned the quality of the evidence informing them as they considered it outdated. Similarly, Baynouna Al Ketbi and Zein Al Deen (2018) conducted focus groups with 25 physicians in the United Arab Emirates. The authors reported that although recommendations in guidelines were valued by participants, HCPs reported being concerned that some recommendations might not apply to all patients. Likewise, Alexander et al. (2016) interviewed physicians in Canada and reported that overall guidelines were seen as useful, however, some participants expressed reservations and concerns about the quality of the evidence used during guideline development as, according to them, guidelines were not developed by primary care doctors. However, a note of caution is due here since this study reported findings based on 10 interviews. The authors stated that most physicians reported having time constraints and been too busy to participate, which reflects some of the challenges of interviewing HCPs.

Moreover, many physicians reported that guidelines were not as explicit as they would have liked and lacked clarity with regard to the recommendations (Alexander et al., 2016). Similarly, Carlsen and Norheim (2008) reported from their focus groups with HCPs in Norway that transparency in the development of guidelines and the inclusion of insights from GPs, or a

multidisciplinary group, would provide them with a sense that these are not developed by economic motivation and may take into account the complexity of general practice. In the same way, Luijks et al. (2015) reported that GPs in the Netherlands expressed a need for more detailed guidelines, particularly for patients with multimorbidities because single disease guidelines can sometimes be conflicting and unclear. Some HCPs considered that guidelines sometimes are more focused on cost-efficiency rather than patients' individual needs, and in the case of some complex diseases, such as diabetes and hypertension, HCPs from South Africa and Sweden, have suggested that guidelines might have limited applicability (Daniels et al., 2001, Milos et al., 2014).

Adherence to guidelines

Qiu et al. (2015) concluded from their surveys with physicians in the US that one of the main impediments to diabetes guideline adherence may be related to the complexity and uniqueness of each patient. In the same way, GPs in Sweden interviewed by Ingemansson et al. (2014) expressed that the use of clinical guidelines depended on each patient's situation since it is common that many people who they see in primary care have multiple health problems. This aspect entails two elements to consider. Firstly, that HCPs may often perceive that clinical guidelines reduce patients to "simple figures" (Aujoulat et al., 2015, p. 3), and secondly, narrowing HCPs' role by not allowing them to exercise their own clinical judgement (Aujoulat et al., 2015, Ingemansson et al., 2014). This is exemplified in the work undertaken by Le et al. (2015) who interviewed GPs working in primary care in Denmark, and reported that guidelines may be implemented in different ways depending on the practice's structure and internal organisation as some had organised collective activities to discuss and implement guidelines. Furthermore, in this study, GPs mentioned that guidelines were something from which to find inspiration, compare ideas or to have an opinion about but not something to which they have to adhere to strictly (Le et al., 2015).

Other studies have also reported that HCPs often refer to their own knowledge and clinical experience to assess whether the recommendation should apply to particular patients with particular health conditions because the main factor influencing their decisions is patients' safety. For instance, HCPs might deviate from a guideline's recommendations whenever they consider it necessary, and overall, recommendations seemed most likely to be followed in the case of younger and relatively healthier patients than for elderly or more complex patients with multiple diseases (Luijks et al., 2015).

Moreover, research on HCPs' views on guidelines for people with multimorbidities or chronic illness (Luijks et al., 2015, Hunt et al., 2012), and diabetes (Alexander et al., 2016) have reported that HCPs' decisions also varied depending on the patient's circumstances, which included the patient's life expectancy or stage of the disease. According to the HCPs, some of the guidelines' recommendations were not often applicable to all patients, and sometimes guidelines lacked clear solutions, which led them to adapt their decisions to patients' characteristics and specific situations (Alexander et al., 2016, Luijks et al., 2015, Hunt et al., 2012). Similarly, GPs in the Netherlands who participated in focus groups conducted by Luijks et al. (2015) expressed that although useful, the applicability of clinical guidelines is limited for people with multimorbidities, GPs particularly expressed the need for better support in diagnosing, treating and managing priorities in people with multimorbidities.

Furthermore, HCPs' have reported that high workload, high demand for efficiency in their work, and time constraints increased stress among them and hindered the optimal use of guidelines. For instance, some HCPs reported that, given their lack of time, the omission of some recommendations, such as lifestyle advice, might have happened due to their high workload and limited consultation length (Daniels et al., 2001, Ingemansson et al., 2014). Despite the views mentioned above, clinical guidelines were valued and considered fundamental as an aid when initiating

or intensifying pharmacological treatment. In general, when making decisions on pharmacological treatment, Milos et al. (2014) reported from their interviews with Swedish GPs that a key motivating factor for guideline adherence was time saved as GPs often lacked time to self-inform about new drugs and treatments. Thus, having the evidence-based information synthesised in a guideline was seen as useful, and when the need arose, HCPs based their decisions about drug prescription on guidelines' algorithms which need to be constantly updated and discussed, especially when new drugs became available (Milos et al., 2014). However, constant changes or updates of guidelines made it more difficult for HCPs to adhere to them, especially if the guideline's topic was not of their own interest (Le et al., 2015).

Some studies have reported that HCPs repeatedly expressed their dislike of long guidelines, with a lot of facts. Long guidelines were regarded as difficult to scan through and use and, together with time-constrains in primary care, length was believed to have become a hurdle to the application of guidelines (Ingemansson et al., 2014, Kinnunen-Amoroso, 2013). Tracy et al. (2003) reported from their interviews with family physicians in Canada that heavy workloads was one of the barriers most commonly reported by participants to the use of guidelines. In a similar way, some participants in the study conducted by Alexander et al. (2016) described being concerned about guidelines' length, especially because there are several guidelines for different diseases and consulting all of them is a highly time-consuming task. Furthermore, Solà et al. (2014) who conducted focus groups with 46 physicians in Spain, reported that many physicians suggested that the format and presentation of clinical guidelines could be enhanced by using plain simple language, with no ambiguities, in an electronic format and a summarised version available with the most important recommendations for clinical practice (Solà et al., 2014).

HCPs' perceptions of their own role may be an important factor in guideline adherence. For instance, Tracy et al. (2003) described that Canadian physicians reported to use guidelines as a starting point but favour their intuition and clinical experience when making decisions. This view is supported by Ingemansson et al's study where it was reported that some GPs saw guidelines as a set of instructions to be followed and thus, felt controlled and disrespected in their role as healthcare provider, as by following guidelines they felt they would have little input into what and little chance of learning from their own experiences (Ingemansson et al., 2014). Equally, GPs interviewed by Aujoulat et al. (2015) reported that treating to target narrowed their role of health promoter by not allowing them to provide the health care that they considered their patients to need and, also, reducing patients to simple figures *"A patient cannot be reduced to figures! Figures alone cannot reflect the complexity of clinical cases. Every situation is unique! We do have targets for our patients, but targets need to be adapted to every patient's individual situation"* (Aujoulat et al., 2015, p.3). Hence, HCPs want to exercise their own clinical judgement when treating their patients. Likewise, Mayer and Piterman (1999) conducted focus groups with GPs in Australia. The authors reported that GPs often described to exercise their own clinical judgement based on their experience and taking into account their patients' context and their issues rather than following guidelines strictly. In this instance, Pather and Mash (2019) reported from their interviews with family physicians in South Africa that these HCPs described a need for contextualising guidelines for the local use and the user (i.e. physician, nurse).

Variation in clinical guidelines adherence and implementation

HCPs' role within the healthcare team (i.e. nurse, doctor) might have an influence on whether and to what extent guidelines are used. Kinnunen-Amoroso (2013) carried out qualitative semi-structured interviews with doctors and nurses to explore their attitudes towards evidence-based

guidelines and the barriers and facilitators to using and implementing them. It was reported that, in general, doctors were more familiar with the guidelines than nurses. However, nurses reported greater adherence to guidelines than physicians; the author described that while doctors were more proactive in the search of new information, nurses considered themselves as “obedient” (Kinnunen-Amoroso, 2013, p.614) and use the information that was provided to them by their employers. Regarding differences in HCPs’ role, Daniels et al. (2001) who undertook interviews and focus groups with doctors and nurses involved in diabetes care in South Africa, reported that nurses considered guidelines especially useful for understanding physicians’ decisions on treatment (Daniels et al., 2000). However, the authors did not provide any insight about this finding.

Moreover, Lawton et al. (2016), and Gabbay and May (2004) reported from their interviews with HCPs in the UK that GPs usually felt more autonomous and were able to deviate from procedures to tailor patient care, and often they only would look through guidelines to reassure themselves that there was nothing major that needed changing, and if it was, it would be discussed with other colleagues. Conversely, nurses were generally more stringent and followed procedures and policies. This might be related to that they feel more pressured than GPs to achieve targets; however it is also reported that nurses would turn to guidelines when faced with an unfamiliar problem, and once they were familiar with the procedure they would rarely if ever look at the guideline again. Gabbay and May (2004) reported, from their ethnographic study in two primary care practices in England, that clinicians privileged experience over any other form of knowledge and usually acquired what they thought was the best evidence from their professional networks. This was particularly true for GPs who, compared to nurses, had more opportunities for external networking with other doctors (Gabbay and May, 2004).

The work undertaken by Ingemansson et al. (2014) and Le et al. (2015) have shown that the implementation of guidelines varies between practices. For instance, GPs interviewed by Ingemansson et al. (2014) reported that when new guidelines arrived, they reviewed them through structured group-dialogues in their primary healthcare centres. In these group-dialogues, GPs expressed they had a great opportunity for exchanging knowledge, receiving feedback and being socially and intellectually stimulated.

In the same manner, Le et al. (2015) reported that GPs in Denmark implemented guidelines in different ways. While some informally discussed new clinical guidelines, others did so in formalised meetings and made informal oral agreements to make changes, based on guidelines, in their practices. Furthermore, some prepared protocols for the practice's staff modifying clinical guidelines according to their practice's needs (Le et al., 2015). However, this study is limited by its sample size since the authors only interviewed seven GPs.

2.3.2.2.1 Patient-centred care

Having discussed HCPs' attitudes to and implementation of clinical guidelines, I will now move on to discuss their views and perceptions of patient-centred T2DM care. As argued previously, HCPs perceived adherence to guidelines as sometimes conflicting with tailored care as, with the former, specific patients' characteristics are not taken into account. For example, some Swedish GPs expressed that they felt free to deviate from guidelines as, according to them, the aims of guidelines are not always in alignment with patients' needs and mostly were concerned with drug costs (Milos et al., 2014). Thus, having a holistic view of patients when making patient-centred decisions may often result in deviation from guidelines or omission of some recommendations (Lawton et al., 2016, Luijks et al., 2015).

However, before describing the literature on patient-centred care, I would like to refer to a term commonly used in the literature on patient-centred care:

shared decision-making. In a recent publication by the Scottish Government entitled *"What works to support and promote shared decision making: a synthesis of recent evidence"*, shared decision-making is described as encompassing the assurance that the people are completely aware of risks and benefits to better inform the consent process, and that it is incorporated the person's values and preferences, when making clinical decisions, to enable a person-centred approach. Moreover, decisions should be made by utilising the expertise of the clinician and the knowledge of the patient and what matters to them. The benefits of shared decision-making are the recognition of the patient's right to be involved in their healthcare decisions and the focus on treatments and options with more beneficial outcomes to the patients. In Scotland, it has been recognised that conducting realistic medicine by recognising patient's preferences may bring greater benefits to the healthcare system and its users (The Scottish Government, 2019).

In relation to T2DM, Alexander et al. (2016) reported from their interviews with physicians in Canada that these individuals often reported having a similar approach to treatment for diabetes, regardless of disease duration. Thus, they described that when managing patients with long-term T2DM or with a recent diagnosis they sought to provide education, guidance and shared decision-making. HCPs pointed out that each patient is different; they often have different expectations of their treatment and have different levels of commitment and adherence to their disease management. Therefore, given the uniqueness of each patient, treatment would usually encompass shared decision-making (Alexander et al., 2016). However, the authors only conducted 10 interviews, and participants were purposively sampled, participants were excluded if they reported not using clinical guidelines routinely; hence, findings may not be generalisable due to the small number of interviews and the HCPs expressed use of clinical guidelines, which may have particular perceptions of patient-centred care.

Similarly, Aujoulat et al. (2015) reported that GPs in Belgium, who participated in group interviews to elucidate their beliefs about clinical inertia, described involving patients in their decision-making. Thus, they based their treatment approach on patients' goals, possibilities and preferences. GPs also mentioned that sometimes not treating could be the result of complex clinical reasoning and not necessarily failure to initiate GLM in a timely manner. Additionally, GPs believed that patients should have an active role in the consultation and clinical decision-making (Aujoulat et al., 2015).

2.3.2.2.2 Pay for performance schemes

So far, the evidence suggests that generally, treatment decisions made by HCPs are the result of a complex interaction between patients' characteristics, time resources and clinical guidelines. However, HCPs also have to act in accordance with national frameworks, such as pay for performance schemes implemented by the healthcare system. This following section seeks to examine HCPs' interpretation and approach to pay for performance schemes, which may bring greater insight into clinical decision-making in the pharmacological management of people with T2DM.

As previously mentioned, guidelines for diabetes care and management usually include, among other things, targets for glycaemic control. Compliance with these targets is, to some extent, monitored by frameworks; such as QOF, although, as described in the previous chapter, this has now been decommissioned in Scotland. These frameworks are commonly developed as pay-for-performance schemes that measure achievement of indicators related to processes and outcomes of health conditions (ISD Scotland, 2016c, Roland and Guthrie, 2016).

The literature search yielded five studies which looked at pay-for-performance schemes. A narrative account of the studies focused on such schemes is presented in this last sub-section. Given that in Scotland the QOF was recently decommissioned, it is important to include studies which

may bring insights on the impact that this scheme potentially had on the management of some diseases.

Moreover, these schemes can shape the relationship between HCPs and their patients and between HCPs. This has been exemplified in the work undertaken by Lawton et al. (2016) who interviewed GPs, nurses and practice managers in the UK, many of the participants considered that, for effective implementation and achievement of indicators, it was important to have effective communication between HCPs and their patients, between colleagues and between primary and secondary care. However, GPs also reported that trying to reach targets imposed by frameworks could negatively influence consultations by adding an extra pressure that may affect their rapport with patients, and that some targets might be inappropriate for some patients, such as the elderly and those on multiple medications.

Furthermore, the implementation of new policies requires reorganisation of HCPs' roles. In relation to QOF, McDonald (2008) conducted an in-depth qualitative case study in two general practices in England to investigate mechanisms and perceptions of control of their autonomy following the implementation of the pay-for-performance contract in general practices. The practices observed varied in size. The largest practice had an individual lead staff member for each of the QOF target areas who was free to decide how to organise their workload in order to achieve the required performance levels. GPs in this practice adopted a surveillance and feedback approach and considered QOF implementation as something positive. However, they also expressed that QOF resulted in only small changes to their existing practices. In contrast, the medium size practice had one GP responsible for overseeing and leading the whole process. Nurses had a particular perspective on the framework; they described feeling demotivated by the constant criticism of their performance by the GP responsible for monitoring the processes. Nurses also expressed concerns about the targets and their

potentially negative consequences for patient-centred care (McDonald, 2008).

In a similar study conducted by McDonald et al. (2007) in which they sought to explore the impact of financial incentives for quality of care on practice organisation, clinical autonomy, and internal motivation of doctors and nurses working in primary care. HCPs from two general practices in England expressed the view that they were concerned about the need to collect information, which they thought could affect the quality of consultations, and that the desire to reach targets would lead to patients be treated as conditions and not as people. This view was again more prevalent among nurses than doctors (McDonald et al., 2007). Overall, most HCPs expressed support for the scheme. However, a small number of doctors complained about surveillance by colleagues, and some respondents described potential distortions of clinical practice through neglect of non-incentivised aspects of care, although they described these as occurring in other practices, not their own (McDonald et al., 2007).

In the study by McDonald (2008), HCPs from both practices expressed dissatisfaction about financial rewards associated with QOF. However, McDonald et al. (2007) also reported that sometimes the quality incentive scheme was a source of professional motivation, especially for nurses who were assigned responsibility for monitoring one or more target areas. Conversely, GPs who were not clinical leads sometimes waited until they were found out by the lead partner responsible for the surveillance, rather than proactively pursuing targets. However, there was no evidence that QOF implementation was a threat to internal motivation or HCPs' core values (McDonald et al., 2007).

Pay-for-performance schemes are not always considered as positively by HCPs. For instance, qualitative interviews conducted with clinicians in the US by Hunt et al. (2012) suggested that pay-for-performance programs may

further contribute to polypharmacy. One interviewee reported, *"I wouldn't really like to admit it, but the insurance companies making a financial carrot is probably one impetus for really cracking down on my diabetics to get them 7.0% or less."*(Hunt et al., 2012, p.456). Moreover, Hunt et al. (2012) reported that patients with chronic diseases managed in primary care usually were started on GLM after having moderately elevated test results. According to the authors, this may be because HbA1c threshold levels changed just before the study was conducted (Hunt et al., 2012).

Overall, GPs expressed a professional ideology that defended patients' needs over clinical goals. Moreover, some GPs suggested that financial incentives might shift the focus from the patient's benefit to the immediate financial reward. Some GPs were concerned that incentives could lead to perverse consequences arguing that it is unethical for prescribing targets to be dependent upon remuneration since effective prescribing should be a professional responsibility. Furthermore, GPs also suggested that the financial return was too little for the increased workload demanded (Prosser and Walley, 2007).

2.3.3 Section summary

This section has discussed HCPs' experiences of views about T2DM care and management. Moreover, HCPs attitudes towards clinical guidelines and frameworks were presented. Although there is a relatively large body of literature which has looked at HCPs' attitudes and perspectives about clinical guidelines, few studies have looked at these issues in the context of T2DM.

Most of T2DM care and management is conducted by HCPs working in primary care. Although HCPs are responsible for treatment choices, clinical decision-making is a complex process that involves the HCP, the patient and the healthcare system. In the studies presented above, HCPs reported informing their decisions by considering patients' characteristics and attitudes. However, studies conducted by Lee et al. (2012) and Zafar et al.

(2015) showed that HCPs' approach to managing T2DM may vary depending on clinicians' expertise and special interest in T2DM.

HCPs also described their views and attitudes towards clinical guidelines. Overall, HCPs had different approaches to guidelines depending on their professional role and their responsibilities in their implementation. Moreover, HCPs reported a need for more transparency in the development of guidelines' recommendations; particularly clinicians who expressed a need for including input from primary care colleagues. This plea for transparency is of great importance as, in order for strategies to be implemented, it is essential that those executing them to believe in their value. Otherwise, guidelines' development might be interpreted by some HCPs as a failure to appreciate the complexity of medical practice, and perceived as a mere intention of standardising prescribing practices. Furthermore, to be considered as a reliable source of information and provide feelings of trust, guidelines need to be constantly updated. It is important noting that most of the studies presented about clinical guidelines did not particularly focus on T2DM.

Patient-centred care, which was considered fundamental by HCPs, entails knowing the patient's characteristics and conditions. However, the lack of continuity of care and time constraints were described as sometimes making difficult for HCPs to familiarise themselves with particular patients. Furthermore, HCPs had diverse views on pay for performance schemes, while some considered them as a professional motivator, others believed it was a drawback in person-centred care.

The scope of this section was limited to qualitative evidence where the researchers recruited participants from specific geographical locations and time. Thus, the findings here summarised might not be representative of the healthcare system in the UK or the current context in terms of guidelines and frameworks.

2.4 Summary

This chapter has attempted to summarise all relevant literature about GLM initiation, particularly among people with newly diagnosed T2DM. However, as I identified in the literature search, little attention has been paid to the period soon after diagnosis, in both quantitative and qualitative research.

Patterns of drug prescriptions for people with T2DM have previously been studied in the UK (Gallagher et al., 2015, Hamada and Gulliford, 2015, Higgins et al., 2016a, Sharma et al., 2016, Sinclair et al., 2012). However, most of these studies have focused on treatment intensification rather than treatment initiation and factors associated with it. Similarly, the literature review made evident the dearth of studies on HCPs' reasons for initially prescribing GLM in people with recently diagnosed T2DM.

Furthermore, this review highlights the complex variety of factors, which may affect approaches to the management of diabetes. These factors include HCPs' characteristics, their approach and views about clinical guidelines and patients' characteristics. Additionally, in relation to GLM prescription in people with newly diagnosed T2DM, the review of the literature made evident some research gaps. For instance, there was a lack of information about the differences between people who received drug prescription and those who did not. Likewise, most studies about treatment initiation have focused on HbA1c levels but there is a need for more information on other clinical aspects that might be related to drug treatment initiation, and to know to what extent HCPs take into account patients' opinions when deciding to initiate GLM. Moreover, few studies have looked at potential differences according to HCPs' professional role (GPs vs nurses) and the use of clinical guidelines for T2DM. Lastly, it still remains to be known the perceived impact on diabetes care after QOF's decommissioning in Scotland.

The literature here presented served as the foundation of this PhD, this chapter highlighted a gap in knowledge regarding GLM in people with newly

diagnosed T2DM. Very few studies have described the factors associated with time to GLM initiation in people recently diagnosed with T2DM. Moreover, there is a need to gather more up-to-date data, and to include a qualitative research component in order to understand the reasons underlying and informing treatment patterns and decision-making about when to initiate medication. Thus, based on these gaps and the results from the literature review I informed the design and conduct of a mixed-methods study which I will describe in the following chapter.

Chapter 3 Research Design

3.1 Introduction

This chapter describes the mixed-methods research design used to address the research questions. The aims, objectives and research questions are presented as well as the rationale for the decision to use a mixed-methods design. In addition, the specific methods for each strand of the study (quantitative and qualitative) are presented. Finally, an overall summary of the chapter is given.

3.2 Aims and objectives

This study aimed to describe factors associated with the initiation of GLM in people with newly diagnosed T2DM and the underlying reasons for starting pharmacological treatment in a Scottish primary healthcare context. The purpose of this convergent parallel mixed-methods study was to combine quantitative and qualitative data to allow a deeper insight into GLM initiation in people with T2DM. Thus, the study was formed by two strands: one quantitative and one qualitative.

The quantitative strand comprised a retrospective cohort study design, which was used to generate data describing GLM prescription patterns, specifically exploring factors associated with time to initiation of GLM amongst people with newly diagnosed T2DM. For the qualitative strand, interviews with HCPs working in primary care were undertaken. The interviews were used to identify and explore factors and considerations that might influence clinical decision-making in relation to initiation of GLM in people with T2DM in a Scottish primary healthcare context. Combining two different and complementary kinds of data can produce valuable information. The data generated can inform policymakers about factors that HCPs take into consideration when deciding on initiating GLM in people with newly diagnosed T2DM.

3.3 Research questions

The overarching research question that this study attempted to answer is the following:

What leads to the initiation of glucose-lowering medication in people with newly diagnosed T2DM in primary care in Scotland?

However, in order to provide a sense to what each method can contribute to answering, a mixed-methods research question following Creswell and Plano Clark's approach was developed. This mixed-methods research question is the following:

What factors are associated with GLM initiation, and what are the views and experiences of healthcare professionals working in primary care about when to initiate GLM?

In order to answer the research question, sub-questions associated with each strand of the study were developed. Thus, drawing upon two strands of research into GLM initiation amongst people with T2DM, the sub-questions that this study sought to answer are:

For the quantitative strand:

1. What is the proportion of people with T2DM who have and who have not received prescriptions for GLM within two years after diagnosis, and how do characteristics differ between people who have and who have not received a prescription for GLM within two years after diagnosis of T2DM?
2. What is the proportion of people with T2DM and sub-optimal glycaemic control without a GLM prescription two years after diagnosis?
3. What factors are associated with time to GLM prescription for people with T2DM within two years of diagnosis?

In addition, for the qualitative strand:

4. What are HCPs' reasons for starting GLM in people with recently diagnosed T2DM?
5. What factors and considerations HCPs take into account when starting individuals recently diagnosed with T2DM on GLM?
6. How and in what ways do HCPs use clinical guidelines to inform their decision-making in relation to initiating GLM?

3.4 Methodological approach: mixed-methods

A mixed-methods approach was identified as the best approach to address the research questions. Mixed-methods research combines qualitative and quantitative approaches in the context of one study. Collecting diverse types of data provides a wider and deeper understanding than the two methodologies are capable of providing independently (Kroll and Neri, 2009, Plano Clark and Ivankova, 2016, Tashakkori et al., 2015).

Mixed-methods designs require decisions to be made about the level of interaction between the two strands, the priority and timing of each strand, and the procedures for mixing the strands (Creswell and Plano Clark, 2011, Curry and Nunez-Smith, 2015c). This study adopted a convergent parallel mixed-methods design as described by Creswell and Plano Clark (2011) as its characteristics (see 3.4.2) allow to complement and expand findings from both components to answer the overarching research question.

In the following sub-sections, I will provide an overview of the major mixed-methods designs. Then, I will describe the characteristics of the mixed-methods design I chose for my study. Subsequently, the priority, timing and links between strands will be explained.

3.4.1 Mixed-methods designs

Creswell and Plano Clark (2011) have described six major mixed-methods designs: (1) the convergent parallel, (2) the explanatory sequential, (3) the

exploratory sequential, (4) the embedded design, (5) the transformative design, and (6) the multiphase design. A summary of the characteristics of each of these mixed-methods designs is presented in Table 8.

Table 8. Characteristics of the major mixed-methods designs by Creswell and Plano Clark (2011)

Design type	Purpose	Level of interaction	Stage of integration	Theoretical perspective	Priority
Convergent parallel	To provide a more thorough understanding of a topic and/or validate or corroborate quantitative scales	Independent	Overall interpretation phase	Pragmatism	Equal
Explanatory sequential design	To explain quantitative results	Interactive	Data collection	Post-positivist followed by constructivist	Usually quantitative
Exploratory sequential design	To test or measure qualitative exploratory findings	Interactive	Data collection	Constructivist followed by post-positivist	Usually qualitative
Embedded design	To preliminarily explore an experimental trial To provide a complete understanding of an experimental trial To follow-up explanations after an experimental trial	Interactive	Design level	If concurrent, pragmatism. If sequential, constructivist for the qualitative strand and post-positivist for the quantitative strand.	Quantitative or qualitative
Transformative design	To identify and challenge social injustices	Interactive	Design level	Transformative worldview	Quantitative, qualitative or equal
Multiphase design	To implement multiple phases to address a program, objective, such as program development and evaluation	Interactive	Design level	If concurrent, pragmatism. If sequential, constructivist for the qualitative strand and post-positivist for the quantitative strand.	Quantitative, qualitative or equal

Most mixed-methods designs, such as the sequential ones, require the same group of people to be studied. Although different samples size are required for each strand, they involve the recruitment of the same group in order to explain quantitative results (explanatory sequential) or to generalise qualitative findings (exploratory sequential). Consequently, these designs were not suitable for this research (Plano Clark and Ivankova, 2016, Creswell and Plano Clark, 2011, Kroll and Neri, 2009, Padgett, 2012c).

In an embedded design, mixing occurs at the design level; in other words, one study informs the other. Consequently, collection of additional, or a second set of data for both strands is usually necessary (Creswell and Plano Clark, 2011, Watkins and Gioia, 2015). However, this design is used in combination with a clinical trial. Therefore, this design was not suitable for answering the overarching research question.

Likewise, the other two designs, the transformative and multiphase design were not aligned to the research questions of this study. The transformative design is commonly used in disciplines such as social work as it seeks to identify social injustices in order to generate social change. In this design, the subjects of study are marginalised and underrepresented populations. Therefore, the characteristics of this design were not suitable for this research. Likewise, the multiphase design is used to address a large objective by answering a set of incremental questions. In other words, an initial sequential design is implemented, and then a new study is built based on what was learned from the previous one. This design requires not only time available to conduct the different phases of the study but also for the researchers to have experience in large-scale research, sufficient resources and funding (Creswell and Plano Clark, 2011, Kroll and Neri, 2009, Watkins and Gioia, 2015).

Thus, the convergent parallel mixed-methods design was the most appropriate for this study. The characteristics and reasons for the choice of this design are covered in detail in the next sub-section.

3.4.2 The Convergent Parallel Design

In table 8 presented in the previous section, I provided a summary of the main mixed-methods design that showed that each design is useful for different purposes. The convergent parallel design was chosen as its characteristics matched the research question. This is one of the most well-known and widely used approaches; the purpose of this design is to obtain different but complementary data on a topic. The aim is to balance the strengths and limitations of each method to triangulate the data by comparing and contrasting qualitative findings with quantitative results for corroboration or validation purposes and also to develop a more complete understanding of a phenomenon, which in this study is the initiation of glucose-lowering medication in people with newly diagnosed T2DM (Creswell and Plano Clark, 2011, Curry and Nunez-Smith, 2015c).

For this design, data collection can either derive from different samples or study participants, or one strand might be limited to a sub-sample from the other strand. Therefore, this design allowed the use of two different sources of information: a dataset with clinical data from people with T2DM, and interviews with HCPs. The use of data from different samples has the purpose of maximising the yield of distinct potentially complementary sources of evidence (Curry and Nunez-Smith, 2015b).

Furthermore, during the progression of the research, the researcher may work between the components by switching the focus from one strand onto the other iteratively, depending on the logistics of conducting the study (Curry and Nunez-Smith, 2015c, O'Cathain, 2009, Tashakkori et al., 2015). One of the key differentiators of this design is that the outcomes of each strand are independent of each other. Thus, the timing and order of each strand depend

on the logistics of each study (Tashakkori et al., 2015). The flexibility of this design was a useful aspect that allowed me to conduct the research without pauses during the process. For instance, while waiting for ethical approval to conduct the interviews I was able to select the variables of interest for the quantitative strand; I will further explain the process later on in this chapter.

Moreover, since both strands can be conducted simultaneously this is a time-efficient design. Therefore, the convergent parallel approach is used when there is limited time to collect the data or when only limited quantitative and qualitative data can be collected (Creswell and Plano Clark, 2011). However, the differences in qualitative and quantitative paradigms imply that there is no specific set of standards to ensure validation in mixed-methods research. In order to obtain reliable and valid findings, it is important for the researcher to adhere to standards of rigour, which in mixed-methods requires the researcher to be consistent with the theoretical assumptions underpinning the paradigm of the mixed-methods study design chosen (Giddings and Grant, 2009).

Hence, the characteristics of this design are in line with the overarching research question and it offers a practical way of answering the research questions. The overarching research sought to provide a thorough understanding about the initiation of GLM. The mixed-methods research question posed two different types of queries, the first query was about *"factors associated with GLM initiation"*, which looked for relationships between variables, and thus required use of quantitative methods. The second query related to *"views and experiences of HCPs"*, thus qualitative methods were needed in order to capture the experiences and perspectives of HCPs. Since the data generated by each method was considered complementary, each method was given equal value.

For this study, data about factors associated with GLM initiation were drawn from patients' clinical data. These data allowed testing for associations

between patients' characteristics and prescription initiation. In addition, as they are responsible for prescribing GLM, HCPs were interviewed in order to understand their experiences and rationale when prescribing GLM. Therefore, two different samples were used to generate a more comprehensive understating of the initiation of GLM in people with newly diagnosed T2DM and answer the overarching research question. Further details on the rationale behind interviewing HCPs are presented in section 3.6.3.

3.4.2.1 Research paradigm

In this section, I describe the paradigm that informed the mixed-methods design. This paradigm should not be confused with the theoretical stance adopted for the qualitative study, which will be described in section 3.6.2.

The convergent parallel mixed-methods research bases its knowledge on pragmatic grounds. Therefore, pragmatism is the philosophical foundation or "worldview" of this study. Paradigmatic assumptions guide the choice of methodology and methods of the research and the nature of the research-researcher relationship (Giddings and Grant, 2009).

Pragmatism is based on the assumption that all methods have different research paradigms with their own virtues and limitations, it enhances utility over ideology or philosophy and acknowledges the fallibility of knowledge development. It allows the adoption of a pluralistic stance to gather all types of data to best answer the research questions (Padgett, 2012d, Creswell and Plano Clark, 2011). Thus, a pragmatic approach is problem-centred and oriented towards real-world practice. Given that the priority is to answer the research questions, this viewpoint allows the selection of appropriate methods to best answer them, which in this study comprised a qualitative strand and a quantitative strand (Hesse-Biber et al., 2016).

3.4.2.2 Level of interaction and stage of integration

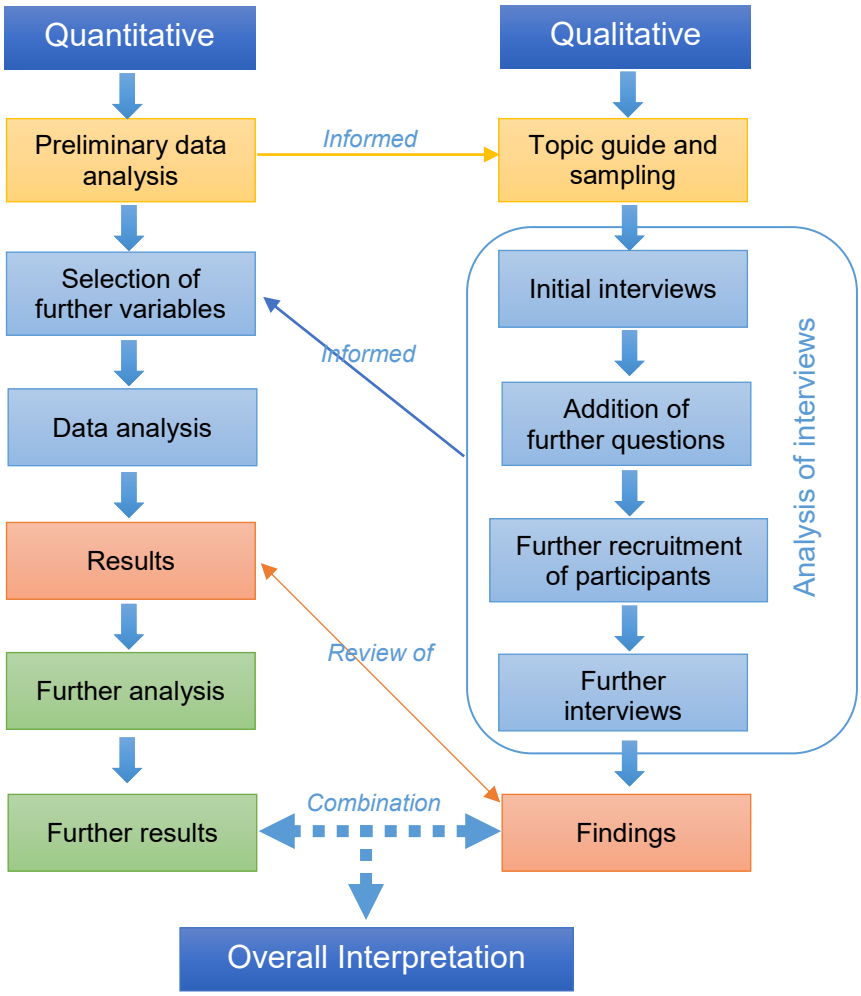
Mixed-methods study designs have different typologies relating to timing, mixing, and priority (Tashakkori et al., 2015). The level of interaction refers to the extent to which each strand of the study is independent or interacts with the other. Accordingly, Creswell and Plano Clark (2011) recognise two different levels, namely independent or interactive. The stage of integration refers to the combination or merging of the strands. This can occur at different stages and typically depends on the major design that is followed. The mixing can occur: (1) during interpretation, (2) during data analysis, (3) during data collection, or (4) at the level of design (Creswell and Plano Clark, 2011).

As previously mentioned, this study used a convergent parallel design which is characterised by adopting an independent level of interaction, meaning that each strand is independent of the other. In other words, research questions, data collection, and analysis are separated, and the strands are only mixed during the conclusions and overall interpretation of the study (Creswell and Plano Clark, 2011). However, Creswell and Plano Clark (2011) hold the view that the options for and combinations of the level of integration, priority, timing and mixing of a mixed-methods research design are limitless and depend on the research question (Creswell and Plano Clark, 2011). Other authors such as Bazeley (2009) have recognised that the purpose and questions of the study should be the main driver for the approach to integration. Equally, Plano Clark and Ivankova (2016) acknowledge that an effective integration requires a “conversation” between the strands. Thus, by informing and enhancing one another, a more comprehensive set of insights can be produced. Hence, for this study, an adaptation to the level of interaction was conducted. While research questions were kept separated for each strand, data collection and analysis followed an interactive process as they were seen as complementary.

As presented in figure 3, the strands of this study interacted during data collection and analysis; yet, the main stage of integration occurred in the discussion. In this manner, each strand was improved by informing the other. For instance, as shown in the yellow boxes, I conducted a preliminary analysis of the cohort, which informed the topic guide that was developed for the interviews with HCPs. In the preliminary analysis I found that HbA1c was one of the main factors associated with initiation of GLM within two years of T2DM diagnosis; however, I also found that non-clinical factors such as age were associated with longer time to drug treatment initiation. These results together with findings from the literature review about factors that inform HCPs' decision-making led me to include in the topic guide a question about other factors besides HbA1c that HCPs consider when choosing a treatment for glucose control.

Similarly, when analysing the interviews and after discussion with the panel during my second-year review, I realised that I needed to include and analyse variables on blood pressure, cholesterol and prescription of other drugs which were not included previously (blue boxes). Then, results from both strands were revised to look for convergency (orange boxes). Although I had found that age was an important aspect, to this point, I had not formally tested or stratified the analysis in relation to this variable. Hence, the green boxes show these further analyses stratified by age. Further variables which were of interest such as the presence of chronic kidney disease or information about prescriber were not possible to be added. Thus, as it has been exemplified in the figure, I sought to enhance each study with findings from the other.

Figure 3. Visual model of the study, based on O'Cathain (2009)



3.4.2.3 Priority and timing of each strand

Another key decision that is necessary to make is about the timing and priority that is given to each strand. For this study, equal priority was given to both strands as they were considered to enhance each other and to increase the potential to understand the phenomenon studied. Therefore, both were considered to have an equally important role in addressing the research question (Creswell and Plano Clark, 2011).

The collection of data in mixed-methods research usually requires more time due to the use of different procedures, and some designs require more time than others. Therefore, the timing of each strand needs to be established, but this is determined by the relationship between them (Curry and Nunez-Smith,

2015c, Halcomb and Andrew, 2009). In mixed-methods studies, timing refers to the completion of the entire strand (i.e. qualitative strand or quantitative strand) and not only to the stage of data collection. Accordingly, a study's timing can be concurrent, sequential, or multiphase (Creswell and Plano Clark, 2011).

Although the major design of this study was convergent parallel, I worked on each strand intermittently. Thus, the timing of each strand was multiphase. As illustrated above in figure 3, I alternated between studies depending on the resources available at the time. For instance, while waiting for ethical approval to conduct the interviews, I was able to work on the quantitative strand by selecting variables of interest. Then, as described above, after conducting and analysing the initial interviews, I added new variables to the dataset.

The use of a multiphase combination timing allowed me to make the greatest use of the time available for the PhD. This timing enabled me to work continually on the research and provided me with the opportunity to enhance each study with preliminary findings from the other.

3.4.3 Time frame

Here the times and procedures in collecting and analysing qualitative and quantitative data are summarised. Further details of each strand are presented later in the sections concerned with quantitative and qualitative methods.

3.4.3.1 Data collection

The elements included in data collection are sampling procedures, obtaining permissions, and collecting information/recording data. Following the general structure of convergent parallel designs, both strands commenced at roughly the same time. However, there was a cyclical fluctuation between strands as can be seen in Table 9. Overall, data collection for both strands was conducted over an 18-month period, from March 2017 to September 2018.

Table 9. Overview of data collection procedures and time frames

Element	Quantitative strand		Qualitative strand	
	Time frame	*Procedure*	*Time frame*	*Procedure*
Sampling	March – April 2017	• Identification of the cohort for the study	July 2017	• Identification of participants for the study • Identification of the sampling and recruitment strategies
Permissions	March 2017	• Taking the e-course "research data and confidentiality" by the MRC	December 2017 – March 2018	• Obtaining Ethical approval
Data Collection	October – November 2017 August 2018+	• Dataset access • Selection of variables of interest • Obtaining final database+	October 2017 – January 2018 March – September 2018*	• Selection of method to collect data • Preparation of topic guide • Interviewing participants*

+ An initial dataset was obtained at the end of the year 2017. However, the identification of new variables of interest led to the creation of a new and final dataset, which was obtained in 2018. * Interviews were conducted after obtaining ethical approval.

3.4.3.2 Data analysis and interpretation

After obtaining access to the quantitative dataset and completing the interviews with the participants, the next steps were (1) to prepare and explore the quantitative and qualitative data, and (2) to analyse and interpret the quantitative and qualitative data. These steps were implemented simultaneously and iteratively; findings from the quantitative strand required me to go back to the interview transcripts, and findings from the qualitative

strand suggested the inclusion of additional variables. Furthermore, in the qualitative strand, the themes identified were intertwined, and the writing process was iterative in order to find the most suitable way to present them. The time frame for the procedures associated with data analysis and interpretation are summarised in table 10

Table 10. Summary of procedures conducted for each strand

Element	Quantitative strand		Qualitative strand	
	Time frame	Procedure	Time frame	Procedure
Data preparation	January – March 2019	• Clean the dataset • Recode and or compute variables • Preparation of analysis plan • Multiple imputations	April – October 2018	• Transcription of the interviews • Anonymisation of participants' data
Data exploration	April 2019	• Inspection of the data visually • Check for distributions	April – October 2018	• Read through data • Identifying and developing themes to code data
Data analysis	April – June 2019	• Analysis of data according to research questions • Use of statistical software	September – December 2018	• Code the data • Interrelate themes
Data analysis representation	June – September 2019	• Writing up results • Elaboration of tables and figures to explain results visually	December 2018 – September 2019	• Writing up results in themes

3.4.4 Ethical considerations

In order to collect data, permission needs to be sought from the individuals who will provide the information (or their guardians/representatives) and sometimes from the sites where the study is conducted (Creswell and Plano Clark, 2011).

With the purpose of obtaining permission to access to the quantitative dataset, I completed the e-learning course assessment for Scotland on "Research Data and Confidentiality". This course is offered by the Medical Research Council and covered the following topics:

1. The concept of confidentiality and how to work within the law
2. Some principles of the Data Protection Act
3. Consent and the issues in accessing data for research without consent
4. Appropriate disclosure and routes for access without consents
5. Accessing data from the Office for National Statistics and the NHS, and
6. Archiving and sharing research data.

After successful completion of this course in March 2017, Professor Sarah Wild and Dr Jeremy Walker – on behalf of the Scottish Diabetes Research Network Epidemiology Group, provided me with access to the dataset. For the qualitative strand of this study, ethical considerations are presented in section 3.6.4.3.

Having defined the key decisions of the study design and described the general procedures of data collection, analysis and interpretation of the strands, I will now move on to describe the challenges of reporting mixed-methods research, which will help to understand the decision-making around the structure of the thesis.

3.4.5 Challenges of reporting mixed-methods research

The mixed-methods approach offers the opportunity to develop a thorough understanding of the topic and flexibility. However, designing and conducting mixed-methods research requires careful consideration to be given to the principles and complexities of this approach. There are many challenges to using mixed-methods; these not only relate to the general approach but also to the design used and the ways to report the research (Andrew and Halcomb, 2009, Creswell and Plano Clark, 2011, Palinkas, 2011). Here I will describe two of the major challenges to reporting mixed-methods research described in the literature: (1) Style, language and voice, and (2) Structure of the presentation.

First, there is often a challenge imposed by differences in jargon for quantitative and qualitative methodologies. Different voices are associated with each strand posing the dilemma of which to use. Researchers can adopt the language associated with each component. However, the paradigm will be relevant when deciding which voice to adopt. For this research, the approach adopted was pragmatism. This approach permits the use of whichever style suits different parts of the report (O'Cathain, 2009, Creswell and Plano Clark, 2011). Thus, in line with the paradigm of the convergent parallel mixed-methods design, a flexible approach to language was adopted for this thesis (Creswell and Plano Clark, 2011). For instance, the first person subjective voice is seldom used in the chapters on quantitative results, whereas for the quantitative sections, this voice was used more frequently.

Second, when conducting mixed-methods research, decisions must be made in relation to the order of data collection, the size of the samples, and whether there will be one or two samples (Curry and Nunez-Smith, 2015a). In the same way, presenting the results poses the challenge of deciding the order of each component. Generally, there are two possible formats: a sequential format where methods and findings of one component are followed by the other component and an integrated format where both

components are incorporated together. While sequential formats are suggested for thesis writing, integrated writing is still preferred in the peer-reviewed literature (O'Cathain, 2009). Table 11 presents the outline of both formats for a doctoral thesis.

Table 11. Formats of report writing based on O'Cathain (2009)

Segregated format		Integrated format
A	**B**	Introduction
Introduction	Introduction	Literature review
Literature review	Literature review	Methods
Quantitative methods	Methods *(quantitative*	Findings based on any or all
Quantitative results	*and qualitative)*	components can be presented in
Qualitative methods	Quantitative results	several chapters (3-4)
Qualitative findings	Qualitative findings	Discussion
Long discussion	Discussion	

In convergent designs, the consequences of having different samples, different samples size and the integration of the findings in a meaningful way need to be considered. (Creswell and Plano Clark, 2011) Therefore, in this thesis, a segregated model B of report writing was considered to be most appropriate because it allowed the presentation of the information in accordance with the mixed-methods design chosen. Furthermore, given that each strand answered complementary research questions, and taking into account that each methodology produces a different type of findings, devoting a dedicated chapter to each strand's findings was considered most suitable.

3.5 Quantitative Methods

This sub-section is concerned with the methods of the quantitative strand of the research. As previously stated, the quantitative strand sought to explore factors associated with time to pharmacological treatment amongst people with newly diagnosed T2DM. The research data for this strand was drawn from an extract of the SCI-Diabetes database, which will be described in the next sub-section.

3.5.1 The SCI diabetes cohort

First, I will describe the source of the data and the criteria used to build the cohort for this study. Then, I will list and define the variables of interest to this research as well as classifying them as dependent and independent variables.

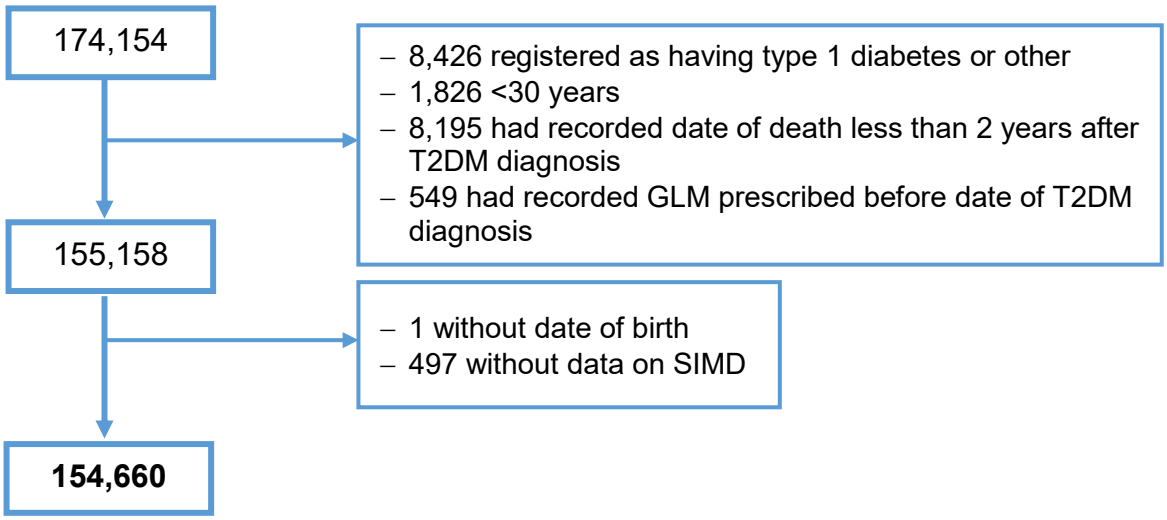
After RCTs, cohort studies are regarded as the most robust design for medical research. Cohort studies provide the opportunity to include a wide range of patients and to compare those exposed and unexposed; this is described as an observational study where the researcher observes the natural events without intervening (Mauricio Barria, 2018, Elwood, 2017). Either data collected as baseline (before an intervention or at the beginning of a study) or existing medical records can be used to identify risk factors for a particular outcome and can deliver findings that can help to understand the relationship between such risk factors and the occurrence of the outcome of interest (Mauricio Barria, 2018).

For this study, the cohort was drawn from an extract of the SCI-Diabetes dataset. The SCI-Diabetes is a dynamic clinical management and information system in which HCPs enter patients' data that is collected nightly from a variety of sources such as primary and secondary care across all 14 health board areas in Scotland (Diabetes in Scotland, 2015, INPS, 2013, Emslie-Smith, 2010). All patients (unless the patient refuses from participation in the SCI-DC) with the following diabetes diagnosis codes are automatically included in the SCI-Diabetes extract: 1) C10% diabetes mellitus, 2) R102 [D] Glucose tolerance test abnormal, 3) R10D0 [D] Impaired fasting glycaemia, 4) R10E [D] Impaired glucose tolerance, 5) L1809 Gestational diabetes mellitus, and 6) 44V2 Glucose tolerance test impaired. Patients records include a classification of their type of diabetes. Moreover, the data included in the SCI-Diabetes includes updated conditions relevant for diabetic monitoring, other data such as test results, blood pressure, height, weight, and updated demographic details to ensure an accurate record of people

actively receiving care. (INPS, 2013, Cunningham et al., 2011). The clinical database provides information to support the treatment of NHS Scotland patients (Diabetes in Scotland, 2015). Pseudonymised extracts of the database are available for research by people with approved data governance training with permission of the Scotland A multi-centre research ethics committee and the Privacy Advisory Committee of National Health Service Scotland (Cunningham et al., 2011).

The dataset used in this study was created for me by Dr Jeremy Walker in 2017 and updated with the addition of new variables in 2018. The initial dataset held information on 174,154 individuals diagnosed with any form of diabetes in Scotland between 01 January 2004 and 31 December 2012. The dataset included for each patient a unique SCI-Diabetes serial number, as well as demographics and clinical data which will be explained in detail in the next sub-section 3.5.2. In order to identify participants suitable for addressing the study aims, participants were selected according to predefined eligibility criteria, which are described in the following sub-section. Overall, based on the eligibility criteria and the addition of further variables of interest, the final dataset which was analysed included information on 154,660 patients diagnosed with diabetes between 2004 and 2012, the flow chart describing selection of participants is presented in figure 4.

Figure 4. Flow chart of selection of participants with newly diagnosed diabetes



3.5.1.1 Eligibility criteria

To limit the possibility of including patients without T2DM and to provide data for follow-up, participants had to meet certain conditions. Primary inclusion criteria for the initial cohort were:

1. Classified as having T2DM diagnosis
2. ≥ 30 years old at diagnosis of diabetes
3. No record of prescription of GLM before the date of diagnosis of T2DM
4. Were followed up and remained alive for at least two years after diagnosis. The inclusion of people who remained alive during the observed period was determined to make certain that prescription prospects were similar amongst participants.
5. Diagnosed between 2004 – 2012

The cut-off age was chosen in order to reduce the chance of selecting patients who may have had T1DM misclassified as T2DM. The requirement for at least two years of follow up after diagnosis is necessary to allow time for measurement of treatment patterns after diagnosis, and to compare the

results with previous research. The date of diagnosis was limited by the research data available at the time of data extract.

3.5.2 Variables of interest

The selection of variables for this strand was based on the literature review and findings from the qualitative interviews. The dependent or outcome variables are drug treatment, time-to-drug treatment initiation, and type of drug prescribed. The independent or exposure variables included demographic variables, metabolic factors such as blood pressure, glucose and cholesterol levels, and the prescription of other drugs such as antihypertensive and lipid-lowering medications.

3.5.2.1 Operational variables definition

A description of each variable of interest is presented in the following sections. First, the dependent variables are presented. Then, a description of the independent variables is provided, which for clarity were grouped into categories such as demographics and metabolic factors.

3.5.2.2 Outcome/dependent variables

A summary of the dependent variables of this study, which were drug treatment and time-to-drug treatment prescription initiation are presented below in table 12.

Table 12. Summary of dependent variables included in the statistical analyses.

Variable	Type	Definition
Drug treatment	Categorical dichotomous variable (yes/no)	The prescription of GLM for T2DM within two years from diagnosis.
Time-to-drug treatment prescription initiation	This variable was treated as a continuous numerical variable for survival analysis and as a categorical variable to allow data stratification as follows:	This refers to the time expressed in days, months or years between the date of diagnosis until the date of first GLM prescription.

	a. 0 to 3 months: consisting of the period from the date of diagnosis to 90 days after diagnosis. b. 3 to 12 months: covering from 91 to 360 days after the date of diagnosis. c. 12 to 24 months: comprising of day 361 to day 730 after the date of diagnosis.	These time frames were chosen in accordance to the SIGN guideline 154 which suggests a review of treatment for glucose-control every 3–6 months when targets are not reached, the Scottish diabetes framework which states that people with T2DM are offered at least an annual review to monitor the progression of their condition. (Scottish Intercollegiate Guidelines Network (SIGN), 2017b, Scottish Government, 2006).
Drug classification	This variable was treated as categorical. It indicates the category of the first drug prescribed within the two years of follow-up. This was created by looking at the anatomical therapeutic chemical (ATC) code corresponding to the patient's first prescription for GLM	Drugs were classified according to their conventional categories as follows: *Metformin:* metformin *Sulfonylureas:* glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide, gliquidone, chlorpropamide *Insulin*: encompassing all insulin formulations. *Others.* Encompassing the following sub-categories: • Thiazolidinediones: rosiglitazone, pioglitazone • Prandial glucose regulator: repaglinide, nateglinide • GLP-1 analogues: liraglutide, exenatide • DPP-4 Inhibitors: sitagliptin, saxagliptin, linagliptin, vildagliptin • Alpha glucosidase inhibitor: acarbose • Herbal: Guar gum

3.5.2.3 Exposure/independent variables

In chapter 2, the need to investigate the combined role of clinical and demographic factors in treatment decisions was highlighted. Hence, I included in the quantitative strand variables related to both, demographic and metabolic factors.

Demographics: Including age at diagnosis of diabetes, ethnicity, sex, socioeconomic status at diagnosis and year of diagnosis. The definition of each variable is presented in table 13.

Table 13. Summary of demographic variables included in the statistical analyses.

Variable	Type	Definition
Age	Continuous numerical variable and categorical, by using the following age ranges: 30-44, 45-59, 60-75, and over 75 years of age. As well as a binary category: ≤65 and >65 years of age.	Represents patients' age at the date of diagnosis. Age categories were selected to facilitate comparison with previous studies, such as Sinclair et al. (2012)
Ethnicity	Categorical in: (1) White Scottish/British, (2) Other and (3) Unknown. However, for the Cox regression analysis, this variable was used as categorical dichotomous: (1) White Scottish/British, and (2) other and unknown.	This refers to the patient's ethnic group.
Sex	Categorical dichotomous: male or female	The person's sex
Socioeconomic status	This variable was used as categorical (quintiles).	Refers to the individual's position within the SIMD condensed to quintiles where 1= most deprived and 5= least deprived. The SIMD is an area-based measure, and it was made by splitting Scotland into small areas and by looking at each

		area indicators such as pupil performance, crime, unemployment, and travel times to the GP among others. Thus, it can be used to find areas of greater need for support (Scottish Government, 2016a).
Year of diagnosis	Numerical	Refers to the numerical variable indicating the year when the person was diagnosed with T2DM. This year was also regarded as the index year.

Metabolic factors: As seen in table 14, these include systolic and diastolic blood pressure, cholesterol, CVD, and BMI, whether the individual was actively receiving a prescription for medication to lower lipids and blood pressure and glycaemic control.

Table 14. Summary of metabolic variables included in the statistical analyses.

Variable	Type	Definition
Antihypertensive medication prescription	Categorical dichotomous (yes/no)	Whether the individual was actively receiving antihypertensive medication at the date of T2DM diagnosis. Antihypertensive medications were included according to the ATC classification system of drugs. The following ATC drug classes were included: i. C02 – Antihypertensives ii. C03 – Diuretics iii. C07 – Beta-blockers iv. C08 – Calcium channel blockers v. C09A – Angiotensin-converting inhibitors vi. C09C – Angiotensin receptor blockers

BMI	Continuous numerical variable and, also as categorical variable based on the WHO's classification of obesity as follows: a. Non-obese: <30.0 Kg/m2 b. Obese: ≥30.0 Kg/m2	Body Mass Index (Kg/m2). The individual's average BMI at the closest date of diagnosis (180 days +/- date of diagnosis).
Cholesterol	Numerical and Categorical variable: (1) normal ≤ 5 mmol/L and (2) High > 5 mmol/L.	An individual's average levels of cholesterol (mmol/L) at the closest date of T2DM diagnosis (180 days +/- date of diagnosis)
CVD	Categorical dichotomous (yes/no).	Indicating whether an individual had a record of admission with a diagnosis of CVD at diagnosis (pre-existing) or during follow-up. The variable was built according to the International Classification of Disease (ICD-10; from i to iii) and the Classification of Surgical Operation and Procedures (OPCS-4; from iv to xi) codes, CVD was identified as having one or more of the following: i. Coronary heart disease I20-I25 ii. Cerebrovascular disease I60-I69, G45 iii. Peripheral vascular disease I70.2, I73 iv. Coronary artery bypass graft K40-K46 (main A position only) v. Percutaneous coronary intervention K49, K50.1, K50.8, K75 vi. Carotid revascularisation L29.4, L29.5, L31.1, L34.4 vii. Aortic aneurysm repair L16.-, L18.-, L19.-, L25.4

		viii. Iliac and femoral bypass/endarterectomy/embolectomy L50.-, L51.-, L52.-, L53.2, L58.-, L59.-, L60.1, .2, L62.2 ix. Transluminal operations including angioplasty L26.1, .2, .3, .8, .9, L31.1, .8, .9 L39.1, .2, .3, .8, .9, L43.1, .2, .3, .8, .9 L47.1, .2, .8, .9, L54.1, .2, .8, .9 L63.1, .2, .3, .8, .9, L71.- x. Major amputation (of leg below, through or above knee) X09.3, 9.4, 9.5 xi. Minor amputation (foot or toe) X10.1, 10.8, 10.9; X11.1, 11.2, 11.8, 11.9 In this study, codes for amputation were included. Although trauma or infection it cannot be discarded as the cause of the amputation, peripheral arterial disease is a common cause (NHS, 2019a).
Diastolic Blood Pressure (DBP)	Numerical and categorical variable according to the SIGN guidelines in (1) Normal ≤ 80 mmHg and (2) High >80 mmHg	The individual's average diastolic blood pressure (mmHg) at the closest day of diagnosis (180 days +/- date of diagnosis).
Glycaemic control	Continuous numerical variable, HbA1c levels were also classified by ranges (<53 mmol/mol, 53-63 mmol/mol, 64-74 mmol/mol, 75-85 mmol/mol, and >85 mmol/mol). Also, according to the SIGN guidelines, HbA1c levels will be classified in optimal/sub-optimal glycaemic control (<53 mmol/mol or >53 mmol/mol).	It is determined by HbA1c levels (mmol/mol). The SIGN guidelines general recommendation for HbA1c target is 53 mmol/mol (7.0%) (Scottish Intercollegiate Guidelines Network (SIGN), 2017b). Baseline data reported the average HbA1c value in the period between 180 days before the date of T2DM

		diagnosis and 180 days after diagnosis.
Lipid-lowering medication prescription	Categorical dichotomous (yes/no)	Whether the individual was actively receiving lipid-lowering medication at the date of diabetes diagnosis For this study, lipid-lowering medications were included according to the ATC classification system of drugs. The C10 “Lipid modifying agents” ATC drug class was included.
Systolic Blood Pressure (SBP)	Numerical and categorical variable according to the SIGN guidelines in (1) Normal < 130 mmHg and (2) High ≥130 mmHg.	The individual’s average systolic blood pressure (mmHg) at diagnosis (180 days +/- date of diagnosis)

3.5.3 Data cleaning

This process was carried out in order to remove potentially inaccurate records from the database. The process was undertaken for the final cohort, including 154,660 patients and consisted of an examination for outliers. Ranges for plausible data were drawn from SCI-diabetes data quality audit in Read (2015) and are presented in table 15.

Table 15. Cut-off points for continuous variables (Read, 2015)

Variable	Lower Bound	Upper Bound
Age	30	105
BMI Kg/m2	15	75
SBP (mmHg)	80	400
DBP (mmHg)	40	300
HbA1c (mmol/mol)	20	304
Total cholesterol (mmol/L)	1.0	15.0

After this, entries outside the cut-off points were removed and treated as missing. Overall, a total of 57 entries were deleted and treated as missing. Detailed information about the variables with implausible data is presented in table 16.

Table 16. Implausible data removed from the original cohort.

Variable	Outliers
BMI at diagnosis	18
SBP at diagnosis	8
DBP at diagnosis	3
Cholesterol at diagnosis	28

3.5.4 Missing Data

After cleaning the data, the proportion of missing data for each of the variables of interest was calculated. The results are presented in table 17.

Table 17. Frequencies and proportions of missing data for variables of interest

Variable	Missing Values	% of missing data
HbA1c at diagnosis	17,756	11.5
BMI at diagnosis	59,810	38.7
SBP at diagnosis	10,295	6.7
DBP at diagnosis	10,290	6.7
Cholesterol at diagnosis	14,999	9.7

Missing data are a common issue where a dataset has information missing for some variables for some cases. Statistical software packages commonly exclude cases with missing information from regression analyses, which can lead to the elimination of an important proportion of cases and biased estimates (Vittinghoff et al., 2012). Different methods to handle missing data have been developed; here, I will describe some of the most commonly used.

3.5.4.1 Handling missing data

There are many different reasons for incomplete data and the simplest method to handle it is by a strategy known as list-wise deletion or complete case analysis (CCA). A CCA is a dataset without missing data due to the exclusion from the analysis of cases with any missing data. As previously discussed, the use of cases with complete data can lead to a substantial reduction of the cases and the introduction of bias. (Allison, 2002, Vittinghoff

et al., 2012) In order to overcome the problem posed by a reduced dataset, it is possible to fill in the missing data to obtain a complete dataset by using standard methods for handling missing data. However, an important step to choosing the best approach is to establish the mechanisms of missing data (Vittinghoff et al., 2012).

3.5.4.2 Mechanisms of missing data

Briefly, data can be missing completely at random (MCAR) when the probability of the data being missing is not associated with any part of the data, thus missingness on a certain variable is not related to missingness on some other variable. Another mechanism for missing data is data missing at random (MAR), which implies a conditional probability of missing data where, for a case, the probability of missing data for a specific variable can depend on another variable related to that particular case but not vice versa. However, it is not possible to test whether the conditions of MAR are met (Allison, 2002, Vittinghoff et al., 2012). Finally, data can be missing not at random (MNAR) when the probability of missingness depends on unobserved quantities; therefore, it is not possible to verify or dismiss MNAR from the observed data. However, under suspicion of MNAR, a sensitivity analysis can be conducted, one way is by multiple imputation (Vittinghoff et al., 2012).

Multiple imputation is often regarded as a reliable method for completing a dataset with missing values; this approach also incorporates random error in order to reflect the degree of uncertainty due to the missing data (Vittinghoff et al., 2012, Allison, 2002). As the name indicates, it is necessary to impute a dataset several numbers of times in order to get valid estimates. The specification of the imputation model requires building a probabilistic model to fill in the missing data, whenever variables are associated with one another, they should be included in the model (Vittinghoff et al., 2012). However, this approach usually requires time to conduct, and although it is recognised as a reliable method, it is not without limitations (Allison, 2002).

One of the most discussed issues is about reliability, which depends on the correct specification of the model (Longford, 2005). I will explain more about this aspect in the following imputation sub-section.

3.5.4.3 Complete case analysis

As previously described, a CCA or list-wise deletion is achieved by excluding all cases with incomplete data. The main advantage of this method is the attainment of a dataset where any kind of statistical analysis can be used. However, if the mechanism of missing data takes any form other than MCAR, the use of a CCA can lead to bias due to the probability of a missing data on an independent variable depending on the values of the dependent variable (Allison, 2002).

3.5.4.4 Imputation

There are different mechanisms of data imputation. In general, these methods imply substituting plausible data for each missing value in order to be able to use a dataset without missing values. Some of the most common mechanisms of imputation are conditional mean imputation, maximum likelihood and multiple imputation which is regarded as more a more efficient method than maximum likelihood and is particularly useful for estimation in a Cox proportional hazards model (Vittinghoff et al., 2012).

Due to its accessibility for a wide range of analyses and availability in some of the main software packages, multiple imputation is becoming the approach preferred for managing partially observed datasets (Carpenter et al., 2012). However, when formulating the imputation model, it is necessary to ensure compatibility with the model of interest. Hence, all the variables in the model of interest should be included in the imputation model, including the response (Carpenter et al., 2012, Vittinghoff et al., 2012).

After considering the different methods of missing data management, a CCA and multiple imputation were chosen for this strand. As previously mentioned, both methods have their limitations. However, their use was

considered necessary to investigate the potential introduction of bias by missing data. Furthermore, as both methods were used, results from the two datasets are presented, as is recommended when imputation is performed. However, as results from both were similar, in the results section it is only presented those for the imputed dataset. The results of the CCA are presented in the appendices.

3.5.5 Complete case analysis

For CCA patients were selected only if they had complete data for the variables of interest. Overall, a total of 66,890 participants had missing information for at least one variable of interest; these cases were deleted and resulted in a complete dataset with no missing data (n= 87,770).

3.5.6 Multiple imputation

Data from the full cohort were analysed to determine the pattern of missing data, e.g. Missing completely at random (MCAR), Missing at random (MAR). Data MCAR will yield a statistically non-significant result when performing a little MCAR test. The little MCAR test for the cohort used in this study was found to be statistically significant, thus failing to prove that data is completely randomly missing. Read (2015) studied the mechanisms of missing data in the SCI-diabetes dataset for people diagnosed with T2DM before 1995 and 2008 plus a sub-analysis of those diagnosed between 2004 and 2008. It was reported that from 2004, once the QOF was introduced, MAR was the missing data mechanism more plausible for the SCI-Diabetes dataset. Moreover, multiple imputation by either predictive mean matching (PMM), multivariate normal (MVN) multiple imputation or multiple imputation using chained equations (MICE) were deemed to be suitable approaches to handling missing data in this dataset. Consequently, as the current study included people diagnosed with T2DM between 2004 and 2012, it was assumed that data is MAR. Here the general approach to handling missing data is described.

The approach to deal with missing data was by means of MICE using the mice package in R software. The imputation model comprised the following variables: age, sex, SIMD, ethnicity, BMI, SBP, DBP, HbA1c, cholesterol, CVD and time-to-drug prescription initiation. Non-normally distributed variables were log-transformed for the imputation process and transformed back for the analysis; this is described more in detail in the section 'Testing assumption of normality'. Furthermore, following what is suggested by the literature, the number of imputed datasets depended on the extent of missing data. Overall, 56.75% of the cases had complete data. Thus a total of 45 datasets were created, which took >48 hours to complete and required me to obtain access to greater computing capacity.

3.5.7 Statistical methods

3.5.7.1 Significance testing

All statistical tests used a significance level of 0.05, and 95% confidence intervals are presented. All p-values were rounded to three decimal places with the exception of p-values that round to 0.0000, which are presented as <0.0001. Any p-value <0.05 was considered statistically significant.

3.5.7.2 Data summarisation

Summary statistics comprised descriptive statistics for the study variables. Percentages and number of responses in each category are described for dichotomous and categorical variables, and the mean and standard deviation are described for continuous variables. In addition, the median and interquartile range are presented when considered appropriate.

All means and percentages were formatted to one decimal place; likewise, the standard deviation was formatted to one decimal place. All summary and comparison tables (e.g. people with and without a record of prescription) have the population sample size for each group of interest in the column heading.

3.5.7.3 Software

RStudio and SPSS version 22 were the statistical software packages used to produce all summaries, listing, statistical analysis and graphs. However, Microsoft Excel was also used to generate some graphs.

3.5.8 Statistical analysis

People diagnosed with T2DM between 2004 and 2012 and who fulfil the inclusion criteria were the main analysis population. The primary outcome of this analysis was the proportion of patients who initiated drug treatment within two years following the diagnosis of T2DM. In addition, the association between patient factors and time to drug prescription was explored.

3.5.8.1 Testing the assumption of normality

Testing the assumption of normality is important for all research; a variable's distribution will determine the appropriate summary statistic and type of analysis to be performed when making comparisons between groups (Sheard, 2018). Therefore, variables were checked for normality. The exploration involved a visual inspection for normality using histograms generated in SPSS.

With the exception of HbA1c, which was positively skewed, the variables of interest followed a normal distribution. Since the multiple imputation method assumes that all quantitative variables follow a normal distribution, a log-transformation of HbA1c was conducted prior to data imputation, and then data were back-transformed. For the subsequent analysis, since the variables had a normal distribution, parametric tests were conducted.

3.5.8.2 Proportions of people with T2DM with and without GLM prescription and their characteristics

Baseline characteristics were assessed using data recorded closest to time of diagnosis; descriptive statistics are presented in tables including demographic data, HbA1c and pre-existing conditions such as CVD. Chi-

square tests and independent-samples t-test were used to examine differences between groups.

The analysis of prescription patterns included only people who received GLM prescription within two years of diagnosis. Descriptive statistics were used to determine the proportion of people who after two years received a certain type of GLM. As previously mentioned, GLMs were classified into four main types: metformin, sulfonylurea, insulin and others.

Further analyses were carried out using age as a continuous variable and stratified by age groups. The Kaplan-Meier estimator was used to show differences in time to drug prescription by age groups.

3.5.8.3 Proportions of people with T2DM with sub-optimal glycaemic control

Participants were categorised into different groups according to their HbA1c levels. The different categories have been previously defined. Descriptive statistics are presented in tables, including demographic data, pre-existing conditions, and whether if received or not a prescription for GLM. Chi-square tests and independent-samples t-test were used to examine differences between groups.

3.5.8.4 Factors associated with time to GLM prescription

For the analysis of the relation between time to drug prescription initiation and covariates, Cox regression models were used. Data were censored for patients who did not receive a GLM prescription during 730 days of follow-up.

Cox proportional hazards models were used to test the association of possible covariates such as age, sex, HbA1c and CVD (both prevalent and incident during follow up) with time to treatment initiation. The Cox proportional hazard model for survival time is a regression analysis used to assess time to events, and there are various continuous or categorical explanatory variables, it is one of the most widely used models for analysis of survival (Vollmer, 2011). The model requires the data to meet the

proportional hazards assumption to be fit for this model; this means that hazard function ratios do not change with time (Vollmer, 2011, Nikulin and Wu, 2016).

Therefore, data were analysed in order to determine their suitability to this model. Further information is presented below.

Checking the assumption of proportional hazards

For continuous variables, the tests to evaluate the proportional hazards assumption were based on the scaled Schoenfeld residuals and tests of non-linearity by plotting the Martingale residuals. These residuals represent the difference between the observed and expected covariate given the risk set at that time, when the assumption is met, a plot of the residuals against individual covariates should be linear (scattered around zero). Overall, the proportional hazards assumption was considered violated when the Martingale residuals plot failed to show a linear relation and the test of the Schoenfeld residuals were statistically significant. Then, if the assumption was violated, the variable was stratified into groups. Thus, it was converted into a categorical variable (Xue and Schifano, 2017).

Table 18 below shows the results of the Schoenfeld residuals. According to these results, it is not possible to assume a proportional hazard in most variables. BMI, SBP, HbA1c, and cholesterol showed a significant relationship which indicates that residuals are not close to zero, and thus refutes the proportional hazards.

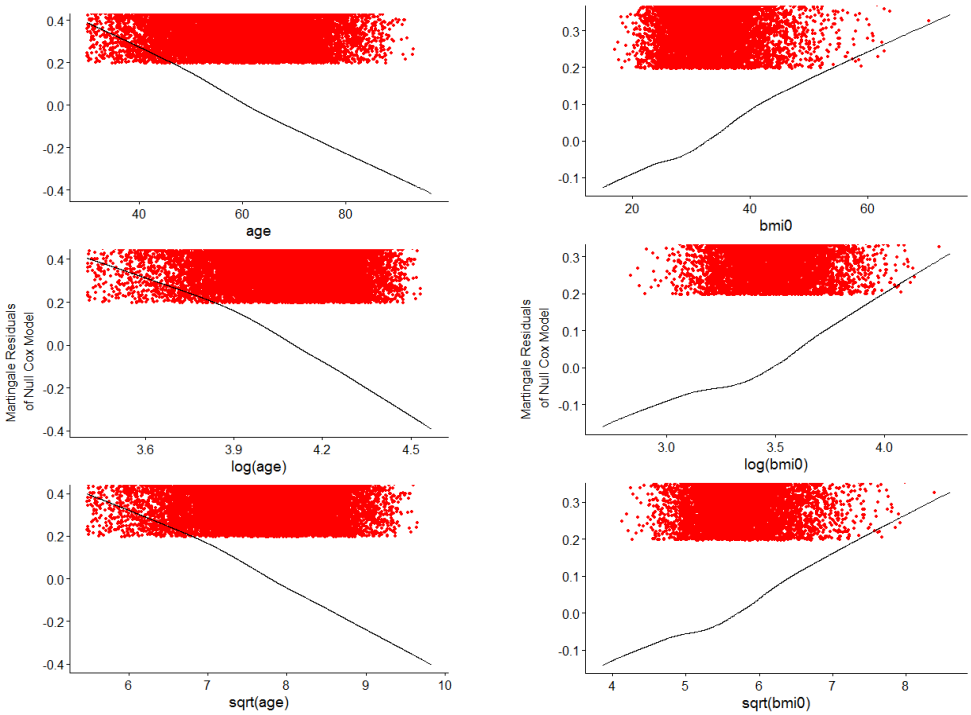
Table 18. Test for the proportional-hazards assumption based on the scaled Schoenfeld residuals

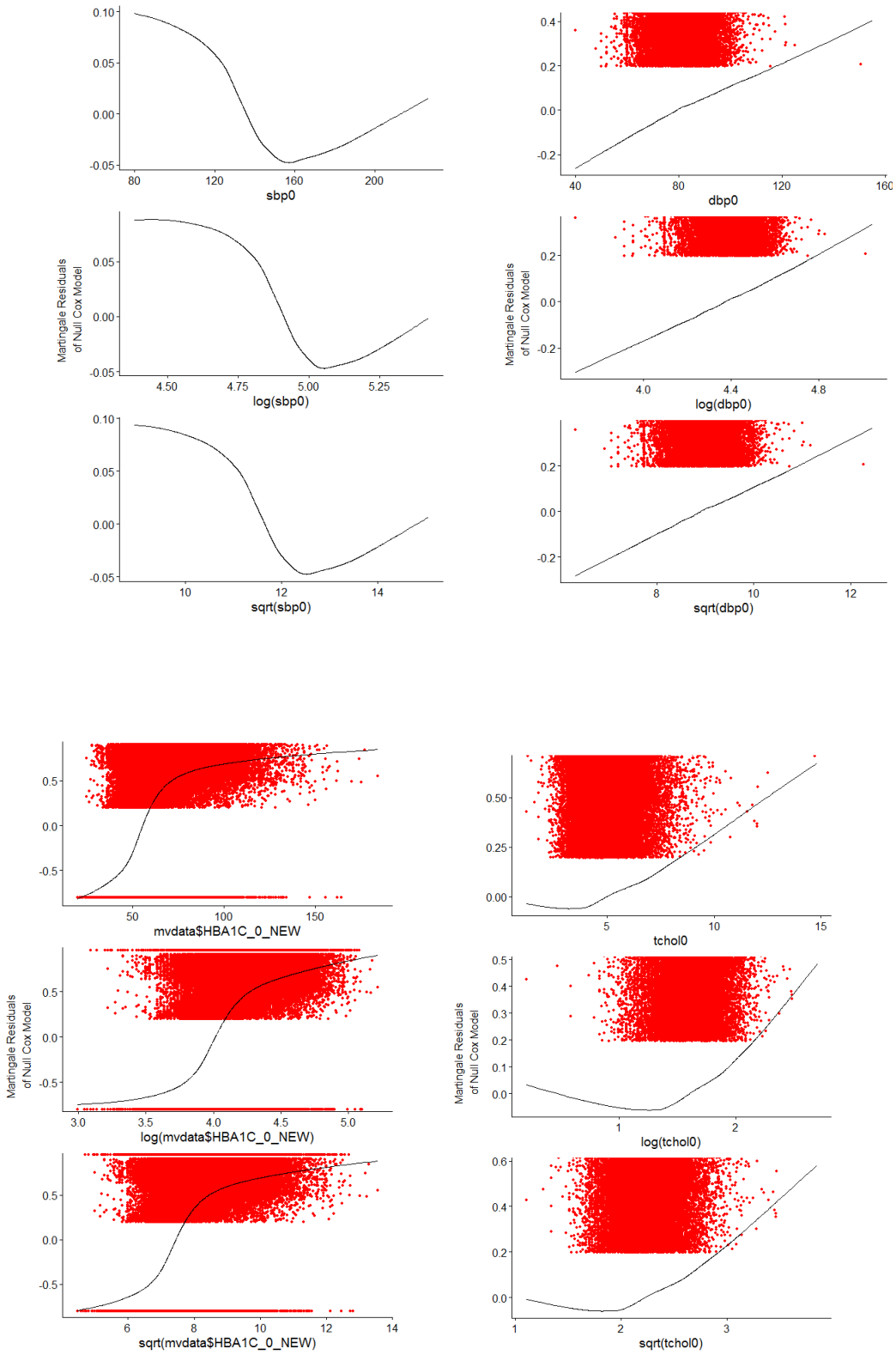
Variable	rho	Chi-square	p-value
Age at diagnosis	0.003	0.496	0.481
BMI	0.051	128.178	<0.0001
SBP	0.019	18.290	<0.0001
DBP	-0.001	0.135	0.714

HbA1c	0.192	1390.122	<0.0001
Cholesterol	0.037	68.632	<0.0001

Figure 5 below presents the plots from the Martingale residuals which help to determine linearity. As indicated in table 18, patterns in BMI, SBP, HbA1c, and cholesterol plots suggest that these variables do not meet the assumption of linearity.

Figure 5. Tests of non-linearity: Martingale residuals plots for age, BMI, SBP, DBP, HbA1c, and cholesterol





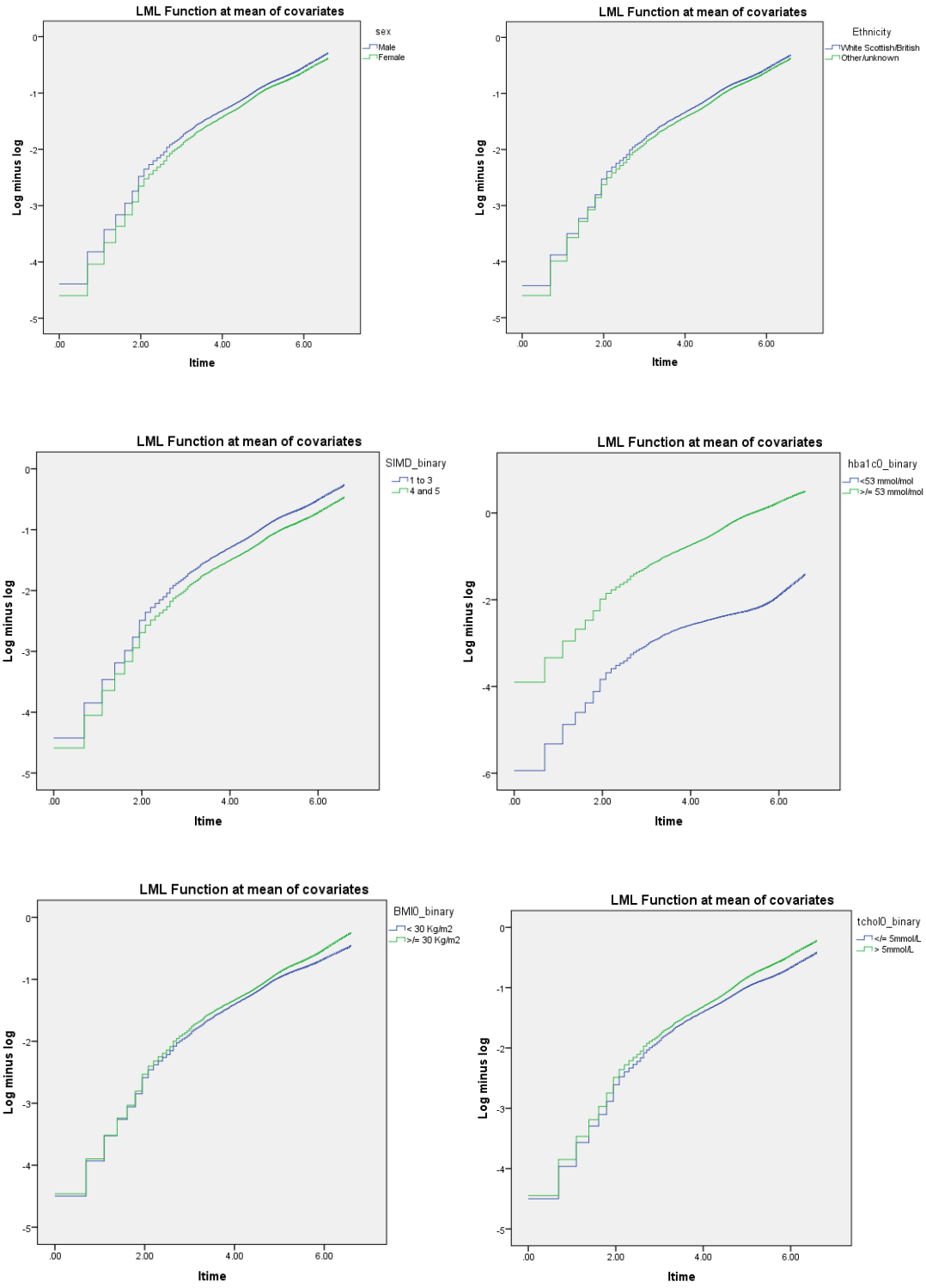
Given than nonlinearity was apparent in some variables such as BMI, SBP, HbA1c, and cholesterol, categories were created for these variables.

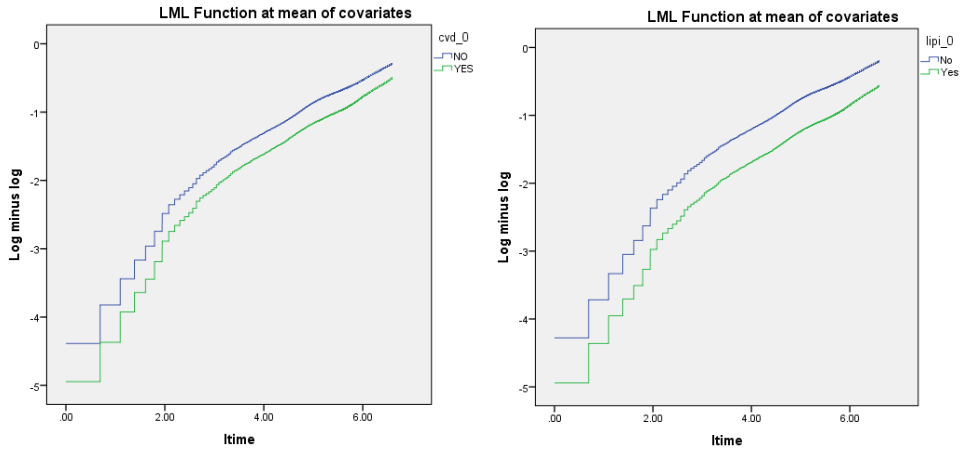
Moreover, although nonlinearity was not an issue for DBP, this variable was used as a categorical variable in order to be consistent with SBP. As described in tables 12-14 in section 3.5.2, the categorisation of the variables was made according to clinical cut-offs with testing of the potential hazards assumption for categorical variables as described below.

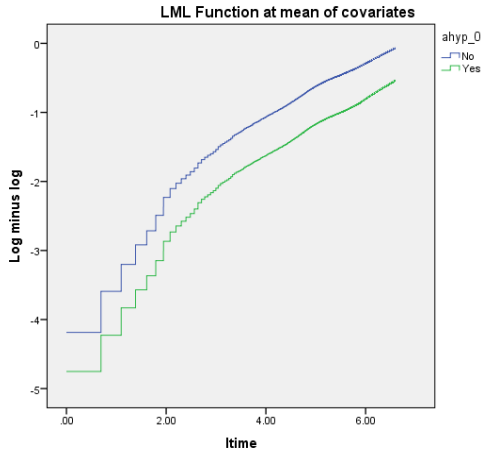
For this analysis, age at diagnosis of diabetes was used as a continuous variable in order to estimate the change in the hazard (GLM prescription initiation) per each year of age. Furthermore, as seen in table 13 and 14, all of the other covariates included in the models were treated as categorical variables, such as sex, CVD at baseline, receiving lipid-lowering medication, receiving antihypertensive medication, cholesterol, BMI, HbA1c, SBP and DBP.

The proportional hazard assumption for each categorical variable was checked using log minus log survival plots. For this purpose, the time to drug treatment variable was log converted, and survival curves were analysed. If the lines were parallel, then the assumption was considered not to be violated. The log minus log survival plots are presented in figure 6. The variables which were checked are sex, ethnicity, SIMD, HbA1c, BMI, cholesterol, CVD, antihypertensive medication and lipid-lowering medication. The proportional hazards assumption was considered to have been met for these variables.

Figure 6. Log minus log survival plots







Further analysis stratified by age

In order to check for a relation between age and HbA1c, a linear regression analysis was conducted to test the homoscedasticity between variables. Then, a Pearson correlation analysis was conducted. Subsequently, adjusted hazard ratios for time to GLM initiation stratified by age categories were conducted.

3.6 Qualitative methods

In this section, I will describe the qualitative strand of the study. As previously described, the qualitative strand of this PhD focused on HCPs' understandings and views in order to develop a better understanding of the factors and considerations that might influence clinical decision-making in relation to initiation of pharmacological treatment in people with T2DM. Thus, this study sought to obtain information which would help to broaden the results of the quantitative analysis and provide greater understanding about clinical decision-making. Moreover, I sought to explore the reasons for differences in HCPs' reported decision-making with regards to initiating GLM.

The following sub-section provides the reasons why a qualitative approach was adopted. Then, I will go on to describe the theoretical framework which informed the study, followed by an account of the strengths and limitations of the method of data collection chosen. A subsequent section moves on to describe the recruitment process and sample selection. Finally, the approach to data analysis is presented.

3.6.1 Rationale behind the qualitative study

Qualitative studies seek to answer the "what" "how" and "why" of a phenomenon, they focus on understanding factors that may contribute to a phenomenon (Britten, 1995, Britten, 2011). Qualitative research uses non-numerical techniques of data production and analysis, they relate to the use of textual data deriving from transcriptions of verbal or observational data, and the use of distinctive theoretical frameworks. Furthermore, qualitative research allows people to express their thoughts in their own terms, which can give rise to unanticipated or unexpected findings. Thus, the use of qualitative methods can allow a deeper understanding of a phenomenon (Holloway, 2005).

Moreover, the scope of qualitative research has been shown to be of value in providing information about views and perceptions of healthcare

professionals on aspects related to healthcare (Britten, 1995). The outputs of qualitative research are valuable to the healthcare environment in different ways; their contributions include the development of conceptual definitions such as “shared decision-making” to the development of new theories (Britten, 2011).

Providing explanations rather than mere descriptions is regarded as one of the most important contributions to healthcare literature (Britten, 2011). Although healthcare decisions have been traditionally based on statistically significant data, qualitative research is an approach that offers means to address important issues related to evidence-based practice and the complexities of organisation and reorganisation of healthcare (Collin, 2010, Caronna, 2010). A crucial way to improve evidence-based medicine is to understand how HCPs adapt elements such as guidelines, and how they perceive them in relation to their clinical autonomy and how they “translate” evidence-based medicine into practice. Thus, the use of qualitative methods in healthcare research helps to identify values and perceptions of various actors and to grasp the complexity of decision-making and structural changes in healthcare delivery (Collin, 2010).

Qualitative research enhances the development and effective implementation of evidence-based policies and programmes. In diabetes research, the inclusion of qualitative research can contribute to understanding stakeholders’ needs and barriers to enhanced healthcare, resources, and processes, especially in areas that have not been widely studied (Hennink et al., 2017). As described in earlier chapters, to date, qualitative research has tended to focus mainly on patients’ experiences of diabetes and the services and support they receive, and lesser attention, by comparison, has been placed on HCPs’ perspectives (Hennink et al., 2017).

Thus far, I have described how qualitative research provides means to gain insights into a phenomenon. Therefore, in order to answer the research

questions previously stated, a qualitative approach was considered most appropriate. In the next sub-section, I will present the theoretical framework chosen to inform this study.

3.6.2 Theoretical stance

The overall aim of this qualitative study was to elucidate clinical decision-making around GLM initiation. Since this study focused on HCPs' decisions and considerations as to when to start pharmacological treatment in people with diabetes, it is important to consider the theories that informed this strand of the research. Principles of the "Normalisation Process Theory" (henceforth NPT) and the basic principles of the social-ecological model (SEM) were adopted as a framework to understand HCPs' reported decision-making and understandings (May and Finch, 2009). The decision to use NPT and SEM was partly the result of the literature review described in chapter 2, which showed the importance of contextual factors and organisational factors on clinical decision-making. Thus, together with findings from the literature review, these theories informed the development of the topic guide and the main themes which framed the data analysis.

NPT theory is used to investigate the routine embedding of material practices and ideologies in their social contexts and is concerned with the social organisation of the work of implementation, which is operationalised through four mechanisms: coherence, cognitive participation, collective action and reflexive monitoring. This theory provides a framework to investigate processes that become components of everyday work such as the use of clinical guidelines or medical devices. For this study, the process relates to HCPs' decisions about when to initiate GLM in people with recently diagnosed T2DM. It is presumed that HCPs have already a set of ideas about diabetes care that was learned, shared, and experienced in their own social contexts (coherence). Such practice is framed by their engagement to it, a shared belief that requires *buying in* the value of providing such care (cognitive participation) which is aimed at an institutional goal that requires a

collective investment of effort (collective action) and constant judgement about their utility and effectiveness (reflexive monitoring). The appraisal of the practice can either be collective or individual and can lead to a modification or reconstruction of the practice. Therefore, all that happens at a particular consultation within a practice will be influenced by contextual factors and individual judgements (May and Finch, 2009). Therefore, this study is underpinned by a theoretical perspective concerned with the processes that lead to the integration of a practice, taking into account the impact of a constantly changing social context. The development of the topic guide for the interviews was partly informed by the four mechanisms of the NPT, this is described in detail in section 3.6.4.2.

In relation to the SEM, Bronfenbrenner developed this perspective for research in human development. In summary, it relates to the interaction of the environment and the development of a person. This model emphasises that an environment is a set of nested structures, each inside the next and that behaviours are shaped by these structures, which have also been referred to as multiple systems or levels of influences. Thus, the use of this model allows one to observe and detect a wide range of influences on an individual's decision-making, such as community (macrosystem), organisational (exosystem), interpersonal (mesosystem) and individual (microsystem); therefore, indicating that an individual's decision-making, will depend on certain characteristics of their context (Bronfenbrenner, 1979). Therefore, the SEM offers a mean to understanding clinical decision-making in a holistic way by considering the interplay between HCPs and their environment.

In this study, the WHO approach of the SEM levels of influence was adapted to take into account the influence of factors such as protocols and resources on clinical decision-making (World Health Organization, 2020a, Dahlberg and Krug, 2002). In this way, the SEM informed the categorisation and deductive

construction of the initial themes and categories used during the data analysis process.

The SEM sees the individual at the centre of a multilevel environment. Since HCPs' clinical decision-making was the focus of this strand, the first theme constructed was *HCPs' role* which relates to the first SEM level (individual). The second level is the interpersonal which relates to close relationships which may shape clinical decision-making, for this level, two themes were built: HCP-patient relationship and patient-related factors. The third level (organisational) is concerned with the social and physical environment, and the fourth level (community) relates to societal and cultural factors such as policies, healthcare system, and economy, among others (Dahlberg and Krug, 2002, World Health Organization, 2020a). As it will be described later in this chapter, these last two levels were joined to build one category named contextual factors. The list of themes and categories built based on the SEM is presented in section 3.6.5.

The SEM has been previously applied to healthcare research; for instance, Misfeldt et al. (2017) used this model to understand issues influencing teams' work in primary care in Canada. Likewise, Suter et al. (2017) studied how policies, regulation and legislations inform the design and implementation of team-based primary healthcare service delivery in three provinces in Canada. These studies found that in primary care settings "the context" refers to legislations, availability of human resources, protocols, organisational leadership and vision, and team leadership and vision, among other factors (Misfeldt et al., 2017, Suter et al., 2017). Thus, the design of this study is underpinned by the SEM and NPT theoretical perspectives, which seek to provide a framework to explain why things become routine components of everyday work and explore how a person's context can influence and shape their decision-making.

Here, I have described the principles of the theories and how they informed this study. The next part of this section will focus on data collection. Accordingly, I will first describe the approach to data collection chosen for this study, interviews, and explain the reason why this was chosen.

3.6.3 Interviews

Qualitative interviews are conducted with the purpose of discovering the interviewee's framework of meanings and understandings (Britten, 1995), which in this study are related to decision making around GLM initiation in the management of T2DM. For the qualitative strand of the research, one-to-one interviews were the method used for data collection.

Interviewing is a method that gives participants the opportunity to describe their experiences in detail. Moreover, it is used to access the participants' understandings of their world. Interviews capture a unique and subjective account and depend on the participant's ability to recall, reflect on and articulate their experiences. Therefore, an interview is unique and cannot be replicated since it is a process that varies from participant to participant and is influenced by the participant's experiences (Holloway, 2005).

Furthermore, interviews are conducted in order to explore in detail the topic being discussed, to learn what is important from participants' perspectives (Britten, 1995, Holloway, 2005). By conducting interviews is also possible to reveal how people view and explain their behaviour and experience their environments. Thus, interviews allow the researcher to explore and discuss past events (Holloway, 2005). The type of questions to be asked during a qualitative interview depend on the topic studied. However, in order to pursue an idea in more detail, less structured interviews with open-ended questions are preferred (Britten, 1995).

3.6.4 Recruitment and sample

In order to expand the results from the cohort analysis, I aimed to interview GPs and nurses, working in primary care because they are the HCPs

responsible for prescribing GLM and managing T2DM. As described in chapter 1, although traditionally GPs are in charge of prescribing, in the UK, registered nurses who have completed additional courses are authorised to prescribe. Furthermore, general practice nurses are in charge of monitoring and managing chronic diseases in which diabetes is included (Scottish Government, 2016b, Scottish Executive Health Department, 2006). In this section, I will outline the recruitment process and the data collection process.

The qualitative strand used a deductive-inductive approach, which is further explained in section 3.6.5. Data collection and analysis commenced simultaneously to find similarities and relationships between interviews and refine the analysis (Gray, 2004). This approach was chosen as it allows findings from early interviews to inform topics and questions asked in later ones. By using this approach, I was also able to inform my sampling, as I describe later on.

3.6.4.1 Sample

In contrast with quantitative research, qualitative studies do not require probabilistic sampling but a proper selection of participants. In other words, in qualitative research statistical representativity is not relevant, however, to involve and seek a sample which includes people with knowledge or life experience related to the research question is needed. Since qualitative research seeks to collect rich-data, participants' ability to provide meaningful information on the topic is important (Namey and Trotter, 2015, Moen and Middelthon, 2015, Tolley et al., 2016). For this study, purposive sampling was used driven by the research questions; this means that respondents were deliberately chosen based on their ability to provide the information needed (Padgett, 2012b, Tracy, 2013).

Initially, I considered interviewing only HCPs with a special interest in T2DM. However, after discussion with my supervisors and my first-year review panel members, I decided to broaden my focus to all GPs and nurses managing

people with T2DM regardless of their interest in T2DM. Overall, by including HCPs' without interest in T2DM, I expected to gather a more diverse set of experiences and views, which would enrich the findings as they are also in charge of prescribing GLM.

Furthermore, I considered it important to include individuals who do not have a special interest in T2DM but still manage people with this condition on a daily basis. First, not every practice has a specialist in T2DM to whom GPs or nurses can approach to discuss treatment options. Second, HCPs' with and without a special interest in T2DM might inform their decisions on the management of T2DM differently. Third, the inclusion of a broader sample would be more likely to mirror the reality of primary care. Thus, I sought to adopt a maximum variation sampling methodology in order to capture heterogeneity across HCPs. However, for the reasons I will describe below, I anticipated that recruiting such a sample would be difficult.

Recruitment represented a significant challenge to this research. There were several reasons to this, which I will now address. To begin with, as a non-British non-medical PhD student, I lacked clinical contacts in Scotland. In addition, this study had very limited funding; thus, no financial or other kinds of incentives could be offered to potential participants. Lastly, the tight schedule of clinicians made this task challenging. The majority of HCPs I had contact with were extremely busy and could only allocate short time-slots to talk to me. Additionally, as mentioned by some HCPs, they were interested in participating; however, their intention to participate vanished in the face of other crucial tasks that they needed to perform. However, by using an initial convenience sample followed by snowballing recruitment, I gained access to the participants of this study. This two-step approach to recruiting participants will be described in more detail in the following paragraphs.

First, a convenience sample was recruited. Convenience sampling is characterised by ease of access to participants, although is less rigorous

than other approaches to sampling, it is often used when the budget is limited and/or there is a short period to recruit participants (Tolley et al., 2016). I followed this approach due to the lack of initial clinical contacts in the UK. Although contacting HCPs directly by their emails is an approach commonly used, for the current study, the reasons to why this was not considered feasible were 1) writing to HCPs as an unknown individual was deemed as not beneficial and 2) it could be perceived as making excessive demands and a *cold way* to contact participants. These two aspects were considered as potentially causing my request to be ignored by HCPs and a less efficient way of recruiting participants. Thus, as a fist-step, I approached clinical colleagues working within the University of Edinburgh who had established networks and contacts in primary care. In this manner, I was able to gain access to an initial sample consisting of academic GPs and GPs working in diabetes care.

Second, access to a convenience sample allowed me to locate further participants by using the snowball method of recruitment. The snowball recruitment method involves the recruitment of one or more, sometimes hard-to-reach participants, and asking them to refer the researcher to other members of their group. Although HCPs are not essentially a hard-to-reach population, for the reasons I have described above, my access to them was limited. The snowballing strategy requires first finding an individual with the desired characteristics, then using the person's social network to recruit similar individuals in a multistage process. After the initial person helps to recruit participants, the participants then will help to recruit others themselves. Therefore, the number of participants increases or "snowballs" as participants help to recruit others by referring them to the researcher (Padgett, 2012b, Sadler et al., 2010).

Recruitment of participants by snowballing is particularly useful when the aim of the study is explorative, qualitative or descriptive. It serves as an alternative when other sampling methodologies are not feasible (Cohen and

Arieli, 2011). Even though this method has been widely used in research conducted in conflict areas, and among seriously ill, gangs and drug users, its use can be extended to other contexts, such as populations that are not hidden but are hard-to-reach for research purposes (Cohen and Arieli, 2011).

Furthermore, snowballing is regarded as one of the most effective methods to obtain access to populations with the advantage of shortening the time and reducing costs (Cohen and Arieli, 2011, Sadler et al., 2010). However, one of the aspects that has received significant criticism is related to sample representativeness, although in qualitative research representativeness is not relevant, a wide and diverse range of people is desired to obtain complex, nuanced descriptions of a phenomenon (Cohen and Arieli, 2011, Moen and Middelthon, 2015). A convenience sampling supplemented by a snowballing approach helped ensure an adequate number of participants took part in the study to allow sufficient data to be collected

Information about participants is presented in chapter 5. I tried to achieve a sample of HCPs working in different settings: rural and urban, small and large, with and without specialists in diabetes, in affluent and deprived areas. However, the sample was skewed towards GPs working in urban areas. This could be attributed to the recruitment methods employed, convenience and snowballing sampling. These have the limitation that the sampling depends on the referrals and on the willingness of them and their contacts to participate, which can lead to the exclusion of individuals who do not belong to the specific network being accessed and might cause unbalance in selected demographic characteristics. Furthermore, these recruitment methods can also lead to the inclusion of the more cooperative participants who are willing to participate in the study (Cohen and Arieli, 2011, Sadler et al., 2010, Tracy, 2013).

Potential participants were provided with invitation packs consisting of a cover letter, participant information sheet and an ‘opt-in’ form. Participants

who opted-in were interviewed, and after interviewing them, I asked them to pass on an electronic invitation pack to colleagues they thought might be interested in participating. However, I informed them that this was not mandatory and would not affect their participation and that I did not need to know the names or personal details of their colleagues, unless they decided to participate. All information packs included my contact details and that of my supervisor, Professor Julia Lawton, to allow participants the opportunity to discuss the study and address any concerns or queries before agreeing to take part. After returning the opt-in form and having the chance to discuss the study, potential participants were sent out a consent form to review in advance of the interview taking place. Written consent was obtained from all participants. All participants were advised of their right to withdraw from the research at any time, without giving a reason, and without repercussions. Participants did not receive any incentives for their participation.

After conducting and analysing the last interviews, I realised that the sample was heavily skewed towards GPs. I tried to interview more nurses; however, this task became very difficult as they were hard-to-reach. Towards the end of the data collection stage, the nurses I managed to get in contact with expressed their lack of time to talk to me. Some of the nurses that I interviewed confirmed this issue and described their time constraints and how they struggled to maintain training and skills in diabetes care in work hours.

Although the initial plan was to interview 20 HCPs, data collection was stopped after 16 HCPs were interviewed. The decision to stop data collection at this point was made because of HCPs' limited availability and lack of resources to incentivise them. Although a bigger sample would have been better, at this point I had collected sufficient data to help answer the questions.

3.6.4.2 Data collection

As previously indicated, one-to-one interviews consisting of broad, open-ended questions were used to enable the discussion to stay relevant to the study aims, while allowing HCPs to express additional information that they considered relevant to their decision-making in relation to initiation of GLM in people with T2DM.

At the beginning of each interview, I introduced myself to the interviewee, discussed the study and answered any question they had. I emphasised that all information that could be used to identify them would be removed from the typed up interviews and that our talk was confidential. The preamble to the interview was essential as it allowed me to clarify my position as a non-medical professional, which I considered vital to disclose in order to obtain more detailed and extended answers. Furthermore, disclosing my position was pointed out as relevant by some participants since after I mentioned my position of non-medical PhD student, they expressed that they would be more clear and explicit with their explanations and terminology.

As indicated in sub-section 3.5.2, the NPT is one of the theories which underpinned this strand. The four mechanisms or principles of the NPT helped frame most of the questions included in the topic guide (see appendix 4). Table 19 shows each mechanism of the NPT and the themes and questions that were included in the topic guide based on them.

Table 19. Themes included in the topic guide based on the NPT mechanisms

NPT Mechanisms	Description of the mechanism	Theme included	Example of questions included
Coherence	Defines and organises a practice *(prescription of GLMs)*, which has a meaning that is learned, shared, and experienced by actors in a	Practice context and structure	*Compared to other practices in the area, how big is this practice?* *What kind of area is the practice in?*

	specific social context *(HCPs in primary care).*		*How many GPs and nurses work in the practice?*
Cognitive participation	Practices are framed by human engagement *(HCPs)*. Includes people implicated in the practice which joins and support it *(task allocation)* and requires buying into the practice *(knowledge on the topic)*.	Division of tasks and their role within the healthcare team Knowledge on the topic	*How is diabetes care organised in the practice? Could you tell me a little bit about yourself and your role in your practice? How do you decide when is appropriate or necessary to prescribe pharmacological treatment for glucose control?*
Collective action	Relates to confidence and trust in the process. Two important qualities 1) skill-set and 2) Incorporation within a social context. Requires collectively invested effort *(inter and intra-professional communication)*.	Development of skills and training Peer-support	*Do you have the opportunity to keep up to date? If so, how do you do this?* *How hard/easy is to keep updated with new policies/guidelines?* *Is there anyone else responsible for care of people with diabetes? How do you divide the workload?*
Reflexive monitoring	Evaluation and monitoring of processes *(Patients' outcomes)*. Includes judgements about the practice utility and effectiveness which may lead to a reconfiguration	Monitoring of patients.	*How frequently do you review patients?* *Are there any reasons about why your decisions about when to initiate pharma treatment might have changed over time?*

However, the development of the semi-structured guide was not only based on the four mechanisms of the NPT but also on findings from the literature review. Hence, other topics which were not considered in the questions informed by the NPT such as those related to QOF were included given their relevance to the research questions. The incorporation of these additional questions led to a transformation of the general structure of the topic guide

used to conduct the interviews, i.e. the order of the questions did not follow the NPT mechanisms but general key areas to be explored.

In this way, three key areas were explored in the interviews with HCPs. First, since the literature review showed that the organisation, implementation and approach to guidelines and frameworks vary between practices, I enquired about their professional background and their practice structure. This included information about their professional training, whether they had taken any courses in diabetes or had an interest in it, information about their practice size and its location, and their patients' socio-demographic backgrounds. The information from this section gave me a general idea of their context, which was useful to tailor some following questions and to identify topics to follow-up. In addition, I took the opportunity to ask about their role in a multidisciplinary team and the organisation of diabetes care. The second area was the management of T2DM. During this part of the interview, I asked participants about their patients' pathways to diagnosis, initial consultations and I also asked them to give me examples whenever was possible. This area in the interview guide was informed by the results from previous studies which described that aspects such as consultation length, workload and continuity of care influence clinical decision-making. Furthermore, I let them know that I was aware of QOF and its recent decommissioning and asked them about their experiences and thoughts about guidelines' usefulness as well as that of other resources available to help them manage T2DM. Some questions that I often asked during this part of interview were related to their perception about the way they prescribe and (if) why they thought it had changed over time, and if they considered the decommissioning of QOF as having an impact on the treatment and care given to patients with T2DM. Third, before closing the interview, I gave each participant the opportunity to add information that was not discussed previously, but which they considered important when deciding to initiate GLM in people with T2DM.

An example of the general topic guide is included in appendix 4. Overall, the topic guide was developed in light of what was found in the literature review, the preliminary findings of the quantitative strand, and taking into consideration the epistemological position, particularly the NPT which has been previously described. Furthermore, my supervisor Julia Lawton, helped me check that the topic was generating the information I needed to answer the research questions by looking at some of the initial interviews. This process also helped to refine the topic guide. In addition, as mentioned before, the inductive approach of this study allowed me to explore issues that early interviewees brought to the conversation. For instance, in light of findings emerging from the initial interviews, I included questions about the assessment of patients' motivation, which were not initially included and not reported in the literature review in chapter 2. Similarly, one participant mentioned that they do things in a particular way, which they considered different from other clinical colleagues. Then, after this interview, I decided to ask every HCP if they thought they did anything different from their colleagues regarding when to prescribe GLM for people recently diagnosed with T2DM. Furthermore, each interview followed a unique structure as I was guided by specific things individuals volunteered and raised.

Interviews were conducted either face-to-face or by telephone, depending on HCPs' preferences; the majority of participants opted for a telephone call. The duration of the interviews varied from 30 to 56 minutes and were conducted between 27 March 2018 and 20 September 2018. All interviews were digitally recorded and subsequently transcribed in full.

3.6.4.3 Ethical considerations

Since the recruitment was through clinical colleagues and snowballing, and not through NHS resources, ethical approval was sought from the Usher Research Review Group (UREG). Approval from the University of Edinburgh, Usher institute's review board, was obtained for the research project to

proceed; date of initial application: 14 December 2017, date of approval: 23 March 2018.

Participants were not asked to disclose patients' data or patients' private information during their interviews and were reminded that their input should be based on their personal opinions, views and experiences. Data generated from the research were kept securely, all hard-copies of data, including consent forms, were stored securely in secure filing cabinets within a locked office at Edinburgh University. Likewise, all audio recordings were downloaded and stored electronically in a private folder on a password-protected computer within a locked office at Edinburgh University, and access to these data was only possible by myself, and my supervisors. The audios were transcribed by myself, and only two interviews were transcribed by a trusted employee of the University, with a confidentiality agreement in place. Transcripts were anonymised, participants were given a unique identifying number, and all identifiable personal information was stored separately.

3.6.5 Data analysis

Analysis of the data is an integral part of the research process, and it is to some extent a shaper of the research process, it helps us to understand "What does it all mean?" (Moen and Middelthon, 2015, Leavy, 2017). Data analysis was an iterative process, a deductive-inductive approach was adopted, and data analysis started as soon as data collection began. Once an interview was conducted, I transcribed it promptly and undertook an initial analysis to identify issues, which also informed subsequent interviews.

The construction of categories in qualitative data analysis depends mostly on the research question and what is known about the subject or field. There are two different approaches to the development of categories: inductive and deductive. First, the construction of categories based on empirical data is referred to as an inductive approach where categories are built by

paraphrasing, generalising and abstracting the original data. Second, in a deductive approach the construction of categories is based on theories and hypothesis about the field studied. These two approaches are not contradictory and may be used combined for qualitative text analysis (Kuckartz, 2014). Thus, as a first step, from what I found in the literature review and based on the SEM, I develop main broad themes and categories, which served as a starting point or searching aid. Secondly, the sub-categories were constructed inductively. For instance, one main category deductively constructed was *"patient-related factors"* as this was something that had emerged from the literature review as a main broad theme. However, sub-themes such as *"psychological readiness"* or *"development and presence of symptoms"* emerged from the analysis of the interviews' transcriptions.

According to the SEM, HCPs' decisions about when to start GLM is the result of a dynamic interplay between individual, interpersonal, organisational and community environments. In table 20 is presented the list of themes and categories that were deductively constructed based on the literature and categorised into themes according to the SEM levels. These themes and categories were used as an initial aid but are not the final ones that will be presented in chapter 5. As it will be explained in the findings chapter, the list was modified by the inductive construction of categories (based on HCPs' accounts).

Table 20. Initial themes and categories deductively constructed as search aid for data analysis.

SEM level	Main theme	Categories
1. Individual	HCPs' role	*Experience, role, and qualifications*
		Perceptions of own role
2. Interpersonal	HCP-patient relationship	*Historical contact with patients*
		Assessment of needs
	Patient-related factors	*Physiological*
		Psychological

3. Organisational	Contextual factors	*Characteristics of the practice*
		Division of tasks
4. Community		*Healthcare system-related*
		QOF/guidelines

Data preparation and organisation consisted of transcribing the interviews. The software NVivo facilitated data retrieval and thematic coding. The initial immersion or exploration to the data took place during the transcription process. I transcribed most of the interviews myself, and I had the opportunity to construct initial sub-thematic codes during this process. Furthermore, I also engaged in an immersive reading and listening of the interviews that were transcribed by someone else. I did this to check the accuracy of the transcriptions, and to engage with their content in the same way as with the other interviews.

Thus, the coding process in which I classified the data into general themes started at the same time as transcription and consisted of an iterative process that continued until the process of writing up the findings. After transcribing the interviews, I employed manual procedures such as colour-coding, and the software NVivo for data coding, thematic development and data retrieval. Coding and thematic development are one of the most common procedures to analyse qualitative data and consists of searching for patterns and central ideas, and assigning names or labels to sections of data in order to develop themes (Holloway and Galvin, 2016, Padgett, 2012a).

The data were analysed using the method of cross-comparison to identify common issues and experiences. Thus, the thematic categories, which emerged from the qualitative text analysis, refer to topics included in different passages within the interviews' transcripts (Kuckartz, 2014). Thematic codes were developed through repeated close-readings of the interview transcripts, although deductively constructed categories were initially developed based on the literature, these were used as a general aid and not as a rigid set of

main themes. I developed an initial mental map to organise in a visual way the themes identified in the interviews. Then, after several meetings and discussions with my supervisor, three main themes were identified, which are presented in chapter 5.

3.6.6 Reflexivity

In this sub-section, I will provide insights emerging from my reflections on my role in the study. Reflexivity is a practice that researchers should pay attention to in order to reduce, or at least acknowledge the impact of personal bias. It requires the researcher to be conscious and to understand their role critically in the decisions that shape the data, and their approach to understanding it (Frattaroli S., 2012, Longhofer et al., 2012).

I would like to address my position as a non-British, non-medical PhD student who speaks English as a second language. As I mentioned above, these aspects made the recruitment process very challenging as I aimed to conduct a study without having a network in the UK. However, once I gained access to initial participants, my position helped me to recruit further participants. Some HCPs seemed to sympathise with my position as a PhD student, and accepted to participate. Furthermore, the majority also agreed to pass on the invitation packs to their colleagues.

Moreover, as mentioned above, during the interviews, I made the interviewees aware of my background. Thus, I informed them that I do not have a medical background and my accent made evident that I was a foreigner and non-native speaker of English. These characteristics, I consider worked in my favour because most of the participants tried to provide clear and explicit answers.

3.7 Integration of quantitative and qualitative findings

As previously mentioned, the research process was iterative, and while each strand was considered independent of the other, I used preliminary findings from the quantitative analysis to inform the topic guide. In addition, I used

themes emerging from the interviews to interpret quantitative data and considered the possibility of conducting further analysis that would have helped to provide greater insight. However, as I will describe in the discussion, further analyses of the dataset were not possible. In brief, the additional variables that I thought of including after analysing the interview data were not available for the cohort dataset.

In order to convey the merged results, I used a combination of approaches to integrating them, such as comparison of convergent and contradictory findings, and triangulation in which I sought to extend and complement findings. The use of these approaches allowed me to bring findings together in order to enhance each other and to increase the potential to understand associations between the different kinds of data.

For this study, triangulation refers to the examination of findings from two different viewpoints (quantitative and qualitative), which provide different angles of a topic. These different sources might produce a fuller and more complete picture of the phenomenon if brought together. Thus, by drawing findings from two different sources, triangulation was used to produce complementary data (Bergman, 2008).

The overall interpretation of the findings is presented in chapter 6. In order to merge the two sets of results, I first identified areas or themes that were represented in both strands. Then, I compared and contrasted them. Finally, I synthesised the results in a discussion where I sought to explain to what extent and in what ways findings converged and related to each other.

3.8 Summary

This chapter has described the overall research aims, the mixed-methods approach used to address the overarching research question as well as the research questions related to each of the quantitative and qualitative strands. It has also provided detailed information about the mixed-methods study

design and methods and outlined the research process for both the quantitative and qualitative strands.

For the quantitative strand, a retrospective cohort study was conducted; participants were drawn from a 2016 extract of the SCI-diabetes dataset. Participants were selected if they were diagnosed with T2DM between 2004 and 2012 and survived for two years after diagnosis. The data cleaning sub-section presented the methodology used to build the dataset for the analysis. However, given the proportion of missing values, methods of managing missing data were discussed. The analysis of the cohort resulted in the creation of two different datasets, a CCA and a multiple-imputed one. The key outcomes were the proportion of patients that initiated drug treatment within two years following diagnosis of T2DM and the association between patient factors and time to GLM prescription initiation. Descriptive statistics, Kaplan-Meier curves and Cox regression models were used.

For the qualitative strand, interviews were conducted with HCPs working in primary care; the normalisation process theory and the social-ecological model informed the study. A deductive-inductive approach was used; thus, data collection and analysis started at the same time. A purposive sample was recruited and supplemented by a snowball method of recruitment. Data were transcribed and analysed using the method of cross-comparison.

The next chapter presents the results of the quantitative strand. Then, chapter 5 reports the findings from the qualitative strand. The integration of both strands of the research is presented and discussed in chapter 6.

Chapter 4 Quantitative results

4.1 Introduction

As explained in the previous chapter in section 3.5.4.3, a CCA was performed initially, and then an imputed dataset was created and analysed. In the chapter that follows, I present only the results of the imputed dataset as it was considerably larger. The results from the CCA, which were similar to the imputed dataset, can be found in appendix 4. A comparison of the findings from the analyses of the imputed and CCA datasets is given at the end of this chapter.

The first section of this chapter is concerned with the description of the characteristics of the people included in the cohort. Then, the differences according to glycaemic control (optimal vs sub-optimal) are provided. Subsequently, the results of the Kaplan-Meier survival analysis and the Cox-regression analysis are presented. Lastly, a summary of the main findings is provided.

4.2 Characteristics of the population

In this section, I will describe the characteristics of the entire cohort, as well as characteristics stratified by age groups. Overall, as observed in table 21, men formed over half of the entire cohort and most age groups, with the exception of patients $\geq$ 75 years of age in which there was a higher proportion of women than men. Furthermore, as seen in table 21 the majority of the participants (39.8%) were in the 60-74 years category.

Demographic characteristics such as ethnicity were distributed similarly across all age groups, where the majority of the people were identified as white Scottish/British. Larger proportions of the population were in the most deprived quintile than in the least deprived quintile and this pattern was more marked in younger than older age groups.

Table 21. Baseline characteristics of people diagnosed with T2DM from 2004 to 2012 in Scotland included in the imputed dataset.

Variable		Entire Cohort (n= 154,660)	Age Groups (years)			
			30 to 44 (n= 17,274)	45 to 59 (n= 53,927)	60 to 74 (n= 61,584)	≥ 75 (n= 21,875)
Age, years (mean ± SD)		61.0 ± 12.5	39.6 ± 3.9	53.2 ± 4.2	67.0 ±4.2	80.2 ±4.1
Gender, male (%, n)		55.9 (86,421)	60.6 (10,465)	60.5 (32,614)	55.0 (33,893)	43.2 (9,449)
Ethnicity (%, n)						
White Scottish/British		70.2 (108,602)	65.7 (11,348)	72.0 (38,825)	71.5 (44,045)	65.8 (14,384)
Other		9.8 (15,091)	17.9 (3,100)	10.4 (5,632)	7.6 (4,690)	7.6 (1,669)
Unknown		20.0 (30,967)	16.4 (2,826)	17.6 (9,470)	20.9 (12,849)	26.6 (5,822)
SIMD quintiles (%, n)						
Most deprived	1	24.2 (37,495)	30.9 (5,346)	25.9 (13,971)	22.5 (13,867)	19.7 (4,311)
	2	23.0 (35,616)	24.3 (4,191)	22.9 (12,356)	23.0 (14,184)	22.3 (4,885)
	3	20.0 (30,990)	18.9 (3,258)	19.6 (10,557)	20.6 (12,662)	20.6 (4,513)
	4	18.2 (28,077)	15.2 (2,623)	17.4 (9,403)	18.7 (11,527)	20.7 (4,524)
Least deprived	5	14.5 (22,482)	10.7 (1,856)	14.2 (7,640)	15.2 (9,344)	16.6 (3,642)

4.3 Proportions of people with T2DM with and without glucose-lowering medication prescription during follow-up and their characteristics

Demographic and metabolic factors such as HbA1c, cholesterol and pre-existing CVD were compared between people with and without GLM prescription initiation at different time points.

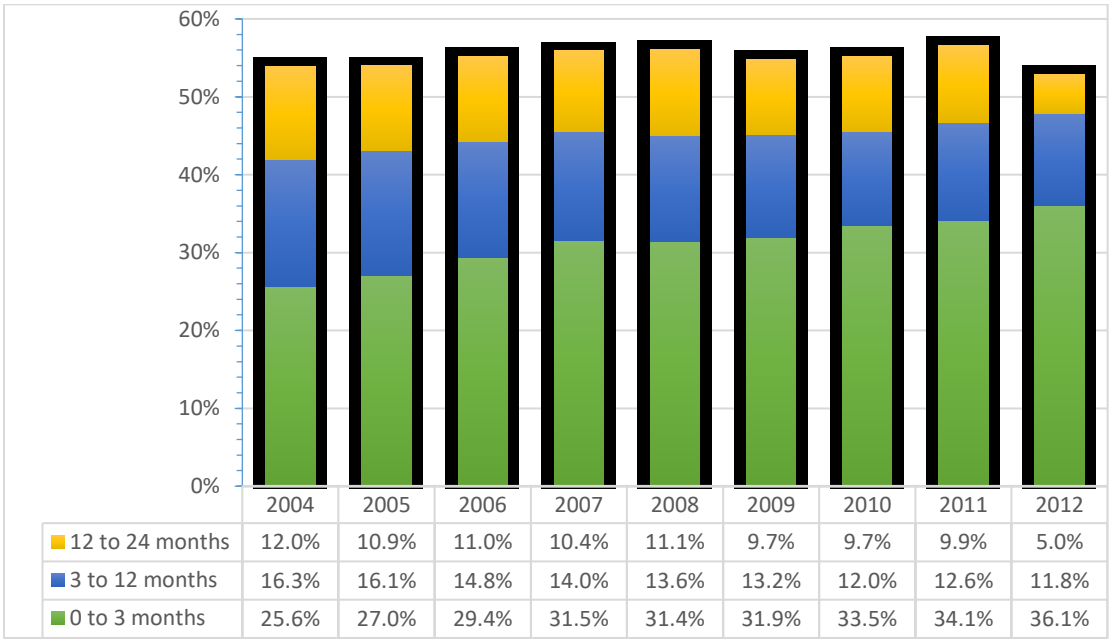
The proportions of people who received GLM prescription initiation by year of diagnosis are described first. Lastly, the baseline characteristics of people who received and did not receive medication prescription by two years after diagnosis are presented.

4.3.1 Differences by year of diagnosis

As shown in figure 7 below, from 2004 to 2012, more than half of the patients received a GLM prescription within two years from the diagnosis of T2DM. The index year with the highest proportion of people receiving a prescription was 2011 with 56.7% and the year with the lowest was 2012 with 52.8%.

Time to glucose-lowering initiation prescription was stratified into three different time-points after diagnosis in a) Diagnosis (0-90 days), b) from 3 to 12 months and, 3) from 12 to 24 months after diagnosis. Overall, of those who received a prescription (n=84,997), 56.8% received it within 90 days after diagnosis, 25.1% between three and 12 months after diagnosis, and 18.1% within 12 to 24 months after diagnosis. Figure 7 shows a clear trend of increasing proportions of people who received medication prescription at diagnosis (0 – 3 months) ranging from 25.6% in 2004 to up to 36.1% in 2012. Moreover, the lowest proportions of people who received GLM prescription for every index year was between 12 to 24 months after T2DM diagnosis.

Figure 7. Proportions of patients in the imputed dataset cohort who received drug treatment, stratified by period of prescription.



	2004	2005	2006	2007	2008	2009	2010	2011	2012
12 to 24 months	12.0%	10.9%	11.0%	10.4%	11.1%	9.7%	9.7%	9.9%	5.0%
3 to 12 months	16.3%	16.1%	14.8%	14.0%	13.6%	13.2%	12.0%	12.6%	11.8%
0 to 3 months	25.6%	27.0%	29.4%	31.5%	31.4%	31.9%	33.5%	34.1%	36.1%

4.3.2 Baseline characteristics of people with T2DM who received GLM prescription vs people with T2DM who did not.

In this section, a description of the differences among people with T2DM that received and did not receive GLM prescription within two years after diagnosis is presented. In order to ease the interpretation of the results, abbreviations for the groups of people who received and did not receive GLM prescription will be used in the following sections. Henceforth, the group of

people who received GLM prescription within two years of diagnosis will be referred to as GLM-2Y, and the group of people who did not receive medication prescription within 2 years will be referred as NM-2Y.

Overall, table 22 shows that GLM-2Y patients were significantly younger (58.9 years) compared to NM-2Y (63.5 years). Distributions of other demographic characteristics such as SIMD and ethnicity were also different. In general, the majority of people in the GLM-2Y group were from the most deprived SIMD quintiles.

There was a significant difference in HbA1c, BMI, SBP, DBP, and cholesterol between the groups. Mean HbA1c was significantly higher in GLM-2Y than NM-2Y. After stratifying by levels of HbA1c, the analysis showed that a larger proportion of GLM-2Y had HbA1c $\geq$53 mmol/mol at baseline than NM-2Y. Likewise, GLM-2Y had a higher mean BMI, and also a larger proportion had a BMI $\geq$30 Kg/m2 than NM-2Y.

Interestingly, mean SBP and the proportion of people with SBP $\geq$130 mmHg were observed to be significantly lower for GLM-2Y than for NM-2Y. Conversely, mean DBP (80.8 mmHg) and proportions of people with DBP >80 mmHg (49.6%) were higher for GLM-2Y than for NM-2Y.

The bottom part of the table shows that almost half of GLM-2Y had baseline cholesterol >5 mmol/L (48.0%), which was statistically significantly higher than for NM-2Y (42.8%). In contrast, GLM-2Y included lower proportions of people with pre-existing CVD, people receiving lipid-lowering medication, and people receiving antihypertensive medication. However, since people in the NM-2Ygroup were older, some of the above associations could be confounded by age.

Table 22. Baseline characteristics of people diagnosed with T2DM in Scotland 2004 – 2012, classified whether they received pharmacological treatment by two years after diagnosis

Variable			Received medication prescription	
			Yes (84,997)	No (69,663)
Age, years (mean + SD)			58.9 ± 12.3	63.5 ± 12.2
Gender, male (%, n)			57.0 (48,419)	54.6 (38,002)
Ethnicity (%, n)	White Scottish/British		71.1 (60,406)	69.2 (48,196)
	Other		10.2 (8,635)	9.3 (6,456)
	Unknown		18.8 (15,956)	21.5 (15,011)
SIMD (%, n)	Most deprived	1	26.2 (22,283)	21.8 (15,212)
		2	24.0 (20,388)	21.9 (15,228)
		3	19.9 (16,922)	20.2 (14,068)
		4	17.0 (14,439)	19.6 (13,638)
	Least deprived	5	12.9 (10,965)	16.5 (11,517)
BMI	Mean Kg/m2 ± SD		32.6 ± 6.9	31.5 ± 6.3
	≥ 30 Kg/m2 (%, n)		61.5 (52,266)	54.9 (38,268)
Systolic Blood Pressure	Mean mmHg ± SD		137.5 ± 15.2	138.6 ± 15.3
	≥ 130 mmHg (%, n)		67.6 (57,439)	71.1 (49,570)
Diastolic Blood Pressure	Mean mmHg ± SD		80.8 ± 8.7	79.6 ± 19.3
	> 80 mmHg (%, n)		49.6 (42,207)	44.9 (31,308)
HbA1c	Mean mmol/mol ± SD		68.2 ± 19.5	49.3 ± 11.1
	≥ 53 mmol/mol(%, n)		78.6 (66,811)	24.8 (17,251)
Cholesterol	Mean mmol/L ± SD		5.1 ± 1.2	4.9 ± 1.1
	> 5 mmol/L (%, n)		48.0 (40,802)	42.8 (29,805)
Pre-existing CVD (%, n)			17.4 (14,774)	21.3 (14,810)
Receiving lipid-lowering medication (%, n)			31.2 (26,488)	38.9 (27,069)
Receiving antihypertensive medication (%, n)			49.1 (41,757)	60.5 (42,179)

Differences between groups were statistically significant for all variables presented in this table (p-value < 0.0001)

4.3.3 Analysis by age groups

In addition to the data presented in the previous section, it is important to describe in greater detail the differences between baseline characteristics of the GLM-2Y and NM-2Y groups stratified by age groups given the potential for confounding by age.

In general, mean HbA1c and the proportions of people with HbA1c ≥53 mmol/mol were higher for GLM-2Y across all age groups (table 23). However, there were some characteristics which consistently changed across age groups. For instance, table 23 shows an inverse association between age and mean HbA1c. A similar inverse association was found between age and mean BMI. However, the comparison within groups showed that whether they received medication prescription or not, BMI was not significantly different for people in the 30-44 years group. In contrast, GLM-2Y from the 45 to 59 years, 60 to 74 years and ≥75 years sub-groups had significantly larger proportions of people with a BMI ≥ 30 Kg/m2 than NM-2Y. The analysis of cholesterol levels showed similar trends to the ones for BMI, proportions of people with cholesterol >5mmol/mol were significantly larger for GLM-2Y than NM-2Y with the exception of the 30 to 44 years group, and an inverse association was found between age and cholesterol levels. Moreover, table 23 also shows an increasing pattern of higher SBP, higher proportions of people with pre-existing CVD, and higher proportions of people receiving lipid-lowering and antihypertensive medication at increased age regardless of whether they received GLM or not. These patterns suggest that age could be a potential confounder between the influence of patients' clinical characteristics and GLM prescription.

For 30-44 years old, mean SBP was significantly higher for NM-2Y, but the proportions of people with ≥130 mmHg were not statistically significantly different. Similar results were found for cholesterol where the mean was higher for GLM-2Y, but no difference was found in the proportions of people with cholesterol >5 mmol/L. In contrast, mean DBP was significantly lower for GLM-2Y. However, no difference was found in the proportions of people with DBP >80 mmHg. With regards to other medications, a lower proportion of GLM-2Y were receiving antihypertensive medication at baseline.

Among people of 45 to 59 years of age, table 23 shows that GLM-2Y patients had higher mean BMI and also a higher proportion of people in the obese category. Moreover, mean HbA1c and the proportion of people with sub-optimal glucose levels were higher for GLM-2Y. In contrast, mean SBP was

lower for GLM-2Y, and lower proportions of people were receiving lipid-lowering medication and anti-hypertensive medication than NM-2Y. No differences were found for DBP, and people with pre-existing CVD.

For people between 60 to 74 years of age at diagnosis of diabetes, table 23 shows that the GLM-2Y group had significantly higher mean BMI, mean HbA1c, mean DBP, and mean cholesterol. Likewise, proportions of people with obesity, sub-optimal HbA1c, DBP > 80 mmHg, and cholesterol > 5 mmol/L were higher amongst GLM-2Y. Contrarily, GLM-2Y had a significantly lower mean SBP and people with SBP $\geq$130 mmHg and also lower proportions of pre-existing CVD, people receiving lipid-lowering medication and people anti-hypertensive medication.

For the oldest age group ($\geq$75 years), similar results to those found for the previous age group can be seen in table 23. Hence, GLM-2Y had significantly higher mean BMI, mean HbA1c, mean DBP, and mean cholesterol. Equally, proportions people with obesity, sub-optimal HbA1c, DBP > 80 mmHg, and cholesterol > 5 mmol/L were higher for GLM-2Y. Conversely, significantly lower proportions of people receiving lipid-lowering medication and anti-hypertensive medication were found for GLM-2Y.

Table 23. Characteristics of people with T2DM from the imputed dataset, stratified by age groups

Variable		All N= 154,660	Age groups (years)											
			30 to 44 n=17,274			45 to 49 n=53,927			60 to 74 n=61,584			≥75 n=21,875		
			Yes (11,973)	No (5,301)	p-value	Yes (33,112)	No (20,815)	p-value	Yes (30,957)	No (30,627)	p-value	Yes (8,955)	No (12,920)	p-value
Gender, male (%, n)		55.9 (86,421)	60.8 (7,277)	60.1 (3,188)	0.428	60.6 (20,082)	60.2 (12,532)	0.307	55.2 (17,083)	54.9 (16,810)	0.461	44.4 (3,977)	42.4 (5,472)	0.003
BMI	Mean Kg/m^2 (±SD)	32.1 (7.1)	34.8 (11.9)	34.7 (12.6)	0.347	33.6 (6.9)	33.1 (6.6)	<0.0001	31.5 (6.3)	30.9 (5.9)	<0.0001	29.2 (5.6)	28.7 (5.6)	<0.0001
	≥30 Kg/m^2, % (n)	58.5 (90,533)	73.2 (8,759)	73.8 (3,914)	0.404	68.5 (22,674)	66.2 (13,785)	<0.0001	56.3 (17,434)	52.6 (16,102)	<0.0001	38.0 (3,399)	34.6 (4,467)	<0.0001
HbA1c	Mean mmol/mol (±SD)	59.7 (18.9)	70.3 (10.3)	51.9 (12.7)	<0.0001	69.1 (19.6)	50.1 (12.1)	<0.0001	66.8 (19.0)	48.6 (9.8)	<0.0001	66.5 (18.6)	48.5 (11.7)	<0.0001
	≥53 mmol/mol, % (n)	54.4 (84,062)	80.3 (9,618)	34.5 (1,828)	<0.0001	79.9 (26,461)	27.7 (5,763)	<0.0001	76.8 (23,760)	22.0 (6,731)	<0.0001	77.9 (6,972)	22.7 (2,929)	<0.0001
SBP	Mean mmHg (±SD)	137.9 (15.3)	132.8 (8.9)	133.4 (6.4)	0.011	136.9 (15.1)	137.4 (15.4)	<0.0001	139.2 (15.1)	139.6 (14.9)	<0.0001	139.9 (15.8)	140.2 (15.6)	0.186
	≥130 mmHg, % (n)	69.2 (107,009)	54.7 (6,548)	56.3 (2,984)	0.576	66.1 (21,877)	68.0 (14,163)	<0.0001	72.5 (22,455)	74.4 (22,774)	<0.0001	73.2 (6,559)	74.7 (9,648)	0.021
DBP	Mean mmHg (±SD)	80.3 (9.0)	83.1 (7.6)	83.8 (11.9)	<0.0001	82.8 (8.7)	82.8 (9.1)	0.795	79.1 (8.3)	78.6 (8.2)	<0.0001	75.8 (8.3)	75.2 (8.3)	<0.0001
	>80 mmHg, % (n)	47.5 (73,515)	59.8 (7,159)	62.6 (3,318)	0.213	59.6 (19,745)	60.0 (12,479)	0.486	41.8 (12,951)	40.3 (12,350)	<0.0001	26.3 (2,353)	24.5 (3,161)	0.002

Table 2*3* (continued) Characteristics of people with T2DM from the imputed dataset, stratified by age groups

Variable		All N= 154,660	Age groups (years)											
			30 to 44 n=17,274			45 to 49 n=53,927			60 to 74 n=61,584			≥75 n=21,875		
			Yes (11,973)	No (5,301)	p-value	Yes (33,112)	No (20,815)	p-value	Yes (30,957)	No (30,627)	p-value	Yes (8,955)	No (12,920)	p-value
Cholesterol	Mean mmol/L (±SD)	5.0 (1.2)	5.4 (0.8)	5.3 (1.8)	<0.0001	5.3 (1.1)	5.2 (1.2)	<0.0001	4.9 (1.1)	4.8 (1.1)	<0.0001	4.7 (1.1)	4.6 (1.1)	<0.0001
	>5 mmol/L, % (n)	45.7 (70,607)	59.3 (7,099)	57.8 (3,062)	0.094	54.3 (17,981)	53.3 (11,100)	0.034	40.7 (12,587)	37.4 (11,443)	<0.0001	35.0 (3,134)	32.5 (4,200)	<0.0001
Pre-existing CVD (%, n)		19.1 (29,584)	3.3 (398)	2.9 (154)	0.160	12.3 (4,082)	12.2 (2,540)	0.676	23.8 (7,365)	25.3 (7,740)	<0.0001	32.7 (2,929)	33.9 (4,376)	0.073
Receiving lipid-lowering medication (%, n)		34.6 (53,557)	9.9 (1,188)	9.2 (489)	0.156	26.1 (8,647)	28.0 (5,828)	<0.0001	41.6 (12,891)	47.6 (14,591)	<0.0001	42.0 (3,762)	47.7 (6,161)	<0.0001
Receiving antihypertensive medication (%, n)		54.3 (83,936)	19.5 (2,340)	21.2 (1,122)	0.014	42.1 (13,939)	48.0 (9,983)	<0.0001	61.8 (19,118)	69.1 (21,155)	<0.0001	71.0 (6,360)	76.8 (9,919)	<0.0001

4.3.4 Prescription patterns

A sub-group analysis of people who received GLM prescription was conducted in order to determine patterns of prescription. The results in table 24 show that overall, metformin was the first medication most commonly prescribed followed by sulfonylureas. Proportions of people prescribed metformin decreased across age groups, the opposite was found for sulfonylureas where proportions increased among older age groups.

Moreover, the proportions of insulin prescription were low across all age groups, and there was a decreasing proportion across age groups. Thus, the 30 to 44 age group had the highest proportion of insulin prescription, and the group of people ≥75 years had the lowest.

Table 24. Patterns of first medication prescribed to people with newly diagnosed T2DM in Scotland

Drug class	Received GLM N=84,997	Age groups (years)			
		30 to 44 n=11,953	45 to 59 n=33,115	60 to 74 n=30,958	≥ 75 n=8,971
Metformin (%, n)	82.3 (69,913)	84.5 (10,095)	86.1 (28,500)	81.1 (25,101)	69.3 (6,217)
Sulfonylureas (%, n)	18.9 (16,077)	16.4 (1,960)	16.2 (5,368)	19.7 (6,107)	29.5 (2,642)
Insulin (%, n)	1.2 (1,037)	3.1 (367)	0.9 (306)	0.9 (287)	0.1 (77)
Other (%, n)	2.8 (2,422)	3.7 (437)	3.2 (1,059)	2.4 (750)	2.0 (176)

Differences between groups were statistically significant for all variables presented in this table (p-value < 0.0001)

It is important to note that, among those who received GLM prescription, only 92.9% (79,039) were recorded as being prescribed monotherapy. The remaining 7.1% were registered as having received two or more drugs for glucose-control. Hence, the numbers in table 24 do not add to 100 percent.

No further analysis was conducted in relation to prescription patterns as this was beyond the scope of this study.

This section addressed the first research question *what is the proportion of people with T2DM within two years after diagnosis who have and who have not received prescriptions for GLM within two years after diagnosis, and how do characteristics differ between people who have and who have not received a prescription for GLM within two years after diagnosis?* The results from the analysis showed that:

- Overall, 54.9% (n=84,997) of people diagnosed with T2DM between 2004 and 2012 received GLM within two years after diagnosis. Moreover, from 2004 to 2012 there was a trend of increasing proportions of people receiving GLM within three months of diagnosis (25.6% in 2004 to 36.1% in 2012)
- In general, age and HbA1c were higher for people who received a prescription by two years after diagnosis of T2DM. Moreover, amongst those who received a GLM prescription proportions of people receiving anti-hypertensive medication and lipid-lowering medication were significantly lower.
- The analysis by age groups showed that regardless of their prescription status, people in the ≥75 years groups had lower BMI, lower HbA1c and cholesterol, but had higher SBP, proportion of pre-existing CVD and were receiving lipid-lowering and antihypertensive medication in higher proportions.

These findings suggest that some clinical factors and their association with prescription of GLM could be confounded by age. Furthermore, this section included a sub-group analysis of prescription patterns of people who received GLM within two years after diagnosis, which showed that the first GLM most commonly prescribed was metformin. The section that follows moves on to

describe in greater detail the glycaemic control of the studied population and the differences between groups according to their HbA1c.

4.4 Glycaemic control and glucose-lowering medication prescription initiation

Having explained the characteristics of people with T2DM by receipt of a GLM prescription within 2 years from diagnosis, I will now move on to address the second research question of this strand. In this section, I describe the role of both HbA1c at diagnosis of diabetes and the additional effect of age in influencing treatment choices

4.4.1 Baseline HbA1c by age groups

In table 25, mean, median and interquartile ranges of HbA1c closest to diagnosis for the cohort and for age groups are presented. Higher mean HbA1c was observed in younger than older groups. The fact that a large proportion of HbA1c values were below the cut-off point for T2DM diagnosis; presumably arises because the diagnosis was based on blood glucose rather than HbA1c.

Table 25. HbA1c closest to diagnosis in the imputed dataset, stratified by age groups

Age groups	All N= 154,660	30 to 44 n= 17,274	45 to 59 n= 53,927	60 to 74 n= 61,584	≥ 75 n= 21,875
Mean (SD), mmol/mol	59.7 (18.9)	64.7 (20.5)	61.8 (19.5)	57.8 (17.6)	55.9 (16.4)
Median (IQR), mmol/mol	54 (47–68)	60 (50–77)	56 (48–72)	52.5 (46–65)	51.5 (45–61)

4.4.2 Differences between people with optimal and sub-optimal HbA1c

People with T2DM were classified according to their HbA1c closest to diagnosis into optimal (< 53 mmol/mol) or sub-optimal (≥ 53 mmol/mol)

groups. The results of the analysis based on this classification are presented in this section.

It can be seen from Table 26 below that people with HbA1c ≥53 mmol/mol in the cohort consisted of 58.2% (48,926) men. Overall, there was a larger proportion of white Scottish/British (70.2%) than other/unknown ethic groups, but proportions did not differ between those with optimal and sub-optimal HbA1c. Furthermore, there was a larger proportion of people from the most deprived SIMD quintiles (1 and 2) in the group with sub-optimal HbA1c. People with sub-optimal HbA1c were significantly younger than those with optimal HbA1c.

Moreover, people with sub-optimal HbA1c had higher mean BMI and higher proportions with a BMI ≥ 30 Kg/m2, than people with optimal HbA1c. Similarly, mean cholesterol and mean DBP were higher for people with sub-optimal HbA1c. In contrast, people with optimal HbA1c included a statistically significantly larger proportions of people with SBP ≥130 mmHg. However, mean SBP was not significantly different between optimal and sub-optimal HbA1c.

Compared to people with sub-optimal HbA1c people with optimal HbA1c were more likely to have pre-existing CVD, possibly due to the fact that this group included a larger proportion of older people who have lower HbA1c. Likewise, a higher proportion of people with optimal HbA1c were receiving lipid-lowering medication and antihypertensive medication.

Table 26. Characteristics of people in the imputed dataset with recently diagnosed T2DM stratified by baseline HbA1c levels, <53 mmol/mol and >53 mmol/mol

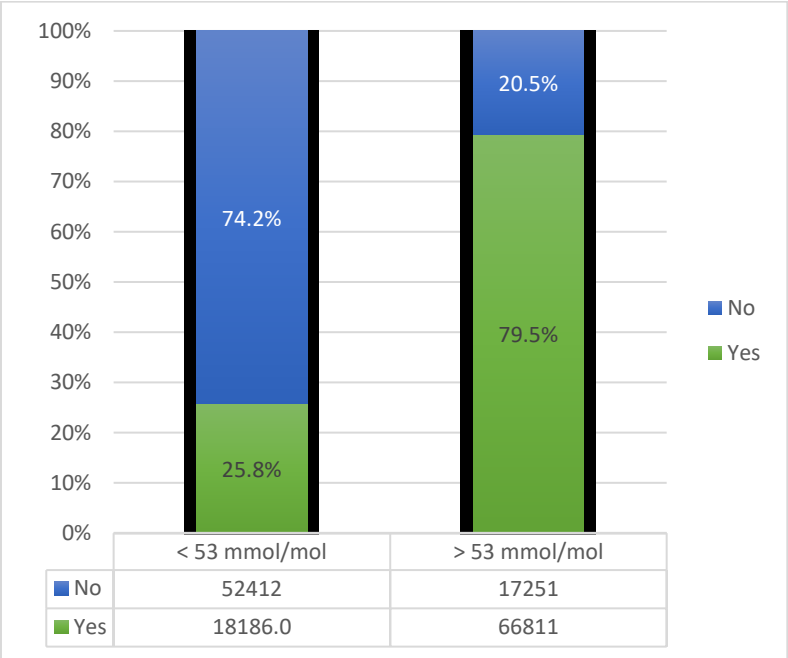
Variable	HbA1c		P values
	<53 mmol/mol	**≥53 mmol/mol**	
Age, years (mean ± SD	62.9 (12.5)	59.4 (13.6)	<0.0001
Gender, male (%, n)	53.1 (37,495)	58.2 (48,926)	<0.0001

Ethnicity, White Scottish/British (%, n)			70.2 (49,592)	70.2 (59,010)	0.349
SIMD (%, n)	Most deprived	1	22.9 (16,191)	25.3 (21,304)	
		2	22.4 (15,786)	23.6 (19,830)	
		3	20.2 (14,276)	19.9 (16,714)	<0.0001
		4	18.9 (13,328)	17.5 (14,749)	
	Least deprived	5	15.6 (11,017)	13.6 (11,465)	
BMI	Mean Kg/m2 ± SD		31.8 (6.9)	32.3 (7.0)	<0.0001
	≥ 30 Kg/m2 (%, n)		57.0 (40,245)	59.8 (50,289)	<0.0001
Systolic Blood Pressure	Mean mmHg ± SD		137.9 (15.4)	137.9 (15.7)	0.862
	≥ 130 mmHg (%, n)		70.0 (49,393)	68.5 (57,616)	<0.0001
Diastolic Blood Pressure	Mean mmHg ± SD		79.5 (9.0)	80.9 (9.3)	<0.0001
	> 80 mmHg (%, n)		44.3 (31,266)	50.2 (42,249)	<0.0001
Cholesterol	Mean mmol/L ± SD		4.9 (1.1)	5.1 (1.2)	<0.0001
	> 5 mmol/L (%, n)		41.1 (29,032)	49.4 (41,575)	<0.0001
Pre-existing CVD (%, n)			22.6 (13,930)	16.9 (12,702)	<0.0001
Receiving lipid-lowering medication (%, n)			41.0 (28,972)	29.2 (24,585)	<0.0001
Receiving antihypertensive medication (%, n)			62.8 (44,318)	47.1 (39,618)	<0.0001

4.4.3 Glucose-lowering medication prescription among people with optimal and sub-optimal HbA1c

Figure 8 below compares the proportions of people with sub-optimal HbA1c with and without GLM prescription within two years of diagnosis. Overall, approximately one-third of people (25.8%) with optimal HbA1c received medication prescription by two years after diagnosis. Conversely, for those with sub-optimal HbA1c, the majority (79.5%) received a pharmacological prescription for glucose control within two years after T2DM diagnosis.

Figure 8. Proportions of people with T2DM in the imputed dataset, by pharmacological treatment status at 2 years after diagnosis.



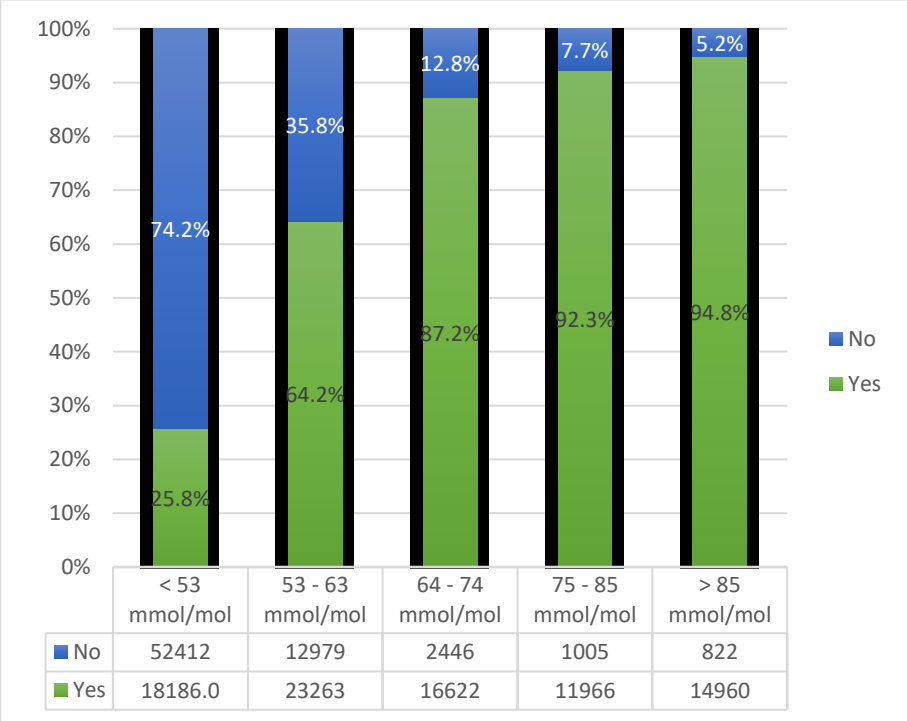
4.4.3.1 Proportions of people who received and did not receive glucose-lowering medication prescription stratified by different ranges of sub-optimal HbA1c

The previous section showed a large difference in proportions of people who received medication prescription by two years after T2DM diagnosis by HbA1c category. As described in the previous section, compared with people with optimal HbA1c (<53 mmol/mol), a larger proportion of the people with HbA1c ≥ 53 mmol/mol received medication prescription within 2 years after diagnosis of T2DM.

The next section describes a sensitivity analysis using different cut-points for HbA1c. Figure 9 below illustrates the breakdown of people with and without GLM prescription stratified by different groups of sub-optimal HbA1c. In general, there is a clear trend of increasing proportions of people with medication prescription. Thus, a larger proportion (94.8%) of people with HbA1c >85 mmol/mol were prescribed GLM prescription by two years after diagnosis.

Overall, more than half received GLM prescription by two years after diagnosis; proportions ranged from 64.2% (23,263) for those with an HbA1c of 53 – 63 mmol/mol to 94.8% (14,960) for those with an HbA1c > 85 mmol/mol.

Figure 9. Proportions of people with T2DM in the imputed dataset by pharmacological treatment status at 2 years after diagnosis, stratified by ranges of HbA1c



	< 53 mmol/mol	53 - 63 mmol/mol	64 - 74 mmol/mol	75 - 85 mmol/mol	> 85 mmol/mol
No	52412	12979	2446	1005	822
Yes	18186.0	23263	16622	11966	14960

4.4.4 HbA1c distribution by age groups

As previously described, 20.5% (17,251) of people with HbA1c ≥ 53 mmol/mol did not receive a GLM prescription by two years after diagnosis. Table 27 presents a comparison of the proportions of people with sub-optimal HbA1c according to age groups.

Table 27 compares the breakdown of sub-optimal HbA1c categories according to age groups. Overall, higher HbA1c was associated with increased proportions of people receiving GLM in all age groups. In addition, proportions of people with an HbA1c of 53 – 63 mmol/mol increased at

increased age group. Conversely, proportions for all other sub-optimal HbA1c groups decreased at increased age groups. Hence, people ≥75 years had lower proportions of people with the highest HbA1c ranges.

Table 27. Proportions of patients in the imputed dataset with HbA1c >53 mmol/mol who did not receive pharmacological treatment by two years after diagnosis, stratified by age groups and HbA1c sub-optimal ranges

HbA1c ranges, mmol/mol	*All* *N= (17,250)*	*Age group (years)*			
		30 to 44 **n= 1,828**	**45 to 59** **n= 5,763**	**60 to 74** **n= 6,731**	**≥ 75** **n= 2,928**
53 – 63 (%, n)	75.2	62.9	69.9	79.7	83.2
	(12,979)	(1,149)	(4,028)	(5,366)	(2,436)
64 – 74 (%, n)	14.2	19.4	16.4	12.1	11.2
	(2,444)	(354)	(947)	(814)	(329)
75 – 85 (%, n)	5.8	9.4	7.2	4.9	3.1
	(1,005)	(172)	(415)	(328)	(90)
> 85 (%, n)	4.8	8.4	6.5	3.3	2.5
	(822)	(153)	(373)	(223)	(73)

This section addressed the second research question of this study, which is: *what is the proportion of people with T2DM and sub-optimal glycaemic control without a GLM prescription two years after diagnosis?* Taken together, the results of this section provide important insights into differences in prescription proportions according to different HbA1c categories.

- Over half of the cohort (54.3%, n=84,062) had a baseline HbA1c ≥53 mmol/mol. Among those who had HbA1c ≥53 mmol/mol, 79.5% (n=66,811) received GLM prescription within two years from diagnosis. The sensitivity analysis illustrated in figure 9 showed that the proportions of people who received GLM within two years from diagnosis increased at increasing HbA1c levels at baseline.
- The analysis of HbA1c closest to diagnosis stratified by age groups presented in table 25 showed that mean and median HbA1c differed

by age group. Mean HbA1c decreased at increased age group. Thus, the 30 to 44 years group had the highest HbA1c mean, and the ≥75 years group had the lowest.

- The analysis of people with baseline HbA1c ≥53 mmol/mol by age and HbA1c ranges (table 25) showed that a larger proportion of people ≥75 years had HbA1c of 53–63 mmol/mol and the youngest group of people with 30–44 years had the lowest proportion. Conversely, the oldest group (≥75 years) had lower proportions of people with HbA1c >63 mmol/mol whereas people of 30–44 years had the highest proportions of people with HbA1c >63mmol/mol. Furthermore, across the HbA1c classification groups, there was an increasing proportion of people with GLM by two years after diagnosis.

4.5 Time to glucose-lowering medication prescription

This section will explain the factors associated with time to GLM initiation by two years after diagnosis for people with T2DM diagnosed between the years 2004 to 2012.

The first part of this section uses Kaplan-Meier curves to describe differences in time to treatment after diagnosis of diabetes by age groups. Next, average days to medication prescription are presented and compared across age groups. Finally, the last part of this section presents the results of the Cox regression analysis.

4.5.1 Time to glucose-lowering medication initiation by age group

4.5.1.1 Kaplan Meier

The results of the Kaplan-Meier survival analysis are presented in figure 10. Overall, proportions receiving a prescription for GLM were 31.2%, 45.0%, and 54.9% for 30 days, 1 year, and 2 years after diagnosis of T2DM. Furthermore, figure 10 shows that the proportion of patients who had

received drug treatment for T2DM within two years of diagnosis decreased with increasing age.

Figure 10. Kaplan-Meier curves for time to glucose-lowering treatment initiation after diagnosis of T2DM by age group

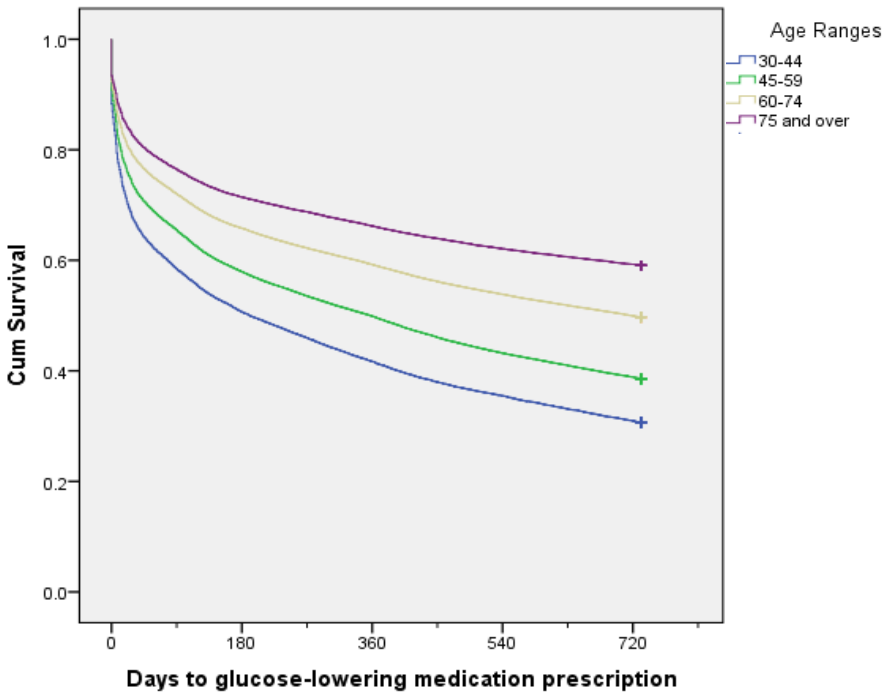


Table 28 below presents the comparison of proportions of people who received GLM prescription by two years after the diagnosis of T2DM and the median time to pharmacological prescription (25^{th}, 75^{th} percentile). Results are presented before and after stratifying by age groups. Overall, mean and median days to treatment were higher for the older age group and lower for the youngest group. Thus, proportions of people who received GLM prescription by two years after diagnosis were 69.3%, 61.4%, 50.3%, and 40.9% for patients in the 30 to 44, 45 to 59, 60 to 74, and $\geq$ 75 age groups, respectively ($p<0.0001$).

It is apparent from the table that, within two years of T2DM diagnosis, younger people have shorter times to GLM initiation. Overall, the number of days to GLM prescription was positively skewed since median values were considerably fewer than mean number of days. Another interesting aspect of

this table is related to the eldest group (≥75 years), although this group had the lowest proportion of people who received GLM prescription within two years after diagnosis. The median and mean days to medication prescription were lower than those for the two previous groups, 60–74 years and 45–59 years.

Table 28. Time to pharmacological treatment initiation by age group among patients over 30 years of age in Scotland 2004-2013 who started drug treatment within two years after diagnosis

Variable	Entire Cohort N=154,660	Age Groups (years)			
		30 to 44 n=17,274	45 to 59 n=53,927	60 to 74 n=61,584	≥ 75 years n=21,875
Patients with drug treatment within 2 years after diagnosis, n (%)	84,997 (55.0%)	11,973 (69.3%)	33,112 (61.4%)	30,957 (50.3%)	8,955 (40.9%)
Median number of days from diagnosis to treatment initiation (IQR)	54 (7 – 258)	40 (5 – 230)	56 (7 – 261)	60 (7 – 268)	53 (7 – 247)
Mean days to time to treatment initiation	155.8	142.9	156.8	160.6	152.7

So far, differences in prescription and time to prescription across different groups have been shown. A more detailed account of the factors associated with time to GLM prescription is given in the following section.

4.5.2 Factors associated with time to drug treatment initiation

In this section, the results of the Cox regression analysis, the univariate and the four adjusted models are presented. Further details about variable selection and the examination of the assumptions of the model were presented in the previous chapter.

Results are presented in table 29 where the first column *"Univariate model"* indicates the results from the model including the single variable described in the left column of the table. The following column *"Adjusted model 1"*

presents the results of the model adjusted by age, sex, ethnicity, and SIMD. Next, the column *"Adjusted model 2"* provides the results from the model, which adjusted for the characteristics included in model 1 plus baseline HbA1c. Then, the column *"Adjusted model 3*" presents results from the model included the variables in model 2 plus other metabolic factors such as BMI, SBP, DBP, cholesterol and pre-existing CVD. Finally, the last column *"Adjusted model 4"* provides the results of the model, including the variables in model 3 with the addition of use of other drugs such as lipid-lowering medication and antihypertensive medication.

4.5.2.1 Hazard ratios for glucose-lowering medication prescription

As expected from previous findings, the data in table 29 also show that older age was associated with longer time to drug treatment initiation. Conversely, HbA1c ≥53 mmol/mol and higher BMI were associated with shorter time to GLM prescription.

Moreover, model 1 suggests that increased age, female sex, other/unknown ethnicity and lower deprivation were associated with longer time to GLM prescription. Results of model 2 were similar to model 1; however, female sex and HbA1c ≥53 mmol/mol were associated with shorter time to medication prescription.

The table below shows that in the adjusted models 3 and 4 increased age, other/unknown ethnicity, and the least deprived SIMD quintiles were associated with longer time to medication prescription. Conversely, female sex, HbA1c ≥53 mmol/mol and BMI ≥30 Kg/m2 were associated with having shorter time to GLM prescription.

With respect to other metabolic factors, model 3 shows that raised blood pressure; SBP ≥130 mmHg and DBP >80 mmHg was associated with longer time to medication prescription. Similarly, cholesterol >5 mmol/L was associated with longer time to GLM prescription; no significant association was found for pre-existing CVD. Moreover, model 4 shows that receiving

antihypertensive medication was associated with having longer time to medication prescription. However, receiving lipid-lowering medication was associated with shorter times to medication prescription; there was no significant association with pre-existing CVD.

Table 29. Hazard ratios for time to initiation of glucose-lowering medication for people with T2DM in the imputed dataset.

Variable	Univariate model		Adjusted model 1		Adjusted model 2		Adjusted model 3		Adjusted model 4	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age at diagnosis	0.98 (0.98-0.98)	<0.0001	0.98 (0.98-0.98)	<0.0001	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001
Sex Male	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001
Female	0.95 (0.92-0.95)		0.98 (0.96-0.99)		1.04 (1.03-1.06)		1.04 (1.03-1.06)		1.04 (1.03-1.06)	
Ethnicity Scottish/British	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001
other/unknown	0.94 (0.93-0.96)		0.95 (0.94-0.97)		0.93 (0.92-0.95)		0.93 (0.92-0.95)		0.94 (0.92-0.95)	
SIMD Most deprived	1.00		1.00		1.00		1.00		1.00	
2	0.95 (0.93-0.97)	<0.0001	0.98 (0.96-0.99)	0.037	0.98 (0.96-1.00)	0.126	0.99 (0.97-1.00)	0.203	0.99 (0.97-1.00)	0.155
3	0.89 (0.86-0.90)	<0.0001	0.92 (0.90-0.94)	<0.0001	0.93 (0.91-0.95)	<0.0001	0.94 (0.92-0.96)	<0.0001	0.94 (0.92-0.95)	<0.0001
4	0.80 (0.79-0.82)	<0.0001	0.85 (0.83-0.87)	<0.0001	0.87 (0.85-0.89)	<0.0001	0.87 (0.85-0.89)	<0.0001	0.87 (0.85-0.89)	<0.0001
Least deprived 5	0.75 (0.73-0.76)	<0.0001	0.79 (0.77-0.81)	<0.0001	0.81 (0.81-0.85)	<0.0001	0.83 (0.81-0.85)	<0.0001	0.83 (0.81-0.85)	<0.0001
HbA1c <53mmol/mol	1.00	<0.0001			1.00	<0.0001	1.00	<0.0001	1.00	<0.0001
≥53 mmol/mol	5.31 (5.22-5.40)				5.11 (5.02-5.21)		5.14 (5.05-5.23)		5.12 (5.03-5.21)	
BMI <30 Kg/m^2	1.00	<0.0001					1.00	<0.0001	1.00	<0.0001
≥30 Kg/m^2	1.17 (1.16-1.19)						1.03 (1.02-1.05)		1.03 (1.02-1.05)	

Table 29 (continued) Hazard ratios for time to initiation of glucose-lowering medication for people with T2DM in the imputed dataset.

Variable	Univariate model		Adjusted model 1		Adjusted model 2		Adjusted model 3		Adjusted model 4	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
SBP <130 mmHg	1.00	<0.0001					1.00	<0.0001		
≥130 mmHg	0.88 (0.86-0.89)						0.93 (0.91-0.94)			
DBP ≤80 mmHg	1.00	<0.0001					1.00	0.007		
>80 mmHg	1.12 (1.10-1.13)						0.98 (0.96-0.99)			
Cholesterol ≤5mmol/L	1.00	<0.0001					1.00	<0.0001		
>5mmol/L	1.14 (1.12-1.15)						0.96 (0.94-0.97)			
CVD No	1.00	<0.0001					1.00	0.519	1.00	0.539
Yes	0.83 (0.82-0.84)						0.99 (0.97-1.01)		1.01 (0.99-1.03)	
Lipid-lowering medication No	1.00	<0.0001							1.00	<0.0001
Yes	0.80 (0.79-0.81)								1.05 (1.03-1.07)	
Antihypertensive medication No	1.00	<0.0001							1.00	0.002
Yes	0.73 (0.72-0.74)								0.97 (0.96-0.99)	

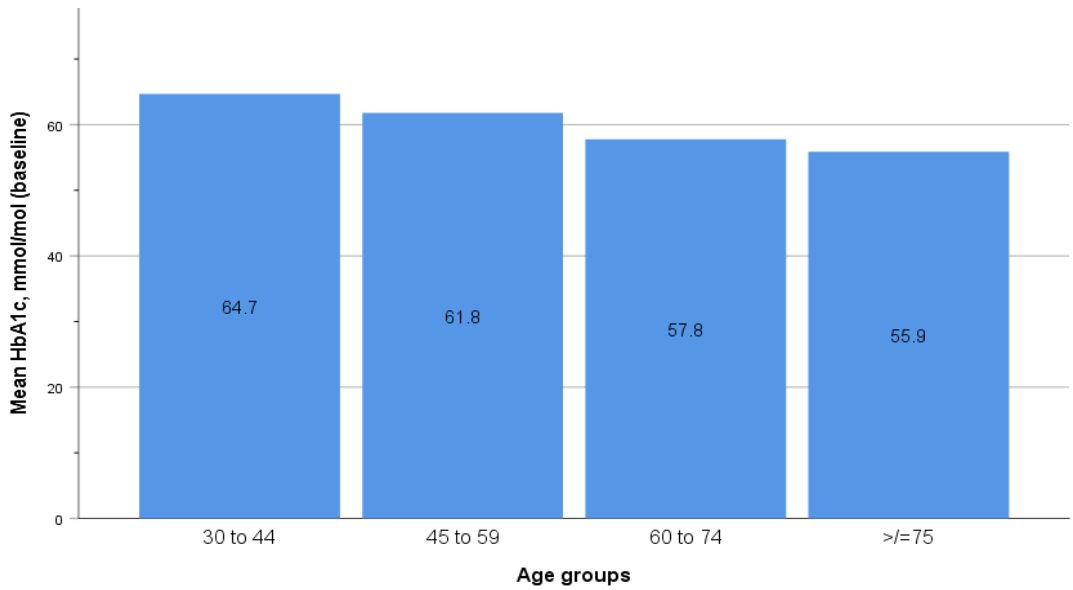
Variables included in each model: ***Model 1:*** sex, ethnicity, and SIMD. ***Model 2:*** age at diagnosis, sex, ethnicity, SIMD, and HbA1c. ***Model 3:*** age at diagnosis, sex, ethnicity, SIMD, HbA1c, BMI, SBP, DBP, cholesterol and CVD. ***Model 4:*** age at diagnosis, sex, ethnicity, SIMD, HbA1c, BMI, CVD, receiving lipid-lowering medication and receiving antihypertensive medication

4.5.2.2 Further analyses on factors associated with time to drug treatment initiation analyses in the imputed dataset, stratified by age

As table 25 in sub-section 4.4.1 showed, there seemed to be a correlation between HbA1c and age. This was further inspected visually and by a formal test of interaction. As shown in figure 11, HbA1c decreased at increased age. The formal test of interaction corroborated this, the test between age and HbA1c showed that age and HbA1c were negatively correlated r= –0.161, p = <0.0001. In other words, a one-year increase on patient's age is associated with a decrease of 0.161 mmol/mol on HbA1c.

Thus, adjusted model 4 analyses (described in section 4.5.2), stratified by age were conducted and are shown in table 30. Although there was an effect on patients' age, HbA1c ≥53 mmol/mol was associated with shorter time to GLM initiation across all age groups. Hazard ratios for time to treatment associated with the higher HbA1c category increased with age and people with T2DM in the oldest group (≥75 years) with HbA1c ≥53 mmol/mol had six-fold times increased in risk of receiving GLM compared with people in the same age group with HbA1c <53 mmol/mol.

Figure 11. Mean HbA1c at baseline by age groups



Moreover, patients' sex and its association with time to GLM prescription differed depending on age groups. While there was no significant association between sexes for the oldest groups (60 to74 years, and ≥75 years), in the group of people aged 30 to 44 years females had shorter time to GLM initiation, and in those aged 45 to 59 years, males had shorter time to GLM initiation. Demographic characteristics such as ethnicity and SIMD showed similar results with previous analyses. Hence, other/unknown ethnicity and least deprived SIMD quintiles were associated with longer time to GLM initiation.

Table 30. Adjusted hazard ratios for initiation of GLM for people with T2DM in the imputed dataset, stratified by age group

Variable		Age groups (years)			
		30 to 44	45 to 59	60 to 74	≥75
		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Age		0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.98 (0.97-0.98)
Sex	Male	1.00	1.00	1.00	1.00
	Female	1.11 (1.07-1.16)	0.93 (0.91-0.96)	1.02 (0.99-1.05)	0.96 (0.92-1.01)
Ethnicity	Scottish/British	1.00	1.00	1.00	1.00
	other/unknown	0.91 (0.87-0.95)	0.93 (0.91-0.96)	0.95 (0.93-0.97)	0.95 (0.91-0.99)
SIMD	Most deprived 1	1.00	1.00	1.00	1.00
	2	0.99 (0.94-1.04)	0.98 (0.95-1.02)	0.99 (0.96-1.03)	0.96 (0.90-1.02)
	3	0.98 (0.93-1.03)	0.91 (0.88-0.94)	0.93 (0.90-0.96)	0.99 (0.93-1.06)
	4	0.90 (0.85-0.96)	0.86 (0.83-0.89)	0.86 (0.83-0.89	0.92 (0.86-0.98)
	Least deprived 5	0.84 (0.79-0.90)	0.81 (0.78-0.84)	0.84 (0.80-0.87)	0.86 (0.80-0.93)
HbA1c	<53mmol/mol	1.00	1.00	1.00	1.00
	≥53 mmol/mol	3.62 (3.45-3.80)	4.78 (4.64-4.92)	5.64 (5.48-5.80)	6.55 (6.22-6.91)
BMI	<30 Kg/m2	1.00	1.00	1.00	1.00
	>30 Kg/m2	0.94 (0.89-0.98)	1.01 (0.99-1.04)	1.05 (1.03-1.09)	1.05 (1.01-1.11)
CVD	No	1.00	1.00	1.00	1.00
	Yes	1.02 (0.91-1.14)	1.03 (0.99-1.07)	1.01 (0.98-1.03)	0.99 (0.95-1.05)
Lipid-lowering medication	No	1.00	1.00	1.00	1.00
	Yes	1.23 (1.15-1.31)	1.12 (1.09-1.15)	0.99 (0.97-1.03)	0.95 (0.90-0.99)

Antihypertensive medication	No	1.00	1.00	1.00	1.00
	Yes	1.01 (0.96-1.06)	0.97 (0.94-0.99)	0.95 (0.93-0.98)	0.99 (0.95-1.05)

Furthermore, in order to be able to compare my findings with the literature presented in chapter 2, a further analysis using binary categories for patients' age was conducted. Table 31 shows the results of the adjusted model 4, which included all variables presented. As shown in table 31, and in accordance with previous analyses, people aged ≥65 years had longer time to GLM initiation than people aged <65 years.

Table 31. Adjusted hazard ratios for initiation of GLM for people with T2DM in the imputed dataset using age in binary categories.

Variable		Adjusted model 4	p-value
Age	<65 years	1.00	<0.0001
	>65 years	0.78 (0.77-0.80)	
Sex	Male	1.00	<0.0001
	Female	1.03 (1.01-1.04)	
Ethnicity	Scottish/British	1.00	<0.0001
	Other/unknown	0.94 (0.93-0.96)	
SIMD	Most deprived 1	1.00	
	2	0.98 (0.96-0.00)	0.018
	3	0.92 (0.90-0.94)	<0.0001
	4	0.85 (0.84-0.87)	<0.0001
	Least deprived 5	0.81 (0.79-0.83)	<0.0001
HbA1c	<53mmol/mol	1.00	<0.0001
	≥53 mmol/mol	5.14 (5.05-5.24)	
BMI	<30 Kg/m2	1.00	<0.0001
	>30 Kg/m2	1.06 (1.04-1.07)	
CVD	No	1.00	0.165
	Yes	0.99 (0.97-1.01)	
Lipid-lowering medication	No	1.00	<0.0001
	Yes	1.04 (1.02-1.05)	

Antihypertensive medication	No	1.00	<0.0001
	Yes	0.94 (0.92-0.95)	

In this section, the third research question: *what factors are associated with time to GLM prescription for people with T2DM within two years of diagnosis,* was addressed. The key points of the analyses presented in this section are:

- The Kaplan-Meier curves showed that time to GLM after T2DM diagnosis increased at increased age group. Thus, in figure 10 it can be observed that the proportion of people who had received GLM by 2 years after diagnosis was higher for the 30-44 years group (69.3%) and lower for the ≥75 years group (40.9%).
- The Cox regression analysis presented in table 29 showed that increased age was associated with having longer time to drug prescription for glucose control. Moreover, HbA1c ≥53 mmol/mol and BMI ≥30 Kg/m^2 were associated with having shorter time to GLM prescription.
- As it was suggested in previous sections, there was a potential association between HbA1c and age. Therefore, an analysis of these variables was performed. Such analysis indicated a negative association (HbA1c decreased at increased age) and further analysis stratified by age groups were conducted.
- However, despite the association between age and HbA1c the association between age and time to treatment persisted after adjustment for HbA1c. The stratified analysis by age in binary categories showed similar results.

4.6 Imputed dataset vs CCA

Here, I will present a brief comparison of the results from the imputed dataset presented in this chapter to the ones related to the CCA that are presented in more detail in the appendix. Although there were many similarities,

interesting differences were found between complete and imputed datasets, particularly with regard to factors associated with time to GLM prescription.

People with complete data available had a higher mean age and slightly lower HbA1c levels than those with missing data. Moreover, one of the main differences between the datasets is that in the youngest age group the proportion of people with a BMI ≥ 30 Kg/m2 was higher amongst the NM-2Y group in the CCA dataset, whereas for the imputed dataset, there was no difference between groups. Overall, for both datasets, HbA1c was higher for the GLM-2Y group. Furthermore, the proportions of people receiving anti-hypertensive medication were significantly higher among NM-2Y across all age groups. Similarly, proportions of people receiving lipid-lowering medication were higher among NM-2Y for the 45 to 59 years, 60 to 79 years and ≥ 75 years groups.

Furthermore, the fully adjusted Cox regression analysis conducted for the CCA showed no statistically significance by receipt of prescription within two years for BMI, unlike the significant difference observed in the imputed dataset. BMI was the variable with the most missing values. This suggests that limiting the analysis to patients with complete data may bias the results. However, the role of chance cannot be eliminated given the smaller size of the CCA dataset. Thus, although results in general for both datasets showed similar figures, the deletion of cases with incomplete data introduced potential bias and results of the CCA should be interpreted with caution.

4.7 Summary of findings

Overall, the cohort consisted of a majority of men (55.9%), majority white Scottish/British (70.0%) and nearly a quarter were from the most deprived SIMD quintile (SIMD I). Furthermore, more than half of people received GLM prescription within two years after T2DM diagnosis, the majority of those who received medication were within three months of diagnosis of T2DM. The

proportions of people receiving GLM within 2 years after diagnosis increased over time.

People who received medication prescription were younger at diagnosis of diabetes, had higher BMI, HbA1c, and cholesterol than those who did not. In addition, people who received GLM prescription included lower proportions of people with pre-existing CVD, receiving lipid-lowering medication and antihypertensive medication, with age differences potentially contributing to this pattern. Overall, metformin was the medication most commonly prescribed across all age groups.

In general, HbA1c at diagnosis of diabetes was higher for the youngest age group (30 to 44 years) and showed a decreasing trend across age groups. Furthermore, there was a positive association between HbA1c at diagnosis and proportion of people who had been prescribed GLM within two years after diagnosis.

Results of the fully adjusted Cox regression analysis of the imputed dataset showed that increased age, other/unknown ethnicity, the least deprived SIMD quintiles and receiving antihypertensive medication were associated with longer time to drug treatment. Conversely, female sex, HbA1c $\geq$53 mmol/mol, BMI $\geq$30 Kg/m2 and receiving lipid-lowering medication were associated with shorter time to drug treatment. After stratification by patients' age, the fully adjusted model showed that although there was an association between older age and longer time to GLM initiation, people in the $\geq$75 years group with HbA1c $\geq$53 mmol/mol had shorter time to GLM prescription.

In summary, older age and male sex were associated with longer time to GLM initiation. BMI and the use of other medications were also associated with shorter time to drug prescription for glucose control. The next chapter describes the findings of the qualitative strand.

Chapter 5 Qualitative findings

5.1 Introduction

In this chapter, I will present the findings of the qualitative strand of the study, which complement and expand the results presented in the previous chapter, particularly about factors associated with longer time to pharmacological treatment initiation, however, other findings that were not quantitatively studied will also be presented. Thus, the findings in this chapter will provide additional insights and broaden the knowledge of the topic studied. First, I will provide an overview of the participants' characteristics. Then, I will outline the three main themes, which elucidate the factors that influenced HCPs' decision-making around medication prescription initiation; namely, individual patient-related considerations, HCP-patient related factors, and contextual factors.

5.2 Participants and settings

The quantitative strand focused on analysing patients' data and did not include information related to the HCPs in charge of prescribing. In this section I present the characteristics of the HCPs who participated in the study, a brief description of the settings where they worked is also included. Overall, 16 HCPs were interviewed; 11 GPs and 5 Practice nurses. Participants were recruited from 12 different practices in Scotland; six in Edinburgh, two in East Lothian, two in West Lothian, one in Midlothian and one in Glasgow.

The following table presents some of the main characteristics of the participants; it includes participants' professional role (general practitioner or nurse), the location of their practice, which has a number appended to it; each number refers to a different practice within that specific region. Furthermore, it includes their years of clinical experience, which have been categorised into five groups (<5, 5-9, 10-14, 15-19, and ≥20 years) whether

they had a special interest in diabetes, and their sex[4]. Each HCP has been allocated a unique identifier which will be used throughout this chapter.

Table 32. Characteristics of participants

Name	Professional role	Practice location	Years of clinical experience[5]	Special interest in diabetes	Sex
GP1	General practitioner	Edinburgh 1	≥20	Yes	Male
GP2	General practitioner	Edinburgh 2	5 – 9	No	Male
GP3	General practitioner	Edinburgh 2	5 – 9	No	Male
GP4	General practitioner	Edinburgh 3	< 5	No	Male
GP5	General practitioner	West Lothian 1	≥20	Yes	Female
GP6	General practitioner	Edinburgh 4	15 –19	Yes	Male
GP7	General practitioner	West Lothian 2	< 5	No	Female
GP8	General practitioner	Glasgow	15 – 19	Yes	Male
GP9	General practitioner	East Lothian 1	5 – 9	Yes	Male
GP10	General practitioner	East Lothian 2	10 – 14	No	Female
GP11	General practitioner	Midlothian 1	≥20	No	Male
PN1	Practice Nurse	Edinburgh 5	5 – 9	No	Female
PN2	Practice Nurse	Edinburgh 6	5 – 9	No	Female
PN3	Practice Nurse	West Lothian 1	15 – 19	Yes	Female
PN4	Practice Nurse	East Lothian 2	10 – 14	Yes	Female
PN5	Practice Nurse	East Lothian 2	≥20	Yes	Female

The information in this table shows a balance in the number of males and females who were interviewed. However, the sample was skewed to male GPs, an issue which has been noted in chapter 3. Furthermore, apart from one South-East Asian individual, all participants were White British. Years of

[4] In qualitative research, gender is the term commonly used. However, in order to be consistent with the terminology used in previous chapters “sex” is used instead through this chapter.
[5] Years of clinical experience was not all necessary in general practice, some might include experience in hospitals.

clinical experience ranged from two to forty. In addition, half of the interviewees did not have a particular interest in diabetes.

Almost all HCPs provided additional information about their practices. Below, table 33 presents information about the size of the practice (number of patients listed), which have been categorised into three groups (<5,000, 5,000–10,000, and >10,000), workforce, which refers to the number of GPs and nurses; workforce has been categorised as follows: three groups for the number of GPs (<5, 5–10, and >11) and two groups for the number of nurses (1–3 and >3). The table also includes other information that HCPs provided about the practice such as patients' socioeconomic status (SES). Since some of the HCPs interviewed worked in the same practice, the information is presented is organised by the name of the practice which corresponds to *practice location* in table 32.

In general, there was variation in terms of practice size and location; however, most practices reported to have patients with low- or mixed SES. Among practices in the cities of Edinburgh and Glasgow, most of them were large practices as they had registered more than ten thousand patients, only one practice was small (<5,000). Practices located in semi-rural areas were from average to large size. Overall, most of the practices (n=7) were reported to serve populations with mixed SES, three reported that most patients were from low SES, and only in one practice the HCP indicated that patients were from middle to high SES.

Table 33. Characteristics of the practices

Name of practice	Practice size	Workforce	SES of patients/ other information
Edinburgh			
Edinburgh 2	5,000 – 10,000	5 – 10 GPs 1 – 3 nurses	Low SES. Average patients' age-wise.
Edinburgh 3	> 10,000	5 – 10 GPs 1 – 3 nurses	Mostly low and mid-SES.
Edinburgh 4	> 10,000	> 10 GPs > 3 nurses	Mixed of high- and low-SES. An important proportion of elderly patients.
Edinburgh 5	> 10,000	5 – 10 GPs	Mixed SES.

		1 – 3 nurses	
Edinburgh 6	5,000 – 10,000	5 – 10 GPs 1 – 3 nurses	Mixed SES. An important proportion of young patients.
West Lothian			
West Lothian 1	> 10,000	> 10 GPs > 3 nurses	Low-SES High proportion of elderly population.
West Lothian 2	5,000 – 10,000	5 – 10 GPs 1 – 3 nurses	Mixed of mid- and low-SES.
East Lothian			
East Lothian 1	5,000 – 10,000	5 – 10 GPs 1 – 3 nurses	Mixed SES Important proportion of elderly patients.
East Lothian 2	> 10,000	> 10 GPs > 3 nurses	Low SES Mixed age of patients.
Midlothian			
Midlothian 1	> 10,000	> 10 GPs > 3 nurses	Mixed SES Average age of patients
Glasgow			
Glasgow	< 5,000	< 5 GPs 1 – 3 nurses	Middle to high SES.

5.2.1 Division of tasks in primary care

None of the participants worked as locums; all were attached to their practices and the division of tasks in relation to diabetes depended on whether there was a specialist in the practice. For the practices where none of the GPs had a special interest in diabetes, all were expected to treat patients with T2DM. Typically, a patient was diagnosed by a GP and then referred to a nurse for follow-up and annual check-ups.

How T2DM was managed in the practices where participants worked is another relevant aspect that needs to be considered before I proceed to describe the findings. Therefore, the next section moves on to describe the process of diagnosing T2DM in primary care and an overview of patients' subsequent pathway once the diagnosis has been confirmed. Usually, these aspects were not influenced by HCPs but by standardised procedures within particular practice's management and the wide healthcare system and included: registration to the practice's diabetes register, the delivery of T2DM diagnosis, initial referrals and the arrangement of follow-up consultations.

5.2.2 Diagnosing T2DM in primary care

Participants indicated that in the practices where they worked there were usually two routes to diagnosing T2DM. The first route involved conducting a blood test if a patient presented symptoms such as polyuria and polydipsia or if they were concerned about a particular patient; for instance, someone with previously impaired glucose, pre-diabetes or with other chronic diseases. The second route was by chance through a routine blood test. Regardless of the route to diagnosis, after diagnosis, patients became part of their diabetes register and recall system. As exemplified in the quote below by GP3, participants described that usually GPs were the HCP in charge of delivering the diagnosis to patients, who then referred patients to the practice nurse. This highlights the importance of both HCPs in the management of T2DM.

> "Diagnosis is usually done by the GP, and then we refer them onto our practice nurse, she can spend more time with them talking a wee bit more about diet and lifestyle and get them set up with that kind of monitoring system." GP 3

Furthermore, some GPs reported spending the first consultation explaining and discussing the diagnosis. Explaining the diagnosis was described by most HCPs as a time-consuming task, some further described needing to book a double appointment to do so.

> "And once the diagnosis has been confirmed, we will get an appointment with the doctor at the practice who will bring the news to the patient that has got type 2 diabetes. We tend to get people on a double appointment so they have a bit more time so we can discuss the diagnosis, get them lifestyle advice, about diet, exercise if possible and some people are elderly and can't do exercise and have limited mobility. We have to look after blood pressure, cholesterol, about past or actual smoking. So we try to address most of this on the first consultation and give them advice." GP6

5.2.3 Patient's pathway

Once a patient was diagnosed, they were usually registered as "diabetic" and thereafter were included in the practice's register of patients with diabetes. Then, a patient's pathway usually continued through a referral to DESMOND; which as described in chapter 1, is a structured education programme for people newly diagnosed with T2DM. Patients also needed to attend their practices for check-ups to monitor their blood pressure, cholesterol levels, protein levels in urine, and assessment of cardiovascular risks.

The frequency of consultations depended on several factors. Some practices had established a management system for diabetes where patients might be linked to a particular GP or nurse who was in charge of conducting routine check-ups at certain time-points after diagnosis; however, the regularity and the timing of consultations depended on patients' individual characteristics.

> "Some people will get seen monthly if necessary, maybe not for the first year but certainly for the first seven, eight months just to make sure we're on top of it and they're on top of it. Again, it depends on their age, depends on their HbA1c, depends whether they've been started on medication and what the medication is."
> GP5

Participants described how follow-up consultations were commonly undertaken at three and six months after diagnosis since HbA1c levels need three months to show any change. Reviews were recommended to be conducted at least every 15 months. Follow-up consultations were described as usually including education about diabetes.

So far, I have presented information about the HCPs who participated in the study, including their clinical experience and interest in diabetes. I have also provided important information that sets the scene for understanding the general conditions and circumstances of HCPs and their practices. In the following section, I provide additional contextual information on HCPs'

opinions and stance on when to start GLM before moving onto describe the findings.

5.3 Prescribing glucose-lowering: the context

The HCPs interviewed described T2DM as a progressive disease characterised by an inevitable reduction in insulin production over time. Therefore, they viewed GLM as something that would be necessary for almost all patients:

> "The natural history is that your insulin production will slow with time. So, there comes a point where you are diagnosed, but then the insulin production continues to drop so you need more and more tables, and eventually, you need insulin, that is the classic interpretation, but we know there's considerable variation." GP1

HCPs viewed the reduction in risk of complications resulting from increased levels of glucose as the primary reason for prescribing GLM.

> "If we have well-controlled diabetes, then we are going to reduce the risk of complications, and that is in essence." GP1

> "I think in terms of reducing risk of cardiovascular disease and retinopathy and peripheral neuropathy, all those sorts of secondary complications of diabetes, it's predominantly the blood sugar that is important to keep at a managed level. The longer that people have blood sugar above recommended then the more likely they are to have secondary complications." GP4

Furthermore, HCPs described many interacting factors which influenced their decisions about when to initiate GLM in patients. In the following sections, I will describe the construction of themes, categories and sub-categories, and discuss the main influencing factors which emerged from my analysis.

5.4 Findings: themes, categories, and sub-categories

As indicated in chapter 3, this strand was informed by the NPT and the SEM theories. While the NPT informed the development of the topic guide, the SEM levels were the basis for the construction of initial themes and categories which were used as an aid in the initial process of data analysis. These categories, however, were not rigid and changed during the analysis of the interviews by the introduction of inductively constructed ones.

Table 34 provides the list of the final themes, categories and sub-categories that will be presented in the following main findings sections. As the table shows, several factors at all levels of the SEM influenced HCPs' decisions about when to initiate GLM. While these factors are reported separately, in many cases, they overlapped and were interwoven.

Table 34. List of final themes, categories and sub-categories describing factors that influence HCPs decisions about when to initiate GLM in people with newly diagnosed T2DM.

Theme	Categories	Sub-categories
1. Individual patient-related considerations	Physiological	Hba1c
		Development and presence of symptoms
		Age
		Comorbidities
	Psychological	Mental health
		Motivation/psychological readiness
		Expectations
	Cultural and religious	Religion
		Cultural views
2. Healthcare professional-patient related factors	HCP-patient interaction and relationship	Historical contact with patients
		Assessment of patient needs
		Cooperative relationship
	Negotiation with patients	Shared decision-making
		Assessment of patients' readiness
		Discussion of complications/ GLMs side effects
3. Contextual factors	Practice	Resources: time and workforce
		Division of tasks/HCPs' role
	HCPs	Keeping updated
		Perception of role within the healthcare team
	NHS	Primary care workload

As previously indicated, the SEM was intended to be used as a framework for reporting the main themes. However, this was not fully accomplished as the order and presentation of the themes were chosen according to what HCPs reported as determinant factors. In this manner, the first theme presented in this chapter relates to individual patient-related factors, this decision was made due to that most of the factors that influenced HCPs' decisions on when to start GLM were attributed to aspects related to patients.

Thus, patients' individual characteristics and conditions were described as a major determinant and are described first. The second theme is healthcare professional-patient related factors, this refers to the interaction between HCPs and their patients, which had the potential to shape HCPs decision-making about the initiation of GLM. The third theme is contextual factors which includes organisational and community aspects, in other words, the context in which HCPs relationship with peers and patients are embedded and can influence HCPs clinical decision-making about GLM initiation.

5.5 Theme 1: Individual patient-related considerations

In accordance with what was found in the quantitative analysis, individual patient characteristics were described as having a central influence on decisions about when to initiate medication, which included the patient's age and HbA1c. Moreover, in the interviews, additional aspects such as whether patients were perceived to be motivated to change their diet and lifestyles, and the existence of other health problems were also considered important. Because of their paramount importance, these individual patient-related considerations will be reported first.

5.5.1 Physiological aspects

In the previous chapter, quantitative data showed that some physiological aspects such as HbA1c and age were related to GLM initiation. In keeping with these findings, HCPs described a patient's HbA1c, age and comorbidities to be among the main aspects related to GLM initiation.

According to the HCPs who were interviewed, at diagnosis, all patients have raised levels that place them in the T2DM diagnosis category; however, some have levels that are considerably above the cut-off points. It was reported that the higher the patient's HbA1c at diagnosis, the more likely it was that pharmacological treatment would be prescribed, especially if the patient had other health conditions such as hypertension and hypercholesterolemia, which increased their cardiovascular risk.

> "If you had, as I said, a very high haemoglobin A1C you are not going to achieve that straight away, so you are not going to achieve a satisfactory level [HbA1c] on diet alone, so you might start medication sooner." GP1

> "If I was kind of thinking this is a patient who probably needs prescription, probably because they got a high initial HbA1c, in which I am thinking that diet and lifestyle interventions may be insufficient." GP2

Furthermore, a patient's HbA1c was also seen as a proxy measure of their ability to succeed with lifestyle and diet interventions. Generally, HCPs suggested that a high HbA1c reflected a patient's unhealthy habits, which were viewed as difficult to modify. Some HCPs suggested that not all patients should be prescribed GLM straight after diagnosis unless their HbA1c was very high. As exemplified below by GP1, some were worried that attaining good control of HbA1c with medication would discourage patients from attempting to manage their diabetes through lifestyle changes. Thus, if patients were given medication immediately, GPs were concerned that they might not see any point in changing their diet and lifestyle.

> “For all patients, it is terribly important that we address the lifestyle straight away. And for the majority of patients, if their HbA1c is not too high, then that’s all we can do in the first instance. Now we would know that if your HbA1c was sky-high is unlikely that you are going to achieve that without some medication, but the dilemma, because if we bring all the control excellent with drugs straight away, then you’ll be less inclined to do your bit of lifestyle.” GP1

Moreover, participants reported that a factor that is commonly associated with increased HbA1c is the presence of symptoms. They suggested that the higher the HbA1c, the higher the chances of patients experiencing symptoms such as polyuria and polydipsia. For some HCPs, the presence of symptoms influenced their decisions about whether the patient was prescribed GLM. The following extracts are interesting examples of how the presence of symptoms, in general, may play a pivotal role in the time to initiation of GLM:

> “The main factor that makes you decide whether to start medication as soon after diagnosis is whether they have symptoms or not in terms of osmotic symptoms. For instance, thirst and passing a lot of urine as a result of having a high sugar level. So, polyuria, polydipsia, you are much more likely to start medication for those patients than those who don’t have thirst and passing a lot of urine.” GP6

> “Symptoms would be if they are very thirsty or they’re passing a lot of urine, or they have a thrush-type infection or something like that. So these people’s symptoms suggest that sugar level’s up, particularly higher, and early medication for them might be a good idea to get on top of their symptoms.” GP9

However, as illustrated in the excerpts below, the decision about when to start pharmacological treatment was not solely based on raised blood glucose levels and associated symptoms; it was also affected by other factors, including the patient’s age and comorbidities. Elderly patients were often seen as more frail, and HCPs were often concerned about the risk of hypoglycaemic events in these patients. Therefore, the HbA1c cut-off used to

start pharmacological treatment for glucose control in these patients was reported as being less rigid than in younger patients.

> "If they were very frail then all we would worry about is whether or not they were having symptoms. But say they were a fit 80-year-old then I would certainly maybe not have their diabetic control as tight as a 30-year-old but at the same time, if they were a fit 80-year-old, the main thing I would be concerned about, apart from them not having symptoms, was not having hypos." GP 5

> "Elderly people we don't want to start really heavily treating them because you can always lead to more problems. You don't want them to get hypoglycaemic if they are elderly if they are frail if they live by themselves because you can put them at further risk of falls or them really becoming unwell and nobody being aware of that. So you would set different targets for different cohorts of patients, really." PN1

These findings suggest that although high HbA1c is a major factor, HCPs consider a large number of other factors related to each patient when making their decisions. For instance, as reported in the quote above by PN1, they would weigh the estimated life expectancy of a patient against their quality of life. Furthermore, as illustrated below in the quote by GP1, elderly patients were more likely to be treated using flexible targets and were started on medication at a higher HbA1c than younger patients. Likewise, the estimated life expectancy was taken into account when making their decisions; HCPs believed people with a longer life expectancy would benefit the most from receiving GLM. Conversely, for people who were thought to have a shorter life expectancy, reaching a low blood glucose level or establishing a tight glucose control was not seen as critical as these patients commonly had other diseases, and are frailer and seen as less likely to benefit from GLM.

> "The decision to start medication would be based largely on what HbA1c is; it would be affected by age, with younger patients we might be more aggressive to try and improve to get good control earlier than we would with somebody who is 80. Because if you are 80

> you are going to live for less time … maybe we would let your blood sugar be slightly higher than if you were 34 when your life expectancy is more and we want you to get good control to reduce the risks of complications." GP1

> "Lowering HbA1c has the benefit of reducing diabetes complications over the course of many years. So, if you don't have a life expectancy that is too long … don't have enough years to kind of benefit from lower HbA1c, so there's no point in starting medication. That is unless … they have a very high sugar level and they get some symptoms, thirst, passing lot of urine, then they have some benefit from starting medication in terms of symptoms relief." GP6

HCPs described mental health conditions such as depression as being common among people with T2DM. These conditions were described as potentially increasing the likelihood of receiving GLM because patients with mental health issues were seen as having difficulties implementing lifestyle changes.

> "Other people have other comorbidities, so particularly mental health; I think that can be quite challenging for people because they're not really necessarily able to want to prioritise physical illness and so it just doesn't come into their minds in the same way because they're just battling with a mental illness." GP4

HCPs' considerations and perceptions of mental health will be further considered in the following section.

5.5.2 Psychological aspects

Regarding psychological aspects, HCPs' views surfaced mainly in relation to patients' motivation to adopt and adhere to a healthy diet and lifestyle. Moreover, psychological aspects also included HCPs' assessment of patients' willingness to start GLM. As described in the previous section, HCPs considered changes in diet and lifestyle as being necessary for all patients who are diagnosed with T2DM, and therefore, all patients were

encouraged to make these changes, including the initiation of physical activity. While it was noted that it could be very challenging for patients to make these kinds of changes, some HCPs observed that diagnosis provided an important opportunity to motivate patients and provide them with information about healthy lifestyles. Several suggested that in the period directly after diagnosis, some patients are more likely to be motivated to make lifestyle changes than others.

> "The point of diagnosis it's quite a powerful time because people are usually a bit shocked about the fact they have diabetes so that can be quite an important time, I think, to move people and discuss lifestyle changes." GP4

> "Some patients do want, when they are first diagnosed, the opportunity to try and adjust their lifestyle, some patients say they're not gonna take any medication." PN4

As the quote above by PN4 suggests, initiation of GLM was sometimes delayed in situations where patients expressed a wish to be given an opportunity to change their lifestyle. Thus, the decision to start pharmacological treatment and the recommendations provided by HCPs varied on an individual basis.

HCPs considered the patient's motivation to be a crucial factor in implementing and maintaining diet and lifestyle changes. They suggested that sometimes it was possible to gauge a patient's engagement with their health and their willingness to make lifestyle changes based on previous interactions (e.g. previous consultations to discuss diabetes-related issues or for other health conditions); aspects related to HCP-patient previous interaction will be further discussed further in section 5.5.1.

As previously stated, mental health conditions were among the factors that HCPs took into consideration when prescribing GLM. As illustrated in the excerpts below, patients who were perceived to be less motivated due to

depression or other mental health conditions were often seen as being in a vicious circle of unhealthy habits and were thus more likely to be started on GLM sooner:

> "Sometimes I don't know, they can be a bit depressed, and maybe that's sort of the cause they're getting diabetes. Maybe they are depressed and not motivated to do much exercise… quite isolated … eating a lot … feeling rubbish … it could be that they're depressed and it's causing them to put on weight in the first place. These people tend not to be overly motivated, so it is up to us to try and encourage them to lose weight." PN2

> "There's also an element of how motivated the individual is, if … they aren't that motivated to change their lifestyle, or … unable to change their lifestyle very much. Then, you think, you've given them lots of advice but they are unlikely to be able to achieve that, and then they're more likely to start medication." GP6

As suggested in the quote below by GP2, patients' wider situation and context were also seen by HCPs as influencing their motivation to manage their glucose levels. For instance, people who had interacted with other people with T2DM or who had knowledge of the complications of T2DM were sometimes perceived as more motivated to tightly manage their glucose levels as they were more aware of the consequences of sub-optimal glucose control.

> "There are the patients who because of experiences; family members have diabetes or patients who know of the diabetes complications. Who are very aware of things like stroke, heart attacks and amputations, who are the patients who'll say no, I want lifestyle interventions and I want medication, and I want to have my HbA1c checked in 3 months' time, not 6 months' time or whatever, I have it checked every 3 months to make sure we are making progress. But again, I think those patients are the minority." GP2

Furthermore, HCPs considered that aspects such as health literacy, and patients' knowledge about diabetes promoted discussion on the initiation of GLM and fostered a more productive conversation with them. Some HCPs perceived people from low socio-economic groups and those with poor health literacy as being less engaged with their healthcare.

> "Sometimes, the sort of lower socioeconomic groups can be a little bit less motivated. They want a quick fix, they just want tablets, and they want it to all be made better, which is not really the attitude that we want to promote." PN1

> "Some patients want a lot of involvement…depending on their health literacy and the education level or their motivation, some people will understand a lot about the medications and be very pleased when you try to, you know, to discuss the medication and give them the choice… I think the media has quite a role in terms of scaring people about medication and their side effects. So the patients will read in newspapers or read on the internet that things that kind of make them scared of the medication." GP6

Furthermore, as reported above by GP6, some patients were exposed to information that was not always reliable or correct. However, the availability of information and exposure to media was also regarded as something that generated discussion and increased patients' engagement with their condition.

5.5.2.1 Patients' needs and observed expectations

HCPs described that the patient had to be the focus of the consultation and thus that patients' opinions were central to decisions as to when to start medication to lower glucose levels. However, participants observed that a significant proportion of their time during consultation was taken up by assessing patients' needs and expectations. As described in the literature review, a typical consultation length in primary care is very limited; this aspect will be further discussed in section 5.6.1.1.

HCPs shared their views that before prescribing GLM, patients needed to be asked about their priorities and goals in the management of their diabetes, a patient's priorities and readiness to start medication were two aspects that were viewed as central to starting pharmacological treatment for glucose-control. Some participants suggested that there was often a discrepancy between HCPs' and patients' health priorities, which could affect the timing of the initiation of GLM. In the quotes below, PN1 and GP10 explained that sometimes controlling their blood glucose was not a priority for patients, especially if they lived with other health conditions. Furthermore, as the first quote exemplifies, conversations with patients had the potential to uncover aspects that could affect treatment for glucose control, such as low mood or lack of motivation.

> "I ask them what matters to them the most: if they want to improve their diabetes or if they want to improve their breathing or sometimes the discussion would lead to finding out they've got low mood. So if they've got low mood then they're not compliant with their tablets because they can't be bothered, they've lost motivation. So generally sort of just having that discussion you can find out a lot about what their aims are, which is really interesting actually." PN1

> "I suppose the main thing is to let the patient talk first to get an idea of what's they're concerned about so you can build on that rather than it all being about what the clinician think needs to be the focus of the consultation." GP10

The development of a relationship with the patient appeared to influence decisions as to when to initiate GLM as it facilitated discussion about patient-related aspects. HCPs mentioned that physiological aspects, such as HbA1c were central when setting goals. However, HCPs noted that realistic goals were necessary in order to avoid demoralising the patient. The comments below illustrate the perceived importance of establishing a HCP-patient relationship where both individuals felt able and confident to discuss

decisions about diabetes management, and presumably decisions about when to start medications for glucose control.

> "Type 2 diabetes by nature is a progressive disease that's important to say to patients, to not be alarmed by the fact that sometimes control can worsen over time in despite of their best efforts because we know that it's the very nature of it. And that's important, so we don't get disillusion with what's going on, they are trying their best, but yeah, their HbA1c is not getting much better, and that's important but also to make them aware that we could have to add therapy should things no improve." GP2

> "It's … a step at a time because if they're gonna be overly tight with their diet, they are gonna feel fully miserable. And that has happened, so that's why I have to be careful, they get depressed because there's nothing that they feel they can eat if they want to keep their HbA1c spot on. It's looking at the person, as an individual very much so, and keep it around their needs, realistic goals and expectations… You always remind patients that is a progressive illness, and for some patient, it will progress faster than others despite them being as good as they can with their diet and their lifestyle…They can do just the best they can do, and you obviously have to support them in that, but make sure they don't get disheartened if they don't achieve it as quickly as they would like." PN5

Overall, the initiation of GLM involved discussion with the patient and HCPs were keen to consider the patient's readiness to start on pharmacological treatment for glucose control. However, HCPs also noted that it was imperative not to delay pharmacological treatment any longer than necessary.

> "It varies from person to person [the time a patient is on diet and lifestyle only]. As long as you don't end up colluding with the patient and just continuing, and before you know, one year, two years elapsed into diagnosis. For some patients we will try a few months, other patients want to try up to six months as long as they are trying to change their behaviour and they are

> maybe showing some improvement in their HbA1c or reduction in weight or some other parameters, showing that they're engaging with the diabetes management and care. Then, I am happy to continue with that." GP9

> "I could be persuaded by someone saying I am gonna lose 2 or 3 stone, if they're gonna do that, that's very effective treatment, it is a negotiation, is not, I don't make the decision on my own. We make a decision together, that's the way we would do about times." GP11

The development of a HCP-patient relationship and negotiation with patients will be further addressed in section 5.5.

5.5.3 Patients' cultural and religious backgrounds

With regard to the patient's background and wider context, cultural differences were deemed a factor that might influence the decision about when to initiate medication for glucose control. Some patients from ethnic and religious minority groups were perceived as being less likely to exercise or to engage in physical activity and, therefore, these patients might be prescribed GLM sooner as they were viewed as more likely to struggle to implement lifestyle changes.

> "I find for my Asian patients, Asian women going to the gym is completely unacceptable because there are men there and, you know, wearing skimpy shorts or skimpy tops, and you know we have to understand the cultural differences." GP8

As reported below, HCPs' also described other cultural aspects, such as the affinity to certain kind of sports like football, which they considered and took into account to provide tailored advice on lifestyle modifications, particularly to incentivise their patients to engage in physical activity.

> "You know, particularly in this place, men particularly like football. So, again is encouraging people to say well can you seek a football team? So, people have a passion for football for example and is actually relatively

> easy for them to find a place to play football once a week... we know once a week is not enough but it's just a start.” GP8

Moreover, GP8 reported that in order to provide such advice, HCPs’ need to know about their patients’ history, interests and preferences. However, it is important to note that GP8 was the GP in charge of all people with T2DM in their practice and had the opportunity to see the same patients over time.

In this section, I have described individual patient-related considerations which HCPs described as the most important aspects to consider for initiating GLM. As discussed above, HCPs took a set of interwoven individual physiological and psychological factors into consideration before prescribing GLM. However, HCPs’ decisions about when to initiate GLM were not solely based on the assessment and recognition of individual-patient related factors, they were also influenced by other issues such as the HCP-patient relationship and contextual factors. The next section addresses aspects related to the relationship between the HCP and the patient, and how this relationship affected prescription practices.

5.6 Theme 2: Healthcare professional-patient related factors

The section below describes HCP-patient related factors that influenced the initiation of GLM. These factors included previous interaction with patients, and negotiation with patients.

5.6.1 Interaction with patients and the development of a HCP-patient relationship

Participants described the importance of building a relationship that strengthens cooperative diabetes management. A number of participants were of the opinion that knowing patients by having seen them historically for other health conditions made consultations easier and facilitated discussion regarding the initiation of GLM. Similarly, the constant interaction with patients by virtue of seeing them for other health conditions helped HCPs to

use their consultation time efficiently, as previous interaction with the patient was seen to reduce the time that HCPs spent gathering information about them. GP10 describes in the quote below, their opinion about how the lack of continuity of care can lead to a situation where their patients have to explain their health problems or other issues to clinicians every time they visit their practice, which was viewed as quite draining for patients.

> "We all probably consult slightly different, and our advice might be slightly different, but if you see the same person, you get consistent messages and probably build a relationship with that person. Certainly, a lot of our patients prefer that, which you can understand, it's better that you build a relationship with a particular clinician, and then they know you and you know them, and you can achieve more in your consultation when you know the background. I think patients don't like having to explain their whole story every time they come in. And, if you got someone who's got a lot of issues with their health, particularly mental health, then that can take time to get someone to get to know you, and you maybe don't achieve much in the consultation because half of the consultation is around information gathering rather than providing information to the patient." GP10

Conversely, continuous contact with patients was described as helping to build a cooperative relationship that supported tailored diabetes management and enhanced discussion and negotiation between HCPs and their patients about their treatment. Some HCPs described having the opportunity to see patients over time, either to manage their diabetes or other health issues. Historical contact with patients was seen as placing HCPs in a position where they might be able to assess people's readiness to change their lifestyle or start GLM. However, the increased demand for health services and the reduced number of HCPs was described as making this kind of ongoing healthcare management more challenging.

> "I think the benefit of being a GP is you get to know your patients and, so you'll see the same people

> several times over the course of their life and often you'd had seen that patient about something else over the precedent years. So, you might have established rapport with them and got to know them and know a bit about their life, what is important to them. And, at the end of the day you cannot, you know, you can't force people to take medication. It's just about having a good conversation, but unfortunately, these outcomes take time, and we are very short of time in general practice." GP6

Moreover, a number of participants also suggested that historical contact with patients helped them to gauge patients' motivation and their likelihood to succeed with diet and lifestyle changes. In the following quotes, HCPs give their accounts of the importance of the HCP-patient relationship and its limitations. In the first quote PN5, who is a specialist in diabetes and was in charge of conducting check-ups and reviews of people with T2DM, described how knowing patients by virtue of having seen them in previous consultations influenced their decisions about when to initiate GLM.

> "We are looking at the patient as an individual; you are looking at what their HbA1c is, whether they would prefer to try the diet before any medication. Again, it would depend, if that is what they ask, then that's obviously what you have to do. It's the patient's choice, you have to let them be aware what the goals are, what are we aiming for, and it might not be fully achievable, but you certainly have to support it 100%." PN5

5.6.2 Negotiation with patients

The initiation of GLM was described as always implying negotiation, which HCPs described as usually being triggered by different aspects previously discussed such as high HbA1c levels, or the presence of symptoms, which were addressed in the previous section. This sub-section seeks to bring insights from the interaction between HCPs and their patients in pursuing shared-decision making about GLM initiation.

In the quotes below some HCPs give an account of shared-decision making. Commonly, the suggestion to initiate GLM by the HCP was determined by individual-patient considerations. Once the recommendation was made, the patient had to be willing to accept the medication. However, some HCPs saw it as part of their responsibilities to advise patients to accept medication when they considered it necessary from a medical point of view.

> "You're going to be much more persuasive if their situation is more serious and HbA1c levels are much higher or they're symptomatic, those are the things for me that would push you towards it being a shared decision, but the doctors are taking a lot more of a burden for all the decision-making." GP4

> "It's a negotiation, is not, I don't make the decision on my own, we make a decision together, that's the way that we would do about times. Guiding people, if someone has HbA1c in the hundreds with significant osmotic symptoms, who has never succeeded in any diet in their lives, then we would have a conversation about the likelihood of them succeeding."GP11

HCPs reported that during the negotiations, diet, lifestyle and consequences of poor glucose control were discussed. As exemplified in the quotes below, GP6 and PN3 described using these consultations to enable their patients to make choices about their health, including about when to start medication to lower blood glucose.

> "I think if you have a good discussion with the patient, with the person, and they make an informed decision to start medication, they're much more likely to comply with the medication, to continue with it cause, you know, comply with the medication means agreement." GP6

> "Well, I would probably be honest with them saying, you know, your HbA1c is at this level, you've tried to get it down over the last few months without success in changing your lifestyle, what are your thoughts about starting medication? Then some of them will say well

> actually, that's fine; I want to start medication if it's going to help me. Others would say, well actually I've not been very good over the last few months what if I want to try and change my diet and then come back. So, it's variable; everybody is different. Some patients are just willing to straightaway accept medication; others are not." PN3

Additionally, as described by GP6, shared decision-making was frequently sought by HCPs. There are various reasons as to why HCPs tried to ensure shared decision-making about when to start on GLM. HCPs described that one of the main reasons to pursue shared decision-making was related to adherence to treatment. Involving patients in the decisions to start pharmacological treatment was believed to increase adherence and to save on NHS resources.

> "You know, it's one thing to prescribe a medicine, it's quite another for somebody to take it. So certainly I've been persuaded by the idea of shared decision-making and just understanding where an individual is at, what they feel is the benefit of taking the medicine." GP4

> "They have to be completely involved in it because it's a waste of time and money to prescribe them something they're not interested in taking, or they don't understand about taking, they don't understand how it's going to help them. It's, yeah, a complete waste of resources." PN1

For most HCPs, the decision to start patients on GLM also included a discussion about the potential side-effects and benefits of medicines. As described in the quote below by GP4, informing patients about the potential side effects of the medication was also perceived to promote dialogue and enable shared-decision making:

> "I think that's crucial to recognise that medicines have effects that aren't wanted and so that's important to let them know about. And it's about being able to inform them so that they can make a decision about whether

> they want to go ahead with that medicine. So that's a big part of shared decision-making" GP4

Having described aspects related to patients and the HCP-patient relationship, the next section of this chapter moves on to consider contextual factors that informed HCPs' decisions about when to start GLM.

5.7 Theme 3: Contextual Factors

The contextual factors described in this section related to the healthcare system, the location and other characteristics of the practice, HCPs' backgrounds, the existence of clinical guidelines (including the recent decommissioning of QOF), and HCPs' perceptions of their roles, and also their roles in relation to the roles of other colleagues in their practice. These factors appeared to have a considerable influence on HCPs' decision-making because, as I will consider further below, they could facilitate or hinder their focus on individual patient-related factors.

5.7.1 Practice-related

As described at the beginning of this chapter, the characteristics of the practices where participants worked varied considerably. Similarly, differences were seen in relation to the length of consultation and the number of HCPs working at practices, which was often related to the size and location of the practice. In addition, while some practices had a GP diabetes specialist working at the practice, others did not, in which case the nurses performed most of the diabetes-related care, including monitoring and reviewing patients annually; consequently, the division of tasks was diverse across practices.

5.7.1.1 Resources

A practice's resources are used here to refer to the time available for consultations and human resources. In most cases, HCPs reported an increase in their practice size over the years, which had led to a rise in the number of HCPs working within their practice. The number of GPs in each

practice ranged from 6 to 11, while the number of nurses ranged from 1 to 5. Some participants reported having lead GPs for different clinical specialisms, including diabetes care.

The majority of participants emphasised that in practices without a lead GP for diabetes, most of the day-to-day diabetes care was carried out by nurses. Many GPs commented that one of the main reasons for this was the short length of consultation times to which they were expected to adhere. Usually, GPs specialists had longer appointment times for diabetes care; some of them indicated that they spent between 15 to 30 minutes with each patient in diabetes-related consultations. However, for the majority of GPs, the standard consultation time was just 10 minutes. In contrast, diabetes-related consultation times with nurses were longer (20 to 40 minutes). As exemplified in the quotes below, short consultations were frequently described as a challenge when delivering diabetes-related care:

> "The appointment is only 10 minutes long… You go into that consultation knowing that's impossible to go through every single thing, to have the opportunity to run through diabetes, the causes, lifestyle factors, lifestyle interventions, medication options, microvascular risk, macrovascular risk. Technically, when you think about all that's involved in a diagnosis and explanation revise you could easily add up to an hour of work, we have 10 minutes." GP2

As the quote above indicates, time restrictions during consultation could limit HCPs' ability to provide information and assess a patient's motivation and needs to achieve optimal glucose levels, which as described in section 5.4.2.1 could influence their decisions about when to start GLM. Similarly, some HCPs discussed their experiences of the scarcity of time and human resources and the implications of these on diabetes care, such as being inclined to prescribe at an early stage and focus more on patients' HbA1c levels instead of looking at their patients' life circumstances. This realisation arose from challenges they faced having short consultation times, as time

constraints did not always permit a productive discussion to take place and that this could potentially result in patients being put onto medication faster.

> "Each patient is entitled to a personalised plan, but also each patient needs resources, but they all require GP time." GP7

> "I think that short consultation times in primary care is part of the reason we prescribe too much probably. You are focusing very much on that because that's what you feel you need to get done in the time, if there isn't medication then that's probably where you focus…I suppose, the doctors, we tend to be more focus on the medication, looking whether we need to put them on medication straight away or lifestyle changes is going to be enough… I suppose partly because our times are quite short we tend to leave a lot of the education to the nurses who have longer appointments and who have more access to the resources." GP10

The excerpt above by GP10 provides an interesting example of how factors such as professional role (e.g. Nurse, GP) and consultation length could influence decisions about when to start GLM. Here, GP10 who works in a practice where the practice nurses are specialists in T2DM, suggested that nurses and GPs might approach diabetes management differently due to different consultation lengths. This is an issue which is explored further in sub-section 5.6.2.1.

> "In an ideal scenario, as GPs, we would have longer availability for new diabetic patients…you could probably go through things in more detail, give the patients more opportunity for questions and answers. We know when doing that, and getting them more involved than having to do information-delivery focused on time, is probably likely to have better outcomes." GP2

Moreover, HCPs suggested that short consultation times could influence the assessment of patient's needs and expectations and the amount of information that could be provided to patients, which in turn could hinder a

patient's ability to make an informed decision about starting GLM. In the quote below, GP6 gives an account of the importance of providing and reinforcing information about diabetes.

> "That often can take several meetings with the patient before they actually, they'd accept the need to start medication. At the end of the day is just a negotiation with the patient, and if you put them in a position to make an informed decision, you know, and they don't want to take the medication then I am very happy with that" GP6

The workforce in primary care was also a factor which, according to some HCPs, can influence the care provided to patients with diabetes. Some practices relied on employing temporary personnel; only one participant suggested that this might lead to a lack of standard in diabetes management. However, as discussed later on, standardisation of care can be enhanced by the use of clinical guidelines, which are of great importance to HCPs.

5.7.1.2 Division of tasks

The short length of consultations and the increased workload burden in practices, which was seen as being caused by lack of personnel or increased demand, were regarded as affecting both GPs' and nurses' professional roles in terms of the tasks they performed. In the example below and in accordance with the information above, a GP gives an account of how the shortage of HCPs in their practice had forced them to diversify their roles when providing diabetes care:

> "Basically I [after the removal of dietician and podiatrist in their practice] had to start a dietary history from the patient, but to me was actually very revealing and it had a significant impact in changing patient management… with podiatry, I then happen to do all the foot checks myself. So, therefore, my workload in the appointment changed quite significantly, and I am having to put a lot more work into the appointment." GP8

Although in the quote above the GP refers to the performance of a task that did not used to be part of their role as something 'revealing', it could impact on the service provided to people with T2DM as their workload is increased. Likewise, nurses also described the diversification of their roles over time, with several participants describing an increasing responsibility and authority in decisions about when to initiate a course of GLM.

Although nurses are often viewed as having an educational role within diabetes care, many HCPs described nurses conducting follow-up consultations and annual check-ups. Nurses who had completed a diploma in diabetes were additionally in charge of initiating, managing and modifying pharmacological treatment. However, the HCP in charge of prescribing varied depending on the practice's characteristics. As it will be discussed in the next sub-section, aspects related to HCPs role (i.e. GP or nurse) could influence decisions about why and when to initiate GLM.

5.7.2 HCP-related

Diabetes care is a dynamic field, and new knowledge is available frequently; therefore, HCPs are continually required to update their knowledge about current medications and guidelines. For HCPs with a special interest in diabetes, keeping up to date with guidelines was described as 'no problem' (GP8). Conversely, for many HCPs without a special interest in diabetes, keeping up to date represented a challenge:

> "As GPs, you are in a position whereby you have to keep up to date with every single speciality, with every single speciality… that is a herculean task." GP2

As described in the quote below, decisions about when to start GLM were influenced by HCPs' knowledge of current drugs. These findings suggest that in general, if they do not feel confident about their knowledge, initiation of GLM might be a challenge to GPs who are non-specialists in diabetes.

> "It's sometimes quite hard to keep up to date with the new medications, you know, and the guidance, yes, they all have complicated names, and they are using quite specific situations so try and remember which drug to use and which specific situation is very difficult. When you're not initiating these drugs that often you do tend to need to look it up just to remind yourself because it might not be that often that you are seeing someone that you need to initiate a drug. Obviously, if you are a specialist in diabetes or work in a specialist clinic, then it would be more often". GP10

> "I hope to keep reasonably up to date with diagnosis and management. Up to probably second-line treatment of diabetes, beyond that, I guess many people struggle with it, even specialists". GP11

5.7.2.1 Healthcare professionals' perceptions of their roles

Here, I consider how HCPs' perceptions of their professional role (e.g. GP, nurse) may play a role in diabetes management. Some HCPs perceived that the decision of when to initiate GLM sometimes differ between themselves and other colleagues. Thus, their thoughts and accounts on these discrepancies are presented in this sub-section.

Given the substantial and increasing role of nurses in chronic disease management; their oversight of annual reviews and in some instances their ability to prescribe GLM, aspects that inform their decisions could help understand differences in prescription patterns. In the quote below, GP10 gives an account of the increasing participation of nurses in chronic disease management such as T2DM.

> "The practice nurse mostly run the diabetic reviews and one of them is a prescriber, another one is nearly finishing her prescribing course, and they are very experienced in chronic disease management, the practice nurses. They've taken on the majority of the type 2 diabetes. I mean, obviously, they also do a lot of other long-term conditions review." GP10

Moreover, some participants suggested that aspects related to HCPs' interest in diabetes might lead to variations in prescription patterns. As previously described, keeping up to date with diabetes was sometimes seen as a challenging and overwhelming task for those without a particular interest in the area, whereas specialists seemed to be more confident about their knowledge. However, this opinion was not shared by all participants, especially by HCPs without a special interest in diabetes. These contrasting views are exemplified in the following quotes from GP9 who has a special interest in diabetes and GP3 who does not. In the excerpt, GP3 suggests that non-specialists could be more likely to inform their practices by the use of guidelines.

> "My colleagues who don't have a special interest, a lot of them just feel overwhelmed by all the changes, the new drug classes, the new guidelines and how to manage." GP9

> "Well I'm sure some GPs may have some more of a special interest in diabetes, but because we have guidelines I'm sure 90% of us will do the same thing." GP3

Furthermore, some HCPs highlighted the importance of having colleagues with a special interest in diabetes as it gave them more confidence and provided them with a sense of support. For instance, in the quotes below, GP8 perceived that his workload increased due to the absence of an old colleague who was interested in T2DM. Likewise, PN4 described the sense of confidence provided by having a specialist in the practice to whom they can inquire about specific aspects related to T2DM management:

> "My nurse, previous nurse was replaced with a very good nurse, but she didn't have the same training in diabetes as my previous nurse did. So again, I dare to say that more work has fallen on my shoulders because of that, in diabetes…the prescribing and the initiation and changes on treatment is all on me, all the time. The present nurse just does all the tick boxing." GP8

> "We don't have any GPs here who have a special interest in diabetes; I know some surgeries will have a diabetes lead or an asthma lead. I know, in my last surgery we did, it was easy, if you had a query you knew there was someone who had an interest, whereas here there is not. Sometimes it can be quite difficult if you need to actually go and ask the GP because they don't know a great deal about some of the stuff." PN4

Therefore, by PN4's narrative, it would seem that HCPs also inform their practices through discussion and interaction with other HCPs. In general, HCPs' roles at their practices were a factor that influenced the perceived need to keep up to date; overall, knowledge about diabetes was described as part of their responsibility. However, specialists allowed themselves more time to stay up to date while non-specialists mentioned that keeping up to date with the essentials was acceptable.

Taken together, these findings suggest that differences in prescription patterns between practices could be related to the HCPs in charge of prescribing and whether they have a special interest in diabetes care. This finding suggested the inclusion of a new variable to the quantitative strand. The variable planned to analysed was in relation to the HCP prescribing (i.e. GP or nurse) and/or whether they have a special interest in diabetes; however, as it will be explained in the next chapter, this was not possible.

5.7.3 Healthcare system related

A number of factors relating to the organisation of resources and people within the NHS also appeared to influence prescription practices with regards to diabetes care. As described in earlier chapters, in the past diabetes care was routinely provided within secondary care. However, it was reported by HCPs that the increased prevalence of chronic diseases and the rising burden on the Scottish healthcare system resulted in the need for more diabetes care to be provided in primary care. With this shift came the need for further training and specialisation of HCPs working in primary care:

> "You have to remember we are just talking about diabetes today. I also have to look after everyone with heart disease, with asthma, COPD, atrial fibrillation, and all of these areas have their own drug classes, their own guidelines development. We live and work in very challenging times in primary care." GP9

Furthermore, as it has been pointed out previously, GPs working within primary care also had to deal with short appointment lengths. The increased workload and short-consultation times might be particularly challenging for GPs without a particular interest in diabetes. As a result, the availability of tools such as guidelines and structured education programmes was seen as crucial.

5.7.3.1 Clinical Guidelines

Participants were aware of national guidelines such as SIGN and NICE and reported using them as a general framework for providing diabetes care and prescribing GLM. The majority of HCPs reported that SIGN guidelines were the ones followed in their practices.

The perceived value of guidelines varied depending on HCPs' training, experiences and background. In most cases, early-career HCPs and those without a particular interest in diabetes considered guidelines to be useful resources that facilitated their job in terms of making decisions regarding treatment initiation. This is of particular importance since these HCPs could be more inclined to decide to initiate pharmacological treatment based on guidelines. In the quotes below, a practice nurse without a special interest in diabetes, and a GP also without special interest in diabetes highlight the usefulness of guidelines to them.

> "It could be a few months since I've done a newly diagnosed diabetic so you want to have something written down so you can say well I have to cover ABCD today and then I'll cover the rest next day." PN2

> "I think for the new diabetic drugs I do find the guidelines helpful because, partly is difficult to remember and you want to look it up, and to have it laid out in a clear fashion, is very helpful." GP10

Although the guidelines' usefulness was recognised, some of the HCPs with a particular interest in diabetes described guidelines as something to be used with caution, presenting them as an aid to prescribing that should not override the need to take into account patients' individual needs and circumstances. In the quotes below, two GPs with a special interest in diabetes, and with a decade of experience each, give their accounts on the utility of guidelines:

> "A lot of the guidelines are very explicit about tailoring the treatment to the individual patient, so there is, you know, sometimes treatments are useful for some patients and not for others." GP6

> "Guidelines are important because they help promote consistency of care; they help promote beneficial recommendations but can also be a disadvantage because guidelines don't often take into account the patient's individualised circumstances… We need to look at it as handrails rather than train tracks, we as doctors and nurses should have the confidence to deviate from guidelines when they benefit that patient that is in front of us." GP9

Hence, individual-patient related factors were indicated once more as the most important aspects such HCPs considered when starting GLM. Furthermore, both nurses and GPs indicated the importance of establishing goals and starting medication in agreement with patients. However, there were perceived differences between them about when to initiate oral GLM. For instance, GPs considered nurses to be more likely to adhere to protocols and guidelines, while nurses perceived their actions to be more consistent with the guidelines:

> “In my experience nurses are much better following protocols, so maybe they’re more likely to stick for three months before start metformin, and the doctors tend to not stick to that quite so in like sort of black and white fashion.” GP6

> “I think, as practice nurses, we are probably more consistent. I think, even when I look at all the GPs, what the GPs do, everybody tend to do things differently. So, I don’t think we’ve always got a great deal of consistency [within their practice]. Some GPs will start people on metformin, and their HbA1c is 49, others could be 60, and they don’t bother. I think there is a lot of inconsistency out there…and I think as well because nurses, I suppose, have to work more to guidelines that we’re probably more consistent, whereas a GP obviously have the flexibility to elude sometimes.” PN4

The quote above by PN4, suggests that nurses might prioritise physiological aspects such as a patients’ HbA1c when making decisions about when to initiate GLM, as they seemed to be more likely to use guidelines to inform their practice. This is an interesting finding given that nurses tend to spend more time with patients and most likely get to know them better than GPs.

In 2016, the QOF, which rewarded practices for registering patients and maintaining them under specific targets for chronic diseases, was decommissioned in Scotland. The QOF included diabetes management in its remit and established specific goals for glucose control. HCPs frequently reported QOF’s implementation as positive for T2DM management since it raised awareness and helped standardise diabetes care and treatment.

> “I think it [QOF] probably raised the standard; I think it probably standardised, almost, the treatment of diabetes and probably raised the awareness of it.” GP5

> “I think QOF was a useful thing when it first came out. A lot of practices had a good quality care for diabetes, but there was a lot of practices that were kind of behind the curve of chronic diseases management by the year of 2000 to 2004, that was four years before QOF came in.

> QOF came in 2004 and forced a lot of practices to improve their chronic disease management, which improved diabetes care. But I also think QOF had a lot of downsides, was very prescriptive so, you know, trying to get everybody's blood pressure to a certain target that wasn't clinical appropriate." GP6

However, as exemplified in the preceding quote by GP6, HCPs' opinions of QOF targets varied, and some considered this to be one of QOF's main downsides, since the incentive to reach certain targets was not considered appropriate for some patients, especially the elderly and those with multi-morbidities. Therefore, the existence of QOF was described as hindering their ability to focus on patient-related factors. Overall, participants believed that the decommissioning of the QOF would not negatively influence diabetes care and GLM prescribing practices. This view was shared by many HCPs who considered that QOF guidelines were still adhered to indirectly.

> "We work through that QOF template even though it's not there anymore; we still keep the template, we still do all the things that they wanted us to do and just because is good practice" PN2

> "People are not paid as of QOF, but they're probably still carrying on clinically as per QOF because that's what's done for the past ten years and there's nothing that actually replaces it. They're probably still using QOF as a guideline because that's what they used for the past ten years". GP8

5.7.3.2 House of Care

Some of the HCPs interviewed worked at practices where the House of Care framework was followed. This patient-centred framework was described as a useful tool that gives patients the opportunity to take control of their health.

> "Is more about getting the patient to be involved in the decision making rather than just about data collection, it is a good idea" GP1

> "I think it's far more patient-centred, far more patient-specific. So, we meet the individual concerns of the patient rather than doing a sort of tick-box exercise for a review" PN1

The House of Care framework was described as influencing decisions regarding diabetes care, such as when to initiate medication for glucose control, as it encourages patients to be active agents in their care and to be involved in establishing treatment goals. HCPs commonly described it as a facilitator for goal setting, primarily due to its person-centred approach, which forced HCPs to take a step back and allowed patients to take control of their health.

> "With the house of care, the idea is that the patients decide. They get a copy of all their results; the idea is that they'll have a read, and then they'll come in, and you'd discuss what they, is there is any concern, what they want to do. Is kind of not meant to us telling them anymore, is meant them saying, you know, my weight's gone up a wee bit I want to focus on that, or I am quite happy with how things are. Some people come in and, I've got a lady who recently lost her husband so at the moment her diabetes is, you know, for her is not a great issue because she's still grieving. It is really meant to be what the patient decides, just sometimes is difficult for us healthcare professionals to take a step back" PN4

5.8 Summary

A variety of intertwined factors and considerations influenced HCPs' decision-making about initiating GLM. These fell into three main categories: individual-patient related considerations, HCP-patient related factors, and contextual factors.

Individual patient-related considerations included patients' ages, HbA1c, whether they were perceived to be motivated to change, their lifestyle and other health problems. HCP-patient related factors included historical contact with patients. The final category, contextual factors, included HCPs' training,

division of labour within their practices, clinical guidelines (including the recent decommissioning of the QOF), and HCPs' perceptions of how their own roles fitted in with those of other colleagues involved in delivering diabetes care.

Individual-patient related aspects were of the utmost importance to HCPs when making the decision of initiating GLM. This was also shown in chapter 4 were aspects such as age, HbA1c and other metabolic aspects showed to play a crucial role. However, other factors relating to the other categories hindered or facilitated HCPs ability to focus on individual factors. For instance, GPs reported having limited consultation times which made difficult for them to assess patients' motivation and needs. Historical contact with patients was often described as facilitating the provision of tailored advice about lifestyle changes.

This chapter has described the set of intertwined and dynamic factors that influenced clinical decision-making in relation to initiation of pharmacological treatment for glucose control in people with T2DM. The chapter that follows moves on to integrate and discuss the findings of both strands of this study, and to present the conclusions.

Chapter 6 Discussion

6.1 Introduction

This study, based in Scotland, aimed to identify factors associated with GLM initiation, and to explore and describe the views and experiences of HCPs working in primary care about the initiation of GLM. In this chapter, I begin by providing a summary of the main results from each strand of the study. Next, I provide a side-by-side comparison of the main findings where is possible to do so. Then, I discuss the overall study findings in the context of the existing literature on the topic. I address the limitations and strengths of the study and finish by describing the implications of my findings and recommending potential directions for future research.

6.2 Summary of main findings

The mixed-methods design allowed me to combine quantitative and qualitative methods in one study. Overall, the dataset analyses and the interviews with HCPs showed that patient related aspects, particularly clinical factors such as HbA1c, were fundamental when HCPs were deciding when to initiate GLM. However, the findings that emerged from the interviews revealed that clinical decision-making on GLM initiation in people with newly diagnosed T2DM is much more complex than being based only on HbA1c and encompasses a set of interwoven aspects.

The retrospective cohort study that formed the quantitative strand of the work included data from 154,660 people with T2DM diagnosed in Scotland between 2004 and 2012 and who survived for at least two years. Overall, people who received GLM prescription within two years of diagnosis of T2DM had higher BMI, HbA1c, and cholesterol than those who did not. Of the 54.9% (n=84,997) receiving prescriptions within two years after diagnosis of T2DM, 56.8% received them in the first three months after diagnosis. The proportions of people receiving a prescription for GLM increased over time, particularly for the proportion of people that received a prescription within

three months of diagnosis. This period reflects the period during which guidelines recommend that lifestyle changes should be attempted in order to control glucose levels. Factors that were independently associated with longer time to drug treatment initiation were increasing age, other/unknown ethnicity, lower deprivation, receiving antihypertensive medication, HbA1c <53 mmol/mol, and BMI <30 Kg/m^2. Moreover, the stratified analysis by age groups showed no significant association between sexes for the oldest groups (60 to74 years, and ≥75 years). However, in the group of people aged 30 to 44 years females had shorter time to GLM initiation, and in those aged 45 to 59 years, males had shorter time to GLM initiation.

The interviews showed that HCPs' decision-making about when to initiate GLM in people recently diagnosed with T2DM is a complex process. Hence, their decision-making entails the formal assessment of metabolic factors such as HbA1c, and the informal assessment, during their interactions with patients, of the patient's motivation, lifestyle and the consideration of other aspects such as perceived life expectancy and quality of life. HCPs' indicated that, although HbA1c is the main aspect to consider, patients' wider circumstances influence and inform their decisions on whether and when to initiate GLM.

In general, HCPs' suggested that older people with T2DM are often frail and/or have other health problems, and a short life expectancy. Thus, for these patients, the benefits of GLM were judged against the individual patient's quality of life, overall health condition and projected life expectancy. Younger people with T2DM were considered by most HCPs to obtain more benefits from attaining and maintaining their HbA1c at optimal levels than older people. The adoption of a healthy lifestyle by following an appropriate diet and performing or increasing physical activity was reported as important, however, most HCPs considered that for some people, such as less motivated patients and some older patients, changing their lifestyle is particularly difficult to achieve.

Some HCPs indicated that the moment of diagnosis can be an important trigger for lifestyle changes. However, HCPs emphasised the importance of considering the patient's motivation, mental health and own priorities when assessing whether lifestyle change is likely to be feasible. Historical contact with patients was deemed to facilitate the provision of information and shared decision-making, but HCPs acknowledged that their increased workload combined with lack of personnel and restricted consultation length sometimes limited their ability to provide patient-centred care.

6.3 Convergence of findings

The findings from each strand enhanced each other, a joint display using a table, and a narrative comparison and interpretation of the combined findings are presented through this chapter. In mixed-methods research, joint displays are means to bring the data together in a visual way through figures, tables, graphs or matrix. The narrative approach to the integration of findings implies that findings from each strand are weaved whenever possible to report a topic or area (Fetters et al., 2013).

Table 35 below summarises the main findings. To facilitate comparison, the table includes a side-by-side topic comparison. In this chapter, a topic does not necessarily relate to the themes presented in chapter 5 but to areas or themes identified in the overall analysis of both strands. Although the findings from each strand cannot be compared on every component or topic, they converged to a certain extent. Hence, the findings from the qualitative strand enhance the understanding of the quantitative results by providing a comprehensive perspective from the HCPs and include themes that could not been assessed quantitatively in the available data but that can help understand some of the associations reported.

As indicated in chapter 3, results from the quantitative analysis informed the qualitative interviews and vice versa. However, the two sets of findings converged only in two, intertwined, broad topics. The first topic relates to time

to prescription for GLM and HCPs' rationale for starting pharmacological treatment in particular individuals. The second theme is concerned with how the characteristics of people with newly diagnosed T2DM played a role in the initiation of GLM.

Furthermore, two additional broad themes that were identified only in the qualitative strand will be discussed: HCP-patient relationship and contextual factors. These themes could not be assessed in the available quantitative data to understand in what ways the two sets of data related to each other, for the following reasons:

a) *HCP-patient relationship and HCPs' perceptions.* These subjective aspects included those concerned with the development of a HCP-patient relationship and the potential differences according to their professional role (e.g. nurse, GP) and/or special interest in diabetes. Information on the professional role of the prescriber was not included in the available dataset so could not be investigated in the quantitative analysis.
b) *Contextual factors.* These factors included guidelines and frameworks, consultation length and continuity of care. HCPs discussed and provided their perspectives on clinical guidelines, particularly focusing on QOF and its recent decommission in Scotland. However, since the cohort study covered the period from 2004 to 2012, I could not test the potential impact on QOF's decommissioning on GLM prescription in the quantitative data. Furthermore, HCPs' historical contact with patients and the limitations imposed by the wider healthcare system such as short consultation length were not possible to analyse because this information was not available in the dataset.

Table 35. Summary of main findings

QUANTITATIVE STRAND	QUALITATIVE STRAND
PRESCRIPTION OF GLUCOSE-LOWERING MEDICATION	
• 55% of the cohort received GLM prescription within 2 years of diagnosis. • Metformin was the most frequent initial prescription. However, its use decreased with increasing age.	• GLM initiation was seen by HCPs as something that would be necessary for almost all patients. • Diagnosis was considered an important time-point to assess patients' motivation and encourage a healthy lifestyle.
PATIENTS' CHARACTERISTICS	
• 79.5% of people with HbA1c ≥53 mmol/mol received GLM prescription within 2 years of diagnosis. • The fully adjusted Cox regression model showed that longer time to GLM prescription initiation was associated with being older, male sex[6], other/unknown ethnicity (compared with British), least deprived SIMD quintiles, HbA1c <53 mmol/mol, BMI <30 Kg/m2, not being on lipid-lowering medication.	• Patient's HbA1c was seen as the most important factor when deciding when to prescribe GLM. • HbA1c was seen by HCPs as a proxy measure of a patient's ability to succeed with lifestyle and diet interventions. • Some HCPs perceived that people from low socioeconomic groups and those with poor health literacy were less engaged with their healthcare. • Tight glucose control was not seen as critical in people who were thought to have a shorter life expectancy.
HCP-PATIENT RELATIONSHIP	
	• Historical contact with patients was deemed as a positive aspect. • HCPs considered that enabling their patients to make choices about their health could increase adherence to treatment.
CONTEXTUAL FACTORS	
	• Guidelines were seen as very useful. • The decommissioning of the QOF was not perceived as affecting diabetes care. • Consultation times were seen as a challenge to patient-centred care. • Prescription patterns could differ between nurses and GPs, and between HCPs with and without a special interest in diabetes.

[6] The stratified analysis by age groups showed that amongst people aged 30 to 44 years females had shorter time to GLM initiation, and amongst people aged 45 to 59 years, males had shorter time to GLM initiation

Having presented the convergence of topics in a side-by-side comparison table, in the following sections I will address each topic by discussing how they compare and can be interpreted in light of the existing literature.

6.4 Prescription of glucose-lowering medication

I explored the prescription of GLM objectively and subjectively by using patients' clinical and demographic data and interviewing HCPs. In general, HCPs considered that the initiation of GLM is something that most patients will need at some point due to the progressive nature of T2DM and that the main goal of prescribing GLM is to reduce the risk of complications resulting from increased levels of glucose. This view of preventing complications instead of managing them is supported by the literature. For instance, Bain et al. (2016) conducted a review which sought to evaluate contemporary diabetes care in the UK, particularly for glycaemic and BMI control. The authors claimed that preventing complications rather than managing them would bring greater health and economic outcomes.

In this cohort of 154,660 people diagnosed with T2DM between 2004 and 2012 in Scotland, the majority of the population were white Scottish/British (70.2%), 9.8% had other ethnic background and 20% of the cohort's ethnicity was unknown. This is broadly in accordance with the population structure in Scotland where, although proportions are slightly different, most of the population is white Scottish/British. The proportion of white Scottish and British was >80% while other ethnic groups represented <10% of the population in the 2011 Scottish census (National Records of Scotland, 2011).

6.4.1 Time to glucose-lowering medication initiation

In the analysis of time to medication initiation, I found that among other factors, in the analyses using age in years as well as in binary categories (<65 years and $\geq$65 years) being male was independently associated with longer time to glucose-lowering prescription in adjusted regression models. However, this finding was not corroborated in the qualitative strand as HCPs

did not report to manage their patients differently depending on whether they were male or female. Moreover, studies that have looked at time to treatment initiation have included sex as part of the patient's demographic variables but not in their analysis (Sinclair et al., 2012, Zhang et al., 2012, Sun et al., 2013), or the analysis did not show a statistically significant difference between male and female patients (Spoelstra et al., 2004).

Recently, a qualitative study conducted in Scotland by Dimova et al. (2019) looked at differences according to patients' gender. People with T2DM and relatives of people with T2DM were interviewed. The authors suggested that depending on their gender, people with T2DM may manage their diet differently; indicating that women often took a more active role in the management of their diabetes than men. Although the study did not focus on GLM initiation, it further suggests that T2DM management may differ according to patients' gender and emphasises the need for studying these possible differences.

Overall, 55% of the cohort received a GLM prescription within two years from diagnosis. Similar proportions of people receiving prescription of glucose-lowering treatment were reported from a UK cohort that included patients with diabetes diagnosed between 2003 and 2005. After two years from diagnosis, 51% of the cohort had initiated GLM therapy (Sinclair et al., 2012). In the current study, metformin was the most frequent initial prescription (82.3%) as either mono- or combined therapy, but its use decreased with increasing age. The SIGN guideline for the pharmacological management for diabetes recommends using metformin with caution in people with moderate renal impairment and with declining kidney function and to avoid its use in people with severe renal impairment (Scottish Intercollegiate Guidelines Network (SIGN), 2017b). Although a variable related to kidney disease was not included in the cohort analyses, kidney disease is more common in older than younger people, thus this may help explain the decreased use of

metformin in older people with T2DM in this study (National Kidney Federation, 2019).

In accordance with the present results, previous studies in the UK that have looked at prescribing in people with T2DM have reported that metformin was the drug most commonly prescribed overall (Whyte et al., 2019), and as first-line treatment (Curtis et al., 2018, Wilkinson et al., 2018). Whyte et al. (2019) reported metformin prescription in 79.2% of their cohort in England, which included all people with T2DM between 2012 and 2016. Curtis et al. (2018) reported that in England, for the period 1998-2016, metformin was the drug most commonly prescribed as first-line treatment. Similarly, Wilkinson et al. (2018) who described drug choices for people with T2DM in primary care in England, Wales, Scotland, and Northern Ireland reported that, overall, 73% of people's treatment was initiated with metformin. Moreover, the use of metformin as first-line GLM is consistent with national guidelines (Scottish Intercollegiate Guidelines Network (SIGN), 2017b) and contemporary research on GLM patterns in the UK (Filion et al., 2009, Sharma et al., 2016, Heald et al., 2018, Sinclair et al., 2012).

Overall, of those who received a prescription (n=84,997), 56.8% received it within three months (90 days) after diagnosis, 25.1% between three and 12 months after diagnosis, and 18.1% within 12 to 24 months after diagnosis. A stratified analysis (chapter 4, figure 7) showed that the proportions of people receiving GLM prescription within three months after diagnosis increased from 25.6% in 2004 to 36.1% in 2012. This pattern could be related to an approach to tight glycaemic control sooner rather than later when treating T2DM. A tight glycaemic target at diagnosis is supported by clinical guidelines which suggest that a target of 48 mmol/mol instead of 53 mmol/mol may be appropriate for some individuals at diagnosis (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). However, this recommendation became available after the period of this study. Moreover, the increased proportions of people who received GLM prescription within

three months may suggest the need for looking at ways to support lifestyle changes.

Some HCPs expressed their willingness to start medication soon after diagnosis if the patients have symptoms of hyperglycaemia or if their HbA1c were considered too high. However, some HCPs believed that attaining good control of HbA1c with tablets would hinder patients' attempt to improve their lifestyle. Unfortunately, data on patients' symptoms are not available in the dataset. However, studies that have looked at patients' perceptions, have shown that some people with T2DM prefer to receive a prescription rather than changing their lifestyle. For instance, Elliott et al. (2016) who conducted a sequential explanatory mixed-methods study (questionnaire → focus groups) in the UK, reported that people with T2DM described that, although they did not like taking them, medicines were sometimes a way to avoid lifestyle changes, as they perceived that their medication did what it takes to improve their HbA1c. However, results from this study may not be fully comparable since it included people with all types of diabetes and excluded people whose English was not their first language.

6.5 Patients' characteristics

6.5.1 HbA1c

Comparison of the two strands of this study showed corroboration of the importance of HbA1c in the timing of GLM initiation. The quantitative strand showed that the majority (79.5%) of people with HbA1c ≥53 mmol/mol received GLM prescription within 2 years of diagnosis as compared to 25.8% in people with HbA1c <53 mmol/mol. This finding was in line with findings from the qualitative strand where HCPs' described that the main aspect they took into account when prescribing was the patients' HbA1c. Although patients' wider circumstances were also considered, HbA1c was seen as a proxy measure of patients' ability to engage with a healthy lifestyle. Hence, if a patient's HbA1c was considered too high their likelihood to succeed with lifestyle changes was considered low. Moreover, HCPs reported that the

higher the HbA1c the likelihood of developing symptoms increased. This helps to better understand why people with high HbA1c may receive GLM sooner. Furthermore, the high proportion of people with HbA1c ≥53 mmol/mol who received a prescription are in line with those of previous quantitative studies presented in chapter 2 which found a higher likelihood of receiving drug therapy the higher the HbA1c (Mor et al., 2015, Sinclair et al., 2012).

Currently, either plasma glucose concentration or HbA1c can be used to diagnose T2DM; however, it was not until 2011 that the WHO recommended the use of HbA1c as a diagnostic test for T2DM (Scottish Intercollegiate Guidelines Network (SIGN), 2017a, World Health Organization, 2011). This aspect may explain the fact that the quantitative analysis on glycaemic control and GLM prescription showed that sometimes HbA1c was below the cut-off point for diagnosis of diabetes (chapter 4, table 25), which presumably had been based on glucose rather than HbA1c.

6.5.2 Other metabolic indicators

The crude comparison of baseline characteristics of people who received and did not receive pharmacological prescription showed interesting results. For instance, there were small but statistically significant differences in the proportions of people with high blood pressure. Those who did not receive medication prescription included a higher proportion of people with higher systolic blood pressure. However, this may be related to the age difference between groups; people who did not receive prescription were older than those who did (63.5 vs 59.9 years). It has been recognised that hypertension is a common issue among elderly, and it is caused by the age-related stiffening of the major arteries (National Institute on Aging, 2019, Tan JL and Thakur K., 2019, Ferri et al., 2017).

In this study, people with baseline HbA1c ≥53 mmol/mol, compared to those with baseline HbA1c <53 mmol/mol, tended to have higher proportions of

people with cholesterol >5mmol/L (41.1% vs 49.4%), and higher proportions of people with BMI ≥30 Kg/m^2 (57.0% vs 59.8%). The WHO have reported risk factor clustering for CVD in which T2DM is included alongside increased BMI, hypertension and dyslipidaemia (World Health Organization, 2018c). Studies conducted with people with T2DM have reported similar risk factor clustering. For instance, Bays et al. (2007) who conducted a national representative survey in the US and performed further analysis comparing their results with those from the National Health and Nutrition Examination Survey (NHANES), reported that the prevalence of T2DM and hypertension increased linearly as BMI increased. The findings of this study are therefore consistent with the clustering of CVD risk factors and the important role of age in terms of CVD risk observed in previous research. However, the study conducted by Bays et al. (2007) investigated the relationship of body mass index with diabetes mellitus, hypertension and dyslipidaemia rather than GLM initiation. Some of the studies on clinical inertia and time to GLM initiation, which were presented in chapter 2, have failed to report the risk factor clustering and mainly focused their analysis on HbA1c levels (Khunti et al., 2013, Sinclair et al., 2012, Spoelstra et al., 2004, Sun et al., 2013, Mata-Cases et al., 2016).

These results reflect those of the qualitative strand in which HCPs reported that patients with high HbA1c and other health conditions, such as hypertension and hypercholesterolemia, were more likely to receive GLM sooner. It can thus be suggested that the clustering of CVD risk factors is one important aspect that HCPs consider when deciding when to initiate GLM in people with recently diagnosed T2DM.

6.5.3 Patient's age and overall health

As previously described, I found that older age was associated with longer time to GLM initiation. This was consistent with findings from the qualitative strand in which HCPs described elderly patients as often being frail and having other medical conditions; therefore, tight glucose control was reported

as being less important for them. In these patients, HCPs gauged aspects such as the presence of symptoms, quality of life and life expectancy. HCPs believed people with a longer life expectancy would benefit the most from receiving GLM which helps explain some findings from the cohort study. There are, however, other possible explanations. Further studies have suggested that older people with T2DM have difficulties in changing their lifestyle. For instance, a study conducted in people with T2DM (n=20) attending primary care in England, reported that older adults were the most reluctant to follow dietary advice and change their diet in order to support the management of their diabetes (Arana et al., 2019). However, this should not be generalised and decisions on treatment to control glucose levels should be based on individual circumstances.

As mentioned above, the results from the quantitative strand showed that older age was associated with longer time to drug treatment initiation. These results are consistent with those reported by Sinclair et al. (2012) in a UK cohort that included newly diagnosed patients during the index period of 2003-2005 where older age (in years) was negatively associated with drug treatment initiation within two years of diagnosis (HR: 0.98, CI: 0.97-0.99). However, HbA1c $\geq$ 7.5% and its interaction with age showed a positive association with drug treatment initiation. Hence, the negative effect of age on time to GLM medication was reduced in people with high HbA1c at baseline. (Sinclair et al., 2012).

Moreover, after formally testing for an interaction between age and HbA1c, the stratified analysis by age groups in the current study showed that across all age groups, people with HbA1c >53 mmol/mol have shorter time to GLM initiation. Moreover, after adjusting by demographic (sex, ethnicity, SIMD) and metabolic characteristics (BMI, CVD) and other variables, the analysis with age as binary categories (<65 years and $\geq$65 years), showed that increasing age ($\geq$65 years) was associated with longer time to GLM initiation (HR:0.78; CI: 0.77–0.80) compared with people <65 years old. Similar results

were reported in the literature review. For instance, by Zhang et al. (2012) from a US cohort of patients diagnosed between the period of 2003-2005 and followed for two years after diagnosis. In this study, after adjusting for HbA1c, BMI and other clinical covariates, increasing age (≥65 years) was associated with longer time to drug treatment initiation than among people <65 years of age (HR: 0.82; CI: 0.75-0.90) (Zhang et al., 2012).

A possible explanation for these findings, in which older people with T2DM were less likely to receive GLM even after adjusting for HbA1c, could be due to their individual health circumstances which demand an individualised approach (International Diabetes Federation, 2013). In 2013, the IDF recommended changing glycaemic goals for older people with T2DM, which included relaxation of glycaemic goals depending on the frailty and degree of independence of the individual with T2DM (International Diabetes Federation, 2013). Currently, the Scottish guidelines for diabetes have no specific glycaemic control target set for the elderly, however, an individualised approach is recommended when setting glycaemic targets (Scottish Intercollegiate Guidelines Network (SIGN), 2017a, Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

One unanticipated finding was that among the youngest group of patients (30 to 44 years), although at baseline 80.3% had HbA1c ≥53 mmol/mol, after two years of diagnosis only 69.3% had received GLM prescription. Zhang et al. (2011) reported that among young patients, one of the main reasons for non-treatment was patients' fear of weight gain (Zhang et al., 2011). In the qualitative strand of the current study, although HCPs' reported to have tight HbA1c targets for younger patients, they reported to be willing to delay the initiation of GLM if the patient requested more time to attempt to improve their glucose levels by lifestyle changes.

6.5.4 Healthy lifestyle: diet and physical activity

The comparison of this topic between strands offered complementary information rather than a corroboration of findings. The quantitative strand showed that a higher proportion of people (61.5%) who received GLM had BMI $\geq$30 Kg/m^2 than those who did not (54.9%), however, it is important to note that in both groups more than half were obese by the WHO criteria (World Health Organization, 2019a). In people with T2DM and overweight or obesity, a hypocaloric diet and regular exercise have shown to improve HbA1c and reduce risk factors for CVD such as cholesterol and blood pressure (Tay et al., 2015, Boniol et al., 2017). I assumed that people who did not receive medication were managed by lifestyle only, however, because it was beyond the scope of the study, changes in HbA1c during follow-up according to the type of treatment (lifestyle only or GLM) were not analysed. It is also possible that effectiveness of lifestyle interventions differed by age.

Before, moving onto discussing the qualitative findings on a healthy lifestyle, I would like to briefly return to chapter 2 where I highlighted the importance of reducing weight in people with T2DM. In particular, I described a study conducted in the UK, the DiRECT trial, which showed that 36% of people who had been diagnosed with T2DM (no longer than six years before recruitment), and who followed a weight-management programme (intervention group) achieved T2DM remission defined as HbA1c in the normal range in the absence of glucose-lowering treatment and sustained normoglycaemia at 24 months (Lean et al., 2019). However, is important to note that people in the intervention group were provided a liquid formula diet to replace their meals (Leslie et al., 2016). This intervention is currently being introduced in clinical practice and may affect treatment choices, at least in some people. A systematic analysis and meta-analysis reported that changing dietary environment rather than diet behaviour in the treatment in people with T2DM has shown greater improvement in the reduction of HbA1c. In this context, a changed environment was considered when all or

most of the food was provided to participants instead of changing dietary behaviour by instruction or education about a healthy diet (Cradock et al., 2017). Thus, the findings from the DiRECT are not unexpected. Although they provide important insights on glycaemic control and diabetes remission, it is not clear whether the results will be widely applicable in a real-world context.

In the current study, HCPs reported that all their patients with T2DM were encouraged to adopt a healthy lifestyle that included advice on diet and physical activity. However, Lawton et al. (2008) who interviewed 32 Pakistani and Indians with T2DM in Edinburgh reported that, although most people described having received advice about a healthy diet during the initial stages of their diabetes, some participants considered that they received limited information. Similarly, Peel et al. (2010) interviewed 20 people with new diagnoses (within six months) of T2DM in the Lothian region of Scotland. Participants reported to have received vague and non-specific guidance about physical activity from HCPs. These discrepancies between HCPs' and patients' perceptions of the advice provided is an aspect that needs further research consideration. However, one likely cause of patients' perceptions of insufficient information from their HCPs may be due to the limited consultation length and HCPs' perceptions of patients' motivation to engage in a healthy lifestyle.

Some HCPs suggested that engaging in physical activity was very difficult for some patients. These findings reflect to some extent those by Khairnar et al. (2019) who surveyed HCPs (n=21) in primary care in the US. The majority (95%) of HCPs considered exercise and healthy diet as very important activities for self-care, however, 85.7% and 80.9% considered moderate exercise and following the recommended diet, respectively, as difficult for their patients; some HCPs considered that their patients were not motivated or interested. However, the reasons were assessed by an open-ended

question as part of a survey; hence, answers lacked a nuance that could have been obtained by interviewing them.

In accordance with the current study findings, Lawton et al. (2005) interviewed Indian and Pakistani people with T2DM in Edinburgh. The authors reported that in general people were aware that they should perform physical activity as part of the management of T2DM. However, few reported to put the advice they received from HCPs into practice. The reasons included lack of time, the presence of other health conditions, such as arthritis or knee pain that made it difficult to perform physical activity, and climatic conditions (participants reported to dislike going out in rain, wind and cold conditions). Moreover, participants raised some cultural/ethnic aspects; these included a generalised belief that diabetes was caused by factors out of their control and that that they could do little to prevent the deterioration of their health. Women reported additional reasons for not performing physical activity, these included: the lack of single-sex facilities in which they would not have to “expose” their bodies to men, and fear that something would happen to them while going out such as fainting or falling. Additionally, Peel et al. (2010) reported that amongst people with recently diagnosed T2DM in Lothian, only a few considered that physical activity was important for their blood glucose control. However, the authors reported that among patients who implemented and maintained physical activity levels, walking dogs played a substantial role. This finding emphasises the need for asking patients about their personal interests that may promote physical activity.

Moreover, results from focus groups conducted by Vinter-Repalust et al. (2004) to explore attitudes and problems that people with T2DM encountered while adhering to the therapeutic regimen provide further interesting insights from patients’ perspectives. The authors reported that, for most patients, having diabetes meant that they would need to change their lifestyle, particularly their diet and to increase their physical activity. However, for some people, it also meant that their family would need to change their

eating habits. Changes to their diets was particularly difficult during family celebrations and special celebrations, and at their work place. Most patients reported preferring taking pills to control their glucose levels than following a healthy diet. Furthermore, although all people with T2DM who participated were highly mobile, physical activity was perceived as being the most difficult to undertake; people reported lack of motivation, lack of willpower, laziness, and time pressures as they reasons. Hence, the views of HCPs that I found in the interviews might reflect patients' expressed difficulty in changing their behaviours.

This leads to another important finding; HCPs pointed out the need for patient-centred care. Certain aspects such as patients' socioeconomic circumstances and occupation have been reported as influencing HCPs decisions. In this instance, Rushforth et al. (2016) conducted a qualitative systematic review of studies that described HCPs perceptions of T2DM management. The authors reported that, in some cases, patients' socioeconomic and occupational circumstances were considered as sometimes limiting the patient's ability to adopt a healthy lifestyle or take their medicines. Similarly, people with T2DM have reported different challenges to the ones reported above in adopting a healthy lifestyle, such as the availability and affordability of healthy food (Rendle et al., 2013, Landa-Anell et al., 2019).

Furthermore, it has been reported that although HCPs perceive the provision of information to people with T2DM as part of their tasks, the adoption of a healthy lifestyle is seen as the patient's responsibility, (Jallinoja et al., 2007, Gómez-Velasco et al., 2019). In this study, I found that HCPs described decision-making as something that is made in negotiation with the patient, as the final decision of whether to take medication or follow dietary advice is the patient's. However, this kind of discussion with patients could be challenging due to the short consultation length and in some cases the lack of continuity of care.

6.5.4.1 Diagnosis

Earlier I described that HCPs would often prescribe GLM at diagnosis of T2DM if the patient described having symptoms caused by increased glucose levels. Moreover, some HCPs suggested that diagnosis of T2DM provides an important moment to foster the adoption of a healthy lifestyle because most patients are more motivated to make lifestyle changes. A possible explanation for this finding may be due to that some people with T2DM have expressed to experience such feelings at diagnosis, which raises the need for assessing patients' understandings and needs at diagnosis of T2DM.

Some studies have reported that patients' experiences and reactions at diagnosis have important variations, which could influence the way in that patients perceive and assimilate the HCPs' advice. For instance, participants in the study conducted by Elliott et al. (2016) mentioned that T2DM diagnosis was a moment of "shock", however, with time their feeling changed and T2DM became more an inconvenience in their lives, time also diminished their motivation to change their lifestyle. This highlights the importance of reinforcing lifestyle advice at later stages of T2DM.

Other studies that have further looked at diagnosis of T2DM have reported different ways in which people react, experience and perceive their diagnosis of T2DM. Peel et al. (2004) interviewed 40 people with newly diagnosed T2DM in Scotland and reported three ways in which patients described arriving at their diagnosis. First, suspected diabetes: people with this narrative presented symptoms they believed were related to T2DM, and by having the suspicion of possible T2DM they were able to prepare emotionally to diagnosis and reduced the "shock". Second, illness: people in this group referred to experience symptoms that they did not relate to T2DM. Participants reported to feel astonished but relief at diagnosis, some mentioned they were relieved that it was not something "worse". Third, routine: where people were diagnosed by a routine test when attending their

clinic or general practice for something else, for some, their diagnosis became something more to be added to their pattern of ill health while others reported a more emotional reaction and to feel scared or shocked. The identification of the way in which a patient arrives at diagnosis may help refer or facilitate tailored interventions.

Similarly, Abreu et al. (2018) conducted interviews with 26 people with T2DM. The authors reported that people with T2DM generally experienced diagnosis in three different ways. First, disruption: people enacting this narrative recalled diagnosis a disruptive moment in where they became self-aware of being at risk, which also caused anxiety, panic and uncertainty. These patients were described by the authors as being from good to excellent in understanding health information and being very independent; and reported as commonly search information and treatments outside the standard healthcare system. Second, empathy: these people usually adjusted their lives and habits strictly following medical recommendations and treatments. These people displayed some understanding of health information and had a more active participation in treatment, their main source of information were HCPs. Third, minimisation: some had a narrative of T2DM as having a low impact in their lives and daily routines. These people often had little understanding of their health condition and were not interested in the details of their condition.

It is possible, therefore, that although HCPs in the current study reported perceiving some of the feelings experienced by their patients at diagnosis, insufficient attention has been paid to the way in which their patients' deal with the diagnosis in order to understand the best approach to manage their diabetes and achieve patient-centred care. Moreover, HCPs' point of view about consultation times should not be overlooked; limited consultation time was regarded by HCPs' as a barrier to assessing patient's motivation and needs. The need for longer consultation times is an aspect that has been recognised as a significant challenge in primary care, particularly for older

patients who are more likely to have multiple conditions (ISD Scotland, 2018a, ICM Unlimited on behalf of the British Medical Association, 2015). Consultation length is an aspect that is discussed in section 6.7.2.

It is important to mention that most HCPs in the current study reported referring people with newly diagnosed T2DM to DESMOND, which as described in chapter 2, is a structured group education programme available in some health boards in Scotland and in England. Winkley et al. (2018) interviewed HCPs working in primary care in the UK in order to determine their views about group structured education for people with newly diagnosed T2DM. HCPs considered that interaction with other people with T2DM was among the positive aspects of DESMOND; however, they reported believing that few patients attend. Some HCPs reported believing that people who need the information the most usually do not attend, these people were particularly those with mental health issues and non-English speakers. Hence, although structured education programmes are important tools which may relieve some of HCPs workload, consideration must be given to potential patients' barriers to attend these programmes.

6.5.5 Socioeconomic status

Some HCPs perceived that people from low socioeconomic groups and poor health literacy were less engaged with their healthcare. This finding is consistent with the quantitative strand which showed that people in the more deprived SIMD quintiles received medication sooner than those in the less deprived quintiles. Some studies have looked at differences in T2DM care depending on socioeconomic status have shown the different perceptions that HCPs have about people from low socioeconomic groups. For instance, Havele et al. (2018) interviewed physicians working in Internal Medicine and Family Medicine departments in a hospital in the US. The authors reported that physicians modified their instructions and were less stringent with people of low socioeconomic status and/or poor literacy because HCPs perceive these people to face more challenges in their disease management.

Moreover, Dao et al. (2019) interviewed HCPs (GPs and nurses) and people with sub-optimal control of T2DM (HbA1c >53 mmol/mol, blood pressure >130/80mmHg, BMI >30 Kg/m^2 and hyperlipidaemia) in a low socioeconomic area of Sydney, Australia. The authors reported that most HCPs reported that their patients were unmotivated or that they were initially motivated but their motivation decreased with time. Many HCPs' considered that mental health conditions, such as depression, was a barrier to some patients and contributed to over-eating and not performing physical activity. Most patients reported to be motivated, however, they also described that their commitments at work or with their families allowed them little time to engage in physical activity or prepare healthy meals. Most patients reported that their main educational source about T2DM were the GP and dietician, and reported to struggle with their diets and to need more support from their GPs or to be referred to a dietician. These findings suggest that HCPs' perceptions on people from low socioeconomic groups may not reflect their patients' levels of motivation. Hence, tailored advice could improve patients engagement with lifestyle changes.

6.5.6 Ethnicity, health literacy and minority groups

In the current study, some HCPs observed that people from some ethnic and religious minority groups, people with depression, and frail patients were less likely to engage with physical activity or exercise. These results reflect those of Ross et al. (2019), who reported that HCPs in the UK believed that some patients such as people with mental health problems, low literacy and non-English speakers require more support. HCPs also considered that these patients were not suitable to attend self-education for diabetes.

The ethnicity of people with T2DM was included in the cohort analysis; however, outcomes were not stratified by ethnic background because of the large proportion of missing data and the small proportion of people of non-white ethnicity in Scotland. However, differences in T2DM care and management, and disease perception by ethnicity have been studied

previously. Ledford et al. (2019) surveyed people with T2DM in the US and reported significant differences between people according to their ethnicity. Compared to Asian Americans, White Americans were reported as having better understanding of the disease process. Likewise, compared with Asian Americans and Black Americans, White Americans perceived a significantly greater longevity of diabetes. However, a note of caution is due here since other characteristics of patients, such as duration of T2DM and the presence of complications or other diseases were not analysed. Moreover, Staff et al. (2017) reported that in Sweden, there was no difference between BMI or reaching targets for blood pressure, LDL, albuminuria or smoking between native Nordics and non-Nordic people with T2DM. However, there was a difference in HbA1c, where few non-Nordic reached HbA1c targets. These results suggest that people from certain ethnic backgrounds may need additional support from their HCPs to achieve and maintain optimal glucose control because they may have different perceptions of T2DM and barriers to optimal management.

6.5.7 Mental health

Variables related to mental health conditions were not included in the cohort, thus, these data cannot be compared between strands. However, the findings of the qualitative strand in which HCPs saw people with mental health conditions as struggling with the implementation of lifestyle changes, are of particular importance since it has been reported that people with T2DM have an increased risk of developing depression (Nouwen et al., 2010). The relationship between depression and T2DM has been reported to be bidirectional. Hence, depression negatively affects T2DM outcomes including glycaemic control, and T2DM complications increase the risk of, and worsening the course of depression (Semenkovich et al., 2015).

Even in people with T2DM without a reported diagnosis of depression, some see their disease as a source of distress and consider treatment for T2DM, either lifestyle changes or medication, as a source of emotional burden

(Stoop et al., 2019). Mental health could also affect the frequency in which people with T2DM seek medical help. In a recent study, people with a lifetime history of depression, with current depressive symptoms and T2DM, were reported to use fewer treatment services to treat their T2DM (Lee et al., 2020). However, the study was conducted in Korea and the findings may not be extrapolated to the Scottish context, although both provide universal access to healthcare (Kwon et al., 2015, Steel and Cylus, 2012), cultural differences might play a role. Nevertheless, these studies underline the importance of taking into account patients' mental health. In particular, these patients may be prescribed GLM sooner if they are seen as lacking motivation to implement lifestyle changes.

Similarly, comorbid depression may lead to HCPs to prescribe GLM sooner as patients with comorbid depression are often reported as lacking motivation. This finding is supported by Ciechanowski et al. (2000) who reported that severity of depression in people with T2DM is associated with significantly worse adherence to diet, which includes the type of diet followed and the amount of food consumed. The severity of depression has also been associated with the use of oral GLM (Ciechanowski et al., 2000). These findings might help explain why in the current study the perceived reduced likelihood to implement lifestyle changes seemed to be an aspect influencing HCPs' decisions about starting patients on GLM sooner.

6.6 HCP-patient relationship

Overall, HCPs reported that aspects such as previous interaction with patients were reported as facilitating shared decision-making and cooperative healthcare management. HCPs emphasised that the initiation of GLM implied negotiation with patients, which included a discussion about patients' lifestyle. Moreover, all HCPs reported seeking and encouraging shared decision-making, however, some HCPs suggested that the approach to diabetes care differs between HCPs according to their clinical role (nurse, GP) and special interest in T2DM.

6.6.1 Negotiation with patients

The suggestion to initiate GLM by the HCP to their patients was determined by individual-patient considerations. HCPs suggested that shared decision-making increased treatment adherence and saved NHS resources. The discussion with patients was reported as including disclosure about potential side-effects of the medication. As reported in chapter 2, Milos et al. (2014) conducted focus groups with GPs in primary care in Sweden and reported that they would seek to create a dialogue with their patients about the treatment approach. HCPs' considered that written evidence-based information, such as in a leaflet, was a good way to provide information to patients and foster discussion. This finding suggests that people with T2DM may benefit from receiving written information about GLM to inform their decisions.

Moreover, I found that HCPs' often reported that patients' and HCPs' priorities had to be in alignment. Hence, patients need to be "ready" to accept and take GLM. A possible explanation for this may be the fact that people with T2DM and other health conditions, sometimes prioritise the condition that they consider to have a greater impact in their social and physical lives (Boyle et al., 2016). Furthermore, not taking into account the patient's opinions might be disadvantageous. Stoop et al. (2019) reported from their interviews with people with T2DM that for some patients, diabetes care was a source of distress, particularly when they felt not being supported by their HCP and when they perceive the advice that was provided to them was unrealistic and unattainable or that their personal context was not taken into consideration. Discrepancies between HCPs' and patient's perceptions have been previously reported (Woodcock and Kinmonth, 2001, Linmans et al., 2015). Therefore, asking patients about their health priorities can provide important information to HCPs when deciding to prescribe GLM.

In this study, some of the practices where HCPs worked followed the "house of care" model. The house of care model promotes patient-centred care

achieved by care-planning conversations between people and HCPs, promoting shared decision-making. The purpose is to enable patients to express their needs and decide according to their priorities (Health and Social Care Alliance Scotland (the ALLIANCE), 2019, Mathers and Paynton, 2016). The combination of findings so far suggests the adoption of frameworks that support patient-centred care, which are discussed in section 6.7.1.

6.7 Contextual factors

This theme cannot be directly compared with the quantitative strand because variables related to the practices and HCPs were not available in the cohort. However, these findings provide relevant information to understand some of the results previously reported.

6.7.1 Guidelines and frameworks

Thus far, discrepancies in the prescription of GLM seem to be rooted in the evaluation performed by HCPs of their patient's needs and discussion of the patient's preferences. In Scotland, SIGN guidelines are available to HCPs. These guidelines have been developed to provide recommendations, based on evidence, for best practice in the management of diabetes (Scottish Intercollegiate Guidelines Network (SIGN), 2017a). Currently, there is an additional stand-alone guideline, SIGN 154, which covers pharmacological treatment for glucose-control (Scottish Intercollegiate Guidelines Network (SIGN), 2017b).

In this study, HCPs expressed that guidelines are very useful, and many reported consulting them before initiating GLM. However, a need for flexibility depending on the individual was recognised. These findings broadly support the studies presented in chapter 2. For instance, Alexander et al. (2016) conducted a study with physicians in Canada about clinical guidelines for diabetes; physicians' reported taking into account patients' particular life contexts and sought shared decision-making. Similarly, other studies that

have explored HCPs' perceptions of and attitudes towards clinical guidelines in a more general way, have concluded that guidelines are often seen as useful tools that help support evidence-based decision-making (Hunt et al., 2012, Ingemansson et al., 2014).

Moreover, quantitative research conducted by Thepwongsa et al. (2014) who surveyed GPs practising in rural and remote Australia, showed that GPs reported that the main aspects that influence and inform their decision-making were clinical guidelines, consultation with specialists, and professional training. While only 59.1% responded being up to date on new technologies and treatment for T2DM, 85.9% referred finding clinical guidelines useful when providing diabetes care. The findings reported by Thepwongsa et al. (2014) highlight that guidelines are not the only resource used by HCPs which is consistent with findings from the current study. In the qualitative strand, I found that HCPs' reported trying to keep themselves up to date by different means such as attending conferences, meeting and discussing new information with peers; this appeared to be more common among those with a special interest in diabetes.

For the present study, while data for the quantitative strand was drawn from people diagnosed from 2004 to 2012, a period in which the QOF was in force, the interviews with HCPs were conducted two years after it was decommissioned. HCPs perceived that the QOF decommissioning would not negatively affect diabetes care because its guidelines were still adhered to indirectly. Furthermore, some HCPs considered that without incentives to reach targets, they were able to focus more on patient-related factors. Thus, HCPs' views in this study reflect what has been previously reported in the introduction and literature review about the criticism of QOF as hindering person-centred care because it focused on clinical targets (Gillam, 2010, Guthrie and Tang, 2016, McDonald, 2008).

6.7.2 Consultation length and continuity of care

GPs reported that their consultation times in primary care are really challenging, especially for new patients as delivering information becomes quite difficult with the 10-minute slot they usually have. In accordance with the present findings, the National Survey of GPs conducted in 2015 by the British Medical Association reported that in Scotland, 63% of GPs reported that there should be longer consultations for certain groups such as those with long term conditions. Overall, 93% of GPs in Scotland considered that consultation lengths were inadequate (ICM Unlimited on behalf of the British Medical Association, 2015). Likewise, as reported in chapter 2, previous studies have reported time constraints as a barrier to deliver patient-centred consultations (Pooley et al., 2001, Noor Abdulhadi et al., 2013, Daniels et al., 2001, Ingemansson et al., 2014). However, a review conducted by Wilson et al. (2016) reported that, although there is some evidence that increased consultation times led to greater patients' satisfaction, currently there is no strong evidence which supports the alteration of consultation length.

Furthermore, HCPs often reported that historical contact with patients was a positive aspect that helped them reduce the time spent in gathering information about the patient. HCPs described how knowing patients by having seen them previously for other health conditions made consultations easier and facilitated discussion regarding the initiation of GLM and lifestyle change. Previous studies in the UK have reported similar findings about considering continuity of care as a positive aspect. For instance, Alazri et al. (2007) explored GPs' and nurses' experiences of continuity of care for people with T2DM in primary care by interviewing 16 GPs and 18 nurses who managed T2DM. HCPs considered that the care provided for a patient by a named HCP, which could last for a few years to a whole lifetime, helped to encourage patients to follow their advice and provided an opportunity to reinforce such advice. However, HCPs acknowledged that the higher the number of patients registered in a practice the more difficult it was to achieve

continuity in care. In general, HCPs considered that for long-term conditions, such as T2DM, continuity of care was crucial.

Continuity of care might be of particular importance for older patients. Greaves et al. (2003) interviewed 25 nurses in the UK who reported that continuity of care facilitated treatment modifications in elderly patients. However, this finding must be interpreted with caution, not only because the study was conducted more than fifteen years ago, but also due to the authors having focused on views about converting people with diabetes from oral hyperglycaemic agents to injected insulin within primary care. Nevertheless, receiving care from the same HCP has not always been reported as essential, Boyle et al. (2016) reported that people with T2DM in Australia did not consider continuity of care as completely necessary, particularly if they considered that the HCP would mainly be conducting clinical tests and check-ups. It can thus be suggested that, although HCPs' in the current study reported it as a positive aspect, continuity of care is needed only for some people and thus, the patient must be the one who decides whether they desire to see the same HCP over time.

6.7.3 HCPs' perceptions of their roles

The interviews with HCPs revealed potential differences in prescription patterns between nurses and GPs, and between HCPs with a special interest in diabetes and without special interest. However, with a small sample of HCPs, caution must be applied, as the findings may not reflect real practice. Quantitative studies have reported differences in prescription depending on HCPs' characteristics. For instance, Grant et al. (2007) who surveyed physicians reported that compared to specialists, general physicians tended to avoid insulin and prescribed glitazones instead. Likewise, Escalada et al. (2016) reported that GPs, compared to endocrinologists, often delay insulin initiation. However, these studies focused on insulin initiation instead of first-line GLM.

Nurses had increasing participation in diabetes care, and their decisions on when to start drug treatment might be guided more by patients' HbA1c levels and although they also consider individual factors, they might be more likely to try to persuade patients to start at an early stage if the guidelines indicate so. The increasing role of nurses in diabetes care in the UK has been reported in the literature review (National Statistics Scotland, 2013). However, differences in prescription patterns by HCPs role, in the context of newly diagnosed T2DM, has not been reported.

6.8 Reflections on the research

Before addressing the limitations and strengths of this study, I would like to provide a reflection on conducting this research. Mixed-methods studies provide valuable insights into a topic; however, to engage in such endeavour there are some aspects that should not be overlooked.

First, it is essential to consider critically the time element. I initially underestimated the time that I would need for conducting both strands, fortunately, this was pointed out during the first-year review and I made the practical decision to change the sequential design to a convergent parallel design. Although the study design made it feasible for me to obtain experience of both types of research and to switch from one strand to the other whenever it was necessary, this study challenged my time management skills and capability to swap from quantitative to qualitative methods and at the same time to bear in mind that they should form coherent strands of the same study.

Second, since this study had limited funding, incentives to participate were not offered to HCPs to participate in the interviews. In retrospect, considering their busy schedules, there is a possibility that more HCPs might have participated if I had been able to offer an economic incentive. This could have helped by allowing me to have more time with participants to discuss some

aspects in more depth, such as HCPs' approach to management depending on patients' sex and HCPs' perceptions of their role.

6.9 Limitations and strengths

6.9.1 Limitations

This study has limitations, which I will now address. It is important to consider that, due to differences in guidelines and policies between countries, this research may only apply to the Scottish context. Moreover, as described earlier, I would like to acknowledge the differences between years from the patient's data (2004-2012) and the interviews with HCPs (2018). The main change occurred during these years was QOF decommissioning, and although the interviews made evident that there is still a legacy of QOF, differences in prescription patterns in patients diagnosed with T2DM after 2012 may have taken place.

In chapter 2, the systematic search and reviews are subject to inherent limitations of the type of review. Although this type of review incorporates different study types to provide a holistic view of the topic, and the initial search process met the requirements of a systematic review, the consequent steps are not subject to a clearly defined process of synthesis which may result in some subjective selection of evidence (Grant and Booth, 2009). Moreover, since the search, selection process and synthesis were done only by me, and not by two people working independently, the possibility that the selection of articles was influenced by personal bias cannot be discarded. However, some best practice recommendations for systematic reviews were followed where possible. For instance, the development of criteria used to decide which studies were included; although explicit inclusion and exclusion criteria are not required for systematic search and reviews, the Cochrane handbook advises the use of eligibility criteria to help readers understand the scope of the review and provide an argument of why some studies they are aware of were not included. Moreover, an account of the results of the search

was provided in a PRISMA-type flow diagram which summarised the selection process. Similarly, tables were created to summarise the information for each study included as well as tables with information for full-text studies which were excluded (included in appendices) (Page Matthew J et al., 2019, Lefebvre C et al., 2019).

In relation to the cohort dataset, it is not possible to know whether data in the SCI-Diabetes dataset is entirely accurate in terms of emigration as changes depend on practices maintaining accurate lists of active patients. However, updated demographic details are routinely collected and, before recording a new diagnosis onto the system, GPs are encouraged to do a patient search to ascertain their presence on the system (INPS, 2013, Cunningham et al., 2011). Accuracy of other variables in SCI-diabetes is also difficult to assess. However, as described in chapter 3, a search and deletion of implausible data were conducted prior to the analysis of missing data.

The potential inclusion of people with T1DM in the cohort was reduced by selecting those recorded as having T2DM, who were or at least 30 years of age and had no record of GLM prescription before the date of diagnosis of diabetes. However, 1.2% of those who received GLM (0.67% of the whole cohort) were prescribed insulin as first GLM (alone or in combination with another drug) with a mean of 161 days from diagnosis to prescription suggesting that a small proportion of the cohort may have had T1DM. Another important aspect that needs to be taken into consideration is the fact that only people with recently diagnosed T2DM who survived for at least two years of follow-up were included in the cohort. The rationale for this decision was to provide equal lengths of follow-up for all participants and to reduce the influence of potential terminal illness on treatment decisions and HbA1c.

Moreover, there was an important proportion of missing data in the cohort, only 56.7% of the population had data available for all variables of interest. I used multiple imputation, which is considered an appropriate method for

handling missing data, and utilised 45 imputed datasets as recommended by the literature. Furthermore, the comparison of the imputed dataset and the CCA suggested that the use of complete cases may provide biased results because of the differences in characteristics between people with and without missing data. BMI was the variable with the largest proportion of missing values, and the Cox regression for the CCA showed no statistically significant association between BMI and receipt of prescription within two years for BMI whereas the association was statistically significant in the imputed dataset. However, as discussed in the quantitative results section, this discrepancy may be related to power (i.e. chance) rather than bias, since apart from this finding, the results of the imputed dataset were largely consistent with those of the CCA suggesting that there is little evidence of bias in the CCA.

As reported in the literature review, sometimes HbA1c is less reliable in some non-white ethnic groups. While this is not a major limitation of the study since I did not look at the differences between HbA1c across ethnic groups, and the focus was not related to describing ethnic differences, I must observe that the ethnicity of 20% of the cohort was unknown. However, as mentioned previously, the Scottish census of 2011 reported that non-white Scottish/British represented <10% of the population (National Records of Scotland, 2011). Hence, is likely that an important proportion of those whose ethnicity was unknown was indeed white Scottish/British. Another important limitation lies in the dichotomisation of ethnicity into Scottish/British and other/unknown for the Cox regression in the quantitative strand. By utilising these two categories it was not possible to fully compare findings from the cohort analyses with those of the interviews in which some HCPs considered that patients from some minority ethnic groups were less likely to engage in physical activity and so were more likely to be prescribed GLM earlier than the majority white population. Although the univariate regression indicated shorter time to GLM for people of other/unknown ethnicity, the fully adjusted model showed that people from other/unknown ethnicity had longer time to

GLM initiation than Scottish/British. The relationship of other ethnicities in clinical decision-making about when to initiate GLM is still an aspect that needs further exploration. The study has limited power to investigate the association between non-white ethnicity and time to GLM but increasing completeness of recording of ethnicity may make it feasible in the future.

Unfortunately, for the quantitative strand, no data were included about chronic kidney disease, which was reported to be a factor influencing decisions about when to initiate GLM, particularly amongst older patients. It would have been desirable to add this variable to the dataset.

Further limitations arise from the use of HbA1c, as data and changes in HbA1c after initiation of GLM were not included. Baseline HbA1c was defined broadly in terms of the time-frame used to define the variable, which as reported in chapter 3, as the average value between 180 days before and after diagnosis in order to minimise missingness. In relation to this, a study in the UK showed that people with T2DM (mean duration 6 years) who were not taking insulin and were initiating or changing their type or dose of GLM, their HbA1c decreased by 7.1$\pm$1.3 mmol/mol on average after 12 weeks of initiating their new GLM or dose (Hirst et al., 2014). This finding shows that HbA1c values can be quickly reduced by using GLMs. Thus, for people who started GLM soon after diagnosis in the current study and who did not have an HbA1c value recorded prior to treatment, the reported baseline HbA1c values could potentially have been lower than the real HbA1c values at diagnosis.

Although the sensitivity analysis presented in chapter 4 showed that proportions of people who received a GLM prescription increased at higher HbA1c levels, these were not addressed in the analyses. For the Cox regression analysis, HbA1c was dichotomised in either <53 mmol/mol or $\geq$53 mmol/mol. However, while the inclusion of additional categories may have had an impact on the results, the results showed that shorter time to GLM

was strongly associated with HbA1c ≥53 mmol/mol. In the current study, cut-offs points were based on targets in clinical guidelines rather than the curve points or 'bumps' found in the Martingale residuals plots. However, for BMI and HbA1c conventional clinical definitions and bumps in the data were similar.

Lastly, recruiting HCPs for the interviews was rather challenging, particularly since no incentive to take part in the study was offered. HCPs often reported that they were very busy and had no time to participate. Although I obtained enough data to answer the research questions, recruiting more participants, as initially planned may have provided richer and more extensive findings. Moreover, I interviewed relatively few nurses and did not have the opportunity to interview HCPs from across a diversity of areas, for instance remote rural areas.

6.9.2 Strengths

This study has a number of strengths which I will now describe. First, the convergent parallel mixed-methods design, although challenging to carry out, allowed the comparison of two different sets of data to provide greater insight into the timing of GLM prescription in people with newly diagnosed T2DM.

Second, the cohort of patients was drawn from SCI-diabetes which contains patients' records from all health boards in Scotland. Overall, 154,660 people were included in the cohort. Thus, the analyses of a large dataset which is nationally representative provide more accurate estimates about people with newly diagnosed T2DM in Scotland.

Third, the interviews and their analysis commenced simultaneously, this allowed me to use preliminary findings in the subsequent interviews by improving my topic guide. Moreover, by keeping the questions as open as possible HCPs were able to guide the conversation to what they considered more important when deciding when to initiate people with newly diagnosed T2DM on GLM.

Fourth, to my knowledge, this is the first study which has looked at GLM initiation in people with newly diagnosed T2DM using a mixed-methods design. Although some limitations need to be taken into consideration, this study provides important knowledge about the topic and highlights the complex set of factors that play a role when prescribing GLM.

6.10 Implications and directions for future research

Through this study, I sought to determine what factors were associated with GLM initiation, and what were the views and experiences of healthcare professionals working in primary care about when to initiate GLM. The convergent parallel mixed-methods design enabled me to answer this question by using quantitative and qualitative data in a way that would not have been possible with other study design.

The study has identified that in Scotland, older age, living in less deprived areas, being male, having lower BMI and HbA1c were independently associated with longer time to GLM initiation. However, it also showed that clinical decision-making encompasses not only clinical aspects related to the patient but also to the patients' perceived or expressed motivation and readiness to make lifestyle changes, the healthcare system and the HCPs' characteristics. Thus, in line with realistic medicine which encourages HCPs to have an open and honest dialogue with people about their needs, patient-centred care is essential (Realistic Medicine, 2019).

Moreover, the present study raises the possibility that HCPs without a special interest in diabetes might feel less confident in managing people with diabetes, which emphasises the importance of providing them with the opportunity to keep up to date with and to be able to critically appraise and attempt to apply clinical guidelines appropriately to individual patients. The interviews yielded an important implication for current practice. HCPs expressed the need for guidelines with separate goals, particularly for elderly

patients, which now are available in the ADA standards of care but did not exist when this research started.

Hence, this study has added important knowledge to the study of GLM initiation in people with newly diagnosed T2DM. This study provides evidence of the patterns and factors associated with drug initiation in Scotland in the QOF period, which are valuable to compare, once there is sufficient data gathered, with the period after the decommissioning of QOF. After the decommissioning of the QOF, there may be changes to the patterns in GLM prescription partly due to changes to the GP contract and also due to other factors such as increasing interest in the potential for remission of T2DM. Therefore, further analyses are recommended in order to describe treatment patterns in the years after QOF termination.

In the quantitative component of this study, clinical and metabolic variables were included, however, cardiovascular risk scores were not calculated, which may be important to consider in the future. Newer drugs for treating diabetes such as GLP-1 agonists may have a protective effect against cardiovascular disease but are currently only recommended for treating people with existing CVD and hyperglycaemia that has not responded to lifestyle modification and metformin monotherapy (American Diabetes Association, 2019d). Furthermore, during the analysis of both quantitative and qualitative findings further queries related to differences by patient's sex and ethnicity were raised. For future research, it would be valuable to include stratified analyses to identify differences and to examine HCPs' views and perceptions of the role of these aspects in more depth. For the quantitative analysis, it would be interesting to extend this work to include repeated measures of HbA1c and to investigate whether time to glucose-lowering treatment influenced subsequent risk of complications of diabetes.

Likewise, further understanding and review of prescription patterns for certain groups of clinical interest such as elderly and people with comorbidities are

needed given the increasing recognition of the challenges in providing care to people with multimorbidity. In particular, the role of mental health conditions in T2DM management and outcomes emphasises the importance of comprehensive individualised care for people with T2DM.

In addition, it would be interesting to study patterns of prescribing second- and third-line drugs given the introduction of new drug classes in recent years, including GLP-1 agonists and DPP-4 inhibitors that are likely to displace some insulin prescribing. However, such pharmaco-epidemiological analysis would benefit from including repeated, time updated HbA1c measurements and not only baseline measures.

6.11 Conclusion

This study provided novel insights into clinical decision-making, particularly on HCPs' experiences, views and factors they consider when deciding when to prescribe GLM in people with recently diagnosed T2DM. In addition, the qualitative strand showed how decision-making between people with recently diagnosed T2DM and HCPs working in primary care contributes to the timing of initiation of GLM. Both strands identified that there continues to be scope to improve support for people to make beneficial lifestyle changes following a diagnosis of T2DM. Recent RCT results indicating the potential for T2DM remission in people who achieve major weight loss have resulted in extended weight management services (Lean et al., 2018, Lean et al., 2019, Leslie et al., 2016). However, at population level it is important also to identify ways to change the wider environment to make it easier for people to live healthy lifestyles.

By using a mixed-methods approach, I have provided insights on the factors and considerations that influence prescription of GLM in people with recently diagnosed T2DM. I have provided evidence that although HCPs' considered HbA1c as fundamental to informing decisions to prescribe medication to lower glucose levels, their decision was not solely based on this indicator.

HCPs considered the wider context and patient's other circumstances in seeking to provide patient-centred care.

However, some important queries such as potential differences between HCPs according to their role (nurse, GP) or interest in diabetes needs to be addressed in further research. Likewise, future work needs to include sex- and ethnic-specific analysis of prescription patterns in order to identify potential clinically relevant inequities in the management of people with newly diagnosed T2DM. Finally, these findings help to understand why HCPs did not always prescribe glucose-lowering treatment when HbA1c levels might be considered to be sub-optimal.

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Appendix 1 – Search strategies

1A – Search strategy for quantitative studies

a) PubMed

"diabetes mellitus" OR "non insulin diabetes mellitus" OR "type 2 diabetes" OR "diabetic patient*" OR "glycemic control"

AND

"general practic*" OR "physician" OR "primary care" OR "Clinical practice" OR "health practic*"

AND

"Drug therapy" OR "treatment trend" OR prescription OR monotherapy OR "time to treatment" OR "treatment initiation" OR "drug utilization" OR "antidiabetic agent" OR therapy OR "medical decision making" OR "clinical decision making" OR "drug indication" OR "drug initiation" OR "treatment planning" OR "clinical inertia" OR "therapeutic inertia" OR "physician inertia"

b) SCOPUS

(TITLE-ABS-KEY ("type 2 diabetes mellitus" OR "glyc?emic control" OR "people with diabetes" OR "diabetic patient*")) AND (TITLE-ABS-KEY ("general practic*" OR "physician*" OR "primary care" OR "medical practice*" OR "health care professional*" OR "health care personnel")) AND ((TITLE-ABS-KEY ("drug choice*" OR "drug indication" OR "treatment trend*" OR "treatment pattern*" OR prescription* OR monotherapy OR "time to treatment" OR "treatment initiation" OR "drug utili#ation") OR TITLE-ABS-KEY ("therapy delay" OR "drug initiation" OR inertia OR "treatment planning" OR "drug indication")))

c) EMBASE

1. non insulin dependent diabetes mellitus/
2. diabetes mellitus.tw.
3. type 2 diabetes.tw.
4. glyc?emic control.tw.
5. people with diabetes.tw.

6. (non insulin adj2 diabetes).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
7. diabetic patient/
8. professional practice/ or general practice/ or group practice/ or health care practice/ or medical practice/ or private practice/
9. primary health care/
10. health care personnel/
11. general practic*.tw.
12. physician*.tw.
13. (primary adj2 care).tw.
14. drug choice/ or drug indication/ or monotherapy/ or pharmaceutical care/
15. time to treatment/ or therapy delay/ or treatment planning/
16. treatment trend*.tw.
17. treatment pattern*.tw.
18. (time adj2 treatment).tw.
19. treatment initiation.tw.
20. drug utili#ation.tw.
21. (reason* adj3 treat*).tw.
22. drug initiation.tw.
23. ((clinical or therapeutic or physician) adj2 inertia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
24. drug indication.tw.
25. treatment planning.tw.
26. 1 or 2 or 3 or 4 or 5 or 6 or 7
27. 8 or 9 or 10 or 11 or 12 or 13
28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
29. 26 and 27 and 28

1B – Search strategy for qualitative studies

a) EMBASE

1 non insulin dependent diabetes mellitus/
2 diabetes type 2.mp.
3 1 or 2
4 Health care professionals.mp. or health care personnel/
5 GPs.mp.
6 physician/
7 nurses.mp. or nurse/
8 doctors.mp.
9 or 5 or 6 or 7 or 8
10 primary care.mp. or primary medical care/
11 general practice.mp. or general practice/
12 10 or 11
13 experience/ or experiences.mp.
14 views.mp.
15 attitudes.mp. or attitude/
16 13 or 14 or 15
17 3 AND 9 AND 12 AND 16

b) SCOPUS

(TITLE-ABS-KEY ("non insulin diabetes mellitus" OR "type 2 diabetes") AND TITLE-ABS-KEY ("healthcare professional" OR "health care professional" OR gp OR nurse OR physician) AND TITLE-ABS-KEY ("primary care" OR "general practice" OR "family medicine") AND TITLE-ABS-KEY (experiences OR views OR attitudes))

c) PubMed

((((diabetes OR "type 2 diabetes" OR "clinical inertia" OR guidelines OR "decision-making")) AND ("primary care" OR "general practice" OR "primary health care")) AND (GP OR nurse OR physician OR "health personnel" OR "health care professional")) AND ("qualitative research" OR "qualitative study")

Appendix 2 – Full-text articles excluded

2A – Section 1: Quantitative full-text articles excluded

	Author(s)	Title	Year	Reason
1	Armendáriz Cuñado, M., Giménez Robredo, A. I., Jaio Atela, N.	Oral antidiabetics prescription in primary care	2006	No full-text available
2	Bala, M. M., Placzkiewicz-Jankowska, E., Topor-Madry, R., Lesniak, W., Jaeschke, R., Sieradzki, J., Grzeszczak, W., Banasiak, W.	Is newly diagnosed type 2 diabetes treated according to the guidelines? Results of the Polish ARETAEUS1 study	2011	Focused in assessing the proportion of patients achieving diabetic control goals, and described current medication not initial treatment (I.e. only 4.2% were not receiving GLM)
3	Benford, M., Milligan, G., Pike, J., Anderson, P., Piercy, J., Fermer, S.	Fixed-dose combination antidiabetic therapy: Real-world factors associated with prescribing choices and relationship with patient satisfaction and compliance	2012	Not newly diagnosed nor patterns over time.
4	Boudreau, D., Swain, B., O'Connor, P., Nichols, G. A., Raebel, M., Nakasato, C., Newton, K., Selby, J.	Early initiation of metformin in new-onset type 2 diabetes	2011	Conference poster – abstract only.
5	Bramlage, P., Binz, C., Gitt, A. K., Krekler, M., Plate, T., Deeg, E., Tschope, D.	Diabetes treatment patterns and goal achievement in primary diabetes care (DiaRegis) - study protocol and patient characteristics at baseline	2010	Aim was to evaluate the specific characteristics, treatment patterns, quality of life and diabetes related events of T2DM patients who failed oral therapy.
6	Calvert, M. J., McManus, R. J., Freemantle, N.	The management of people with type 2 diabetes with hypoglycaemic agents in primary care:	2007	Does not specify duration of T2DM.

		Retrospective cohort study		
7	Chu, W. M., Ho, H. E., Huang, K. H., Tsan, Y. T., Liou, Y. S., Wang, Y. H., Lee, M. C., Li, Y. C.	The prescribing trend of oral antidiabetic agents for type 2 diabetes in Taiwan	2017	Not newly diagnosed, elderly not UK
8	Conthe, P., Mata, M., Orozco, D., Pajuelo, F., Barreto, C. S., Anaya, S. F., Gomis, R.	Degree of control and delayed intensification of antihyperglycaemic treatment in type 2 diabetes mellitus patients in primary care in Spain	2011	Patients were selected if were already receiving medication or second line combination treatment initiation at least one year prior to study entry
9	Deed, G., Barlow, J., Kuo, I.	Early and tight glycaemic control: The key to managing type 2 diabetes	2012	Review – Australia
10	Dennis, J. M., Henley, W. E., McGovern, A. P., Farmer, A. J., Sattar, N. Holman, R. R., Pearson, E. R., Hattersley, A. T., Shields, B. M., Jones, A. G., on behalf of the, Mastermind consortium	Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010–2017	2019	The primary unit of analysis was line of therapy. Patients who started more than one new therapy contributed to the analysis more than once with different lines of therapy.
11	Ekstrom, N., Svensson, A. M., Miftaraj, M., Sundell, K. A., Cederholm, J., Zethelius, B., Eliasson, B., Gudbjornsdottir, S.	Durability of oral hypoglycemic agents in drug naive patients with type 2 diabetes: Report from the Swedish national diabetes register (NDR)	2015	Durability – continuation/discontinuation of GLMs only.
12	Eliasson, B., Eeg-Olofsson, K., Cederholm, J., Nilsson, P. M., Gudbjornsdottir, S.	Antihyperglycaemic treatment of type 2 diabetes: results from a national diabetes register	2007	The aim was to analyse the clinical characteristics and pharmacological treatment. Therapy only classified as OHA and/or insulin.
13	Gallagher, N., Cardwell, C. Hughes, C., O'Reilly, D.	Increase in the pharmacological management of Type 2	2015	Only proportions of people who received drug therapy but no patterns.

		diabetes with pay-for-performance in primary care in the UK		
14	Gearhart, J. G., Forbes, R. C.	Initial management of the patient with newly diagnosed diabetes	1995	No full-text available.
15	Gelhorn H. L., Stringer S. M., Brooks A., Thompson C., Monz B. U., Boye K. S., Hach T., Lund S. S., Palencia R.	Preferences for medication attributes among patients with type 2 diabetes mellitus in the UK	2013	Hypothetical situation
16	Geier, A. S., Wellmann, I., Wellmann, J., Kajüter, H., Heidinger, O., Hempel, G., Hense, H. W.	Patterns and determinants of new first-line antihyperglycaemic drug use in patients with type 2 diabetes mellitus	2014	Not clear whether people were newly diagnosed and only included those who were not prescribed during the first 6 months from registration to a database.
17	Göktaş, O., Öz Gül, Ö., Ertürk, E.	Changes in the management of type 2 diabetic patients in family medicine practices in the Bursa region	2017	Not newly diagnosed and not EU/US
18	Grant, R. W., Wexler, D. J. Watson, A. J., Lester, W. T., Cagliero, E., Campbell, E. G., Nathan, D. M.	How doctors choose medications to treat type 2 diabetes: A national survey of specialists and academic generalists	2007	Survey/hypothetical
19	Halimi, S., Balkau, B., Attali, C., Detournay, B., Amelineau, E., Blickle, J. F.	Therapeutic management of orally treated type 2 diabetic patients, by French general practitioners in 2010: the DIAttitude Study	2012	Treatment intensification in France
20	Higgins, V., Piercy, J., Roughley, A., Milligan, G., Leith, A., Siddall, J., Benford, M.	Trends in medication use in patients with type 2 diabetes mellitus: A long-term view of real-world treatment between 2000 and 2015	2016	Not newly diagnosed

21	Lang, V. B., Markovic, B. B., Kranjcevic, K.	Family physician clinical inertia in glycemic control among patients with type 2 diabetes	2015	Clinical inertia – not UK
22	Machado-Duque, M. E., Ramírez-Riveros, A. C., Machado-Alba, J. E.	Effectiveness and clinical inertia in patients with antidiabetic therapy	2017	Clinical inertia – not UK
23	Maguire, A., Mitchell, B.	Characteristics of patients initiating oral antidiabetic therapy in the UK: Evidence of delayed treatment?	2012	Abstract only
24	Maguire, A., Mitchell, B. D., Ruzafa, J. C.	Antihyperglycaemic treatment patterns, observed glycaemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: A retrospective cohort study	2014	No data on duration of T2DM or whether these were newly diagnosed.
25	Mahabaleshwarkar, R., Gohs, F., Mulder, H., Wilkins, N., DeSantis, A., Anderson, W. E., Ejzykowicz, F., Rajpathak, S., Norton, H. J.	Patient and Provider Factors Affecting Clinical Inertia in Patients With Type 2 Diabetes on Metformin Monotherapy	2017	Focused only on metformin
26	Marrett, E., Jameson, K., Zhang, Q., Meiler, S., Radican, L., Sinclair, A.	Reasons for non-treatment of newly diagnosed type 2 diabetes mellitus (T2DM) in the United Kingdom	2010	Conference publication – abstract only
27	Marrett, E., Zhang, Q., Narayanan, S., Radican, L.	Why are some older patients with newly-diagnosed type 2 diabetes not treated?	2009	Conference publication – abstract only
28	Mata-Cases, M., Benito-Badorrey, B., Roura-Olmeda, P., Franch-Nadal,	Clinical inertia in the treatment of hyperglycemia in type 2	2013	Clinical inertia – Spain

	J., Pepio-Vilaubi, J. M., Saez, M., Coll-De-Tuero, G.	diabetes patients in primary care		
29	Mata-Cases, M., Franch-Nadal, J., Real, J., Mauricio, D.	Glycaemic control and antidiabetic treatment trends in primary care centres in patients with type 2 diabetes mellitus during 2007-2013 in Catalonia: A population-based study	2016	Not newly diagnosed
30	McEwan, P., Prettyjohns, M., Ketsetzis, G., Evans, L. M., Bergenheim, K.	The impact of clinical inertia in the treatment of type 2 diabetes	2011	Conference publication – abstract only
31	McEwen L., Bilik D., Johnson S., Halter J., Karter A., Mangione C., Subramanian U., Waitzfelder B., Crosson J., Herman W.	Predictors and Impact of Intensification of Antihyperglycemic Therapy in Type 2 Diabetes	2009	Clinical inertia – not UK
32	McGovern, A., Hinton, W. Calderara, S., Munro, N. Whyte, M., de Lusignan, S.	A Class Comparison of Medication Persistence in People with Type 2 Diabetes: A Retrospective Observational Study	2018	Persistence of certain medications
33	Morita, Y., Murayama, H., Odawara, M., Bauer, M.	Treatment patterns of drug-naive patients with type 2 diabetes mellitus	2019	the study was conducted in Japan
34	Muralidharan, R.	Approach to a person recently diagnosed with diabetes	2007	No full-text available
35	Pantalone, K. M., Hobbs, T. M., Wells, B. J., Kong, S. X., Kattan, M. W., Bouchard, J., Yu, C., Sakurada, B., Milinovich, A., Weng, W., Bauman, J., Zimmerman, R. S.	Clinical characteristics, comorbidities, and treatment patterns among patients with new-onset type 2 diabetes in a large integrated health system	2014	Conference publication – abstract only

36	Patel N., Stone M., Chauhan A., Davies M., Khunti K.	Insulin initiation and management in people with Type 2 diabetes in an ethnically diverse population: the healthcare provider perspective	2012	Clinical inertia – qualitative study.
37	Plat, A., Penning-Van Beest, F., Kessabi, S., Groot, M., Herings, R.	Change of initial oral antidiabetic therapy in type 2 diabetic patients	2009	New users rather than newly diagnosed
38	Qiu Y., Qiong L., Tang J., Fan C.,Li Z., Apecechea M., Hegar R., Shankar R., Kurtyka K., Engel S.	Why physicians do not initiate dual therapy as recommended by AACE guidelines: A survey of clinicians in the United States	2015	Guidelines adherence – US
39	Ruiz-Negron N., Wander C., McAdam C., Pesa J., Bailey R., Bellows B.	Factors Associated with Diabetes-Related Clinical Inertia in a Managed Care Population and Its Effect on Hemoglobin A1c Goal Attainment: A Claims-Based Analysis	2019	Clinical inertia – not UK
40	Sabale, U., Bodegard, J., Sundstrom, J., Ostgren, C. J., Nilsson, P., Johansson, G., Svennblad, B., Henriksson, M.	Healthcare utilization and costs following newly diagnosed type-2 diabetes in Sweden: A follow-up of 38,956 patients in a clinical practice setting	2015	Conference publication – abstract only
41	Shani, M., Lustman, A., Vinker, S.	Diabetes medication persistence, different medications have different persistence rates	2017	Not EU/US and focused on persistence between medication.
42	Shaya, F. T., Chirikov, V. V., Bron, M., Howard, D.	Comparison of physician practice patterns for older adults compared to NHANES diabetes	2013	Not newly diagnosed

	Foster, C., Yan, X., Khanna, N., Warrington, V. O.	cohort on oral/other therapy		
43	Truter, I.	An investigation into antidiabetic medication prescribing in South Africa	1998	Not newly diagnosed – not EU/US
44	Tschope, D., Bramlage, P., Binz, C., Krekler, M., Plate, T., Deeg, E., Gitt, A. K.	Antidiabetic pharmacotherapy and anamnestic hypoglycemia in a large cohort of type 2 diabetic patients - an analysis of the DiaRegis registry	2011	Focused on hypoglycaemia – not newly diagnosed – only patients already on medication were selected
45	Walley, T., Hughes, D., Kendall, H.	Trends and influences on use of antidiabetic drugs in England, 1992-2003	2005	Proportions of use, not data on patients' duration of T2D
46	Whyte, M. B., Hinton, W., McGovern, A., van Vlymen, J., Ferreira, F., Calderara, S., Mount, J., Munro, N., de Lusignan, S.	Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: A retrospective cohort analysis	2019	Not newly diagnosed
47	Wiley, J. F.	Blood glucose levels and glycaemic burden in 76,341 patients attending primary care: Bittersweet findings from a 9-year cohort study	2017	Trends in blood glucose levels and glycaemic control – Australia.
48	Wilkinson, S., Douglas, I., Stirnadel-Farrant, H., Fogarty, D., Pokrajac, A., Smeeth, L., Tomlinson, L.	Changing use of antidiabetic drugs in the UK: Trends in prescribing 2000-2017	2018	People were included if they had already been prescribed, and this was considered the diagnosis but no further data. Focus primarily on escalation
49	Yurgin, N., Secnik, K., Lage, M. J.	Antidiabetic prescriptions and glycemic control in German patients with type 2 diabetes mellitus:	2007	Glycaemia – not newly diagnosed

		A retrospective database study		
50	Zafar, A., Davies, M., Azhar, A., Khunti, K.	Clinical inertia in management of T2DM	2010	Review
51	Ziemer, D. C., Miller, C. D., Rhee, M. K., Doyle, J. P., Watkins Jr, C., Cook, C. B., Gallina, D. L., El-Kebbi, I. M., Barnes, C. S., Dunbar, V. G., Branch Jr, W. T., Phillips, L. S.	Clinical inertia contributes to poor diabetes control in a primary care setting	2005	Clinical inertia – not UK

2B – Section 2: Qualitative full-text articles excluded

	Author(s)	Title	Year	Reason
1	Austad B., Hetlevik I., Mjolstad B., Helvik AS.	Applying clinical guidelines in general practice: a qualitative study of potential complications	2016	Focused on complications of using guidelines rather than general views and experiences.
2	Boivin, A., Legare, F., Gagnon, M. P.	Competing norms: Canadian rural family physicians' perceptions of clinical practice guidelines and shared decision-making	2008	Full-text not available
3	Bower, P., Macdonald, W., Harkness, E., Gask, L., Kendrick, T., Valderas, J. M., Dickens, C., Blakeman, T., Sibbald, B.	Multimorbidity, service organization and clinical decision making in primary care: a qualitative study	2011	Focused on management of complex patients only + hypothetical cases.
4	Chimeddamba, O., Ayton, D., Bazarragchaa, N., Dorjsuren, B., Peeters, A., Joyce, C.	The Adoption of Roles by Primary Care Providers during Implementation of the New Chronic Disease Guidelines in Urban	2016	Description of their roles within their healthcare teams

		Mongolia: A Qualitative Study		
5	Ellen, M. E., Leon, G., Bouchard, G., Ouimet, M., Grimshaw, J. M., Lavis, J. N.	Barriers, facilitators and views about next steps to implementing supports for evidence-informed decision-making in health systems: a qualitative study	2014	Explores feasibility to the implementation of evidence-based decision-making in particular settings in Canada
6	Foo, K. M., Sundram, M., Legido-Quigley, H.	Facilitators and barriers of managing patients with multiple chronic conditions in the community: a qualitative study	2020	Not focused on T2DM – management of people with multiple conditions.
7	Fried, T. R., Tinetti, M. E., Iannone, L.	Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions	2011	Therapeutic decisions not T2DM
8	Harrison, S., Dowswell, G., Wright, J.	Practice nurses and clinical guidelines in a changing primary care context: an empirical study.	2002	Focused on asthma and angina
9	Luijks, H. D., Loeffen, M. J., Lagro-Janssen, A. L., van Weel, C., Lucassen, P. L., Schermer, T. R.	GPs' considerations in multimorbidity management: a qualitative study	2012	Management of multimorbidity
10	Macdonald, L., Stubbe, M., Tester, R., Vernall, S., Dowell, T., Dew, K., Kenealy, T., Sheridan, N., Docherty, B., Gray, L., Raphael, D.	Nurse-patient communication in primary care diabetes management: An exploratory study	2013	Focused on effective interaction and analysis of communication with patients and its effectiveness.
11	McDonald, R., Waring, J., Harrison, S., Walshe, K., Boaden, R.	Rules and guidelines in clinical practice: a qualitative study in operating theatres of	2005	HCPs' views on following protocols and guidelines, focused on teamwork rather than diseases.

		doctors' and nurses' views.		
12	McKillop, A., Crisp, J., Walsh, K.	Practice guidelines need to address the 'how' and the 'what' of implementation	2012	Focused mainly on management of patients with cardiovascular risk and the implementation of guidelines in these patients rather than management of T2DM or guidelines in a more general way.
13	Pericas-Beltran, J., Gonzalez-Torrente, S., De Pedro-Gomez, J., Morales-Asencio, J. M., Bennasar-Veny, M.	Perception of Spanish primary healthcare nurses about evidence-based clinical practice: a qualitative study	2014	It focuses on the ways in which nurses seek for information, evidence-based and the difficulties of implementing evidence-based recommendations.
14	Rätsep, A., Oja, I., Kalda, R., Lember, M.	Family doctors' assessment of patient- and health care system-related factors contributing to non-adherence to diabetes mellitus guidelines	2007	Quantitative study – questionnaire
15	Sinnott, C., Hugh, S. M., Boyce, M. B., Bradley, C. P.	What to give the patient who has everything? A qualitative study of prescribing for multimorbidity in primary care	2015	Focused on management of complex patients with multiple diseases.
16	Thepwongsa, I., Kirby, C., Paul, C., Piterman, L.	Management of type 2 diabetes: Australian rural and remote general practitioners' knowledge, attitudes, and practices	2014	Quantitative study
17	Tinetti, M., Dindo, L., Smith, C. D., Blaum, C., Costello, D., Ouellet, G., Rosen, J., Hernandez-	Challenges and strategies in patients' health priorities-aligned decision-making for older		Challenges in making decisions – not T2DM

	Bigos, K., Geda, M., Naik, A.	adults with multiple chronic conditions		
18	Wens, J. Vermeire, E. Royen, P. V. Sabbe, B. Denekens, J.	GPs' perspectives of type 2 diabetes patients' adherence to treatment: A qualitative analysis of barriers and solutions	2006	Focused on compliance to treatment and perspectives of HCPs on patients' barriers to compliance.
19	Wollny, A., Pentzek, M., Herber, O. R., Abholz, H. H., In der Schmitten, J., Icks, A., Wilm, S., Gummersbach, E.	General practitioners' attitudes towards patients with poorly controlled type 2 diabetes: a qualitative study	2018	It focuses only on people with poor glycaemic control
20	Zwolsman, S. E., van Dijk, N., de Waard, M. W.,	Observations of evidence-based medicine in general practice	2013	Use of expressions around evidence-based medicine between HCPs and their patients by observation of practices.

Appendix 3 – Quality assessment checklists

3A – Section 1: Quantitative appraisal[7].

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES	THE JOANNA BRIGGS INSTITUTE CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES
A study can be awarded a maximum of one star for each numbered item, except item 5 were two stars can be given. ***Selection*** 1) Representativeness of the exposed cohort a. truly representative of the average people with T2DM in the community * b. somewhat representative of the average people with T2DM in the community * c. selected group of users. d. no description of the derivation of the cohort 2) Selection of the non-exposed cohort a. drawn from the same community as the exposed cohort * b. drawn from a different source c. no description of the derivation of the non-exposed cohort 3) Ascertainment of exposure a. secure record (e.g. surgical records) * b. structured interview * c. written self-report d. no description 4) Demonstration that outcome of interest was not present at start of study a. yes * b. no ***Comparability*** 5) Comparability of cohorts on the basis of the design or analysis a. study controls for HbA1c/age/duration of T2DM * b. study controls for any additional factor * ***Outcome*** 6) Assessment of outcome a. independent blind assessment * b. record linkage * c. self-report d. no description 7) Was follow-up long enough for outcomes to occur a. yes (at least one year) * b. no 8) Adequacy of follow up of cohorts	A study will be awarded maximum one start per question. 1) Were the criteria for inclusion in the sample clearly defined? a. Yes * b. No c. Unclear d. Not applicable * 2) Were the study subjects and the setting described in detail? a. Yes * b. No c. Unclear d. Not applicable * 3) Was the exposure measured in a valid and reliable way? a. Yes * b. No c. Unclear d. Not applicable * 4) Were objective, standard criteria used for measurement of the condition? a. Yes * b. No c. Unclear d. Not applicable * 5) Were confounding factors identified? a. Yes * b. No c. Unclear d. Not applicable * 6) Were strategies to deal with confounding factors stated? a. Yes * b. No c. Unclear d. Not applicable * 7) Were the outcomes measured in a valid and reliable way? a. Yes * b. No c. Unclear d. Not applicable *

[7] WELLS, G., SHEA, B., O'CONNELL, D., PETERSON, J., WELCH, V., LOSOS, M. & TUGWELL, P. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses* [Online]. Available: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Accessed], MOOLA, S., MUNN, Z., TUFANARU, C., AROMATARIS, E., SEARS, K., SFETCU, R., CURRIE, M., QURESHI, R., MATTIS, P., LISY, K. & MU, P.-F. 2017. *Chapter 7: Systematic reviews of etiology and risk* [Online]. The Joanna Briggs Institute. Available: https://joannabriggs.org/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Analytical_Cross_Sectional_Studies2017_0.pdf [Accessed].

a. complete follow up - all subjects accounted for *
b. subjects lost to follow up unlikely to introduce bias *
c. no description of those lost
d. no statement

9 is the maximum number of stars that can be awarded to each article assessed using this scale.

8) Was appropriate statistical analysis used?
a. Yes *
b. No
c. Unclear
d. Not applicable *

8 is the maximum number of stars that can be awarded to each article assessed using this scale.

3B – Section 2: Qualitative appraisal[8].

Section	Question	Answer
A. Are the results valid?	1. Was there a clear statement of the aims of the research?	a. Yes b. No c. Can't tell
	2. Is a qualitative methodology appropriate?	a. Yes b. No c. Can't tell
	3. Was the research design appropriate to address the aims of the research?	a. Yes b. No c. Can't tell
	4. Was the recruitment strategy appropriate to the aims of the research?	a. Yes b. No c. Can't tell
	5. Was the data collected in a way that addressed the research issue?	a. Yes b. No c. Can't tell
	6. Has the relationship between researcher and participants been adequately considered?	a. Yes b. No c. Can't tell
B. What are the results?	7. Have ethical issues been taken into consideration?	a. Yes b. No c. Can't tell
	8. Was the data analysis sufficiently rigorous?	a. Yes b. No c. Can't tell
	9. Is there a clear statement of findings?	a. Yes b. No c. Can't tell
C. Will the results help locally	10. Is there a discussion of the contribution to existing knowledge or understanding? Identify new areas where research is necessary? Discussion if whether or how findings can be transferred to other populations or a consideration of other ways the research may be used?	a. Yes b. No c. Can't tell

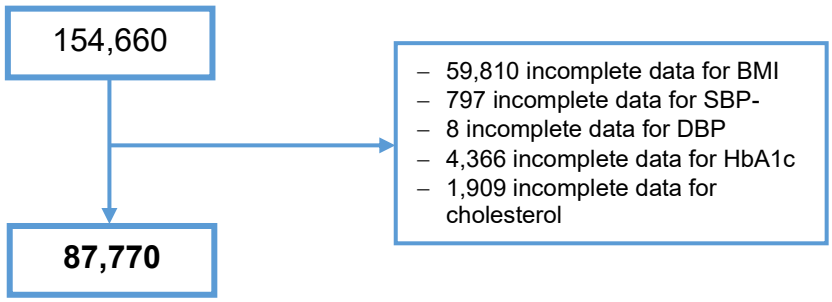
[8] CRITICAL APPRAISAL SKILLS PROGRAMME 2018. CASP Qualitative Research Checklist.

Appendix 4 – Complete case analysis

Results of the complete case analysis

The CCA dataset was built with information for people with T2DM who had complete data available for the variables of interest, which were BMI, SBP, DBP, HbA1c, and cholesterol. After the exclusion of patients who did not have complete data on the variables of interest, the CCA resulted in a dataset including 87,770 patients; people with more than one variable missing were excluded. Thus 66,890 cases were excluded (43.3%). Figure 12 presents in detail, the process followed to build the CCA dataset.

Figure 12. Flow chart of selection of participants.



Complete cases vs incomplete cases

In table 36 the baseline characteristics for patients with complete data and those with incomplete data are described; the latter group is the one that was used for the CCA. As can be seen from the table, patients included in the CCA dataset were significantly older with a mean age of 61.3 years compared to a mean of 60.6 years for patients with incomplete data. Additionally, distributions of patients' sex, ethnicity and SIMD were statistically significantly different between groups. The differences between the complete and incomplete cases suggest that results from the CCA dataset and the imputed dataset might differ even though absolute differences are small.

Table 36. Baseline characteristics for patients with complete and incomplete data

Variable			Complete Data (87,770)	Incomplete Data (66,890)	P values
Age, years (mean ± SD)			61.3 ± 12.2	60.6 ± 12.9	<0.0001
Gender, male (%, n)			56.5 (49,589)	55.1 (36,832)	<0.0001
Ethnicity (%, n)	**White Scottish/British**		71.0 (62,341)	69.2 (46,261)	<0.0001
	Other/unknown		29.0 (25,429)	30.8 (20,629)	
SIMD quintiles (%, n)	**Most deprived**	**1**	23.9 (20,982)	24.7 (16,513)	<0.0001
		2	23.2 (20,328)	22.9 (15,288)	
		3	19.9 (17,506)	20.2 (13,484)	
		4	17.9 (15,703)	18.5 (12,374)	
	Least deprived	**5**	15.1 (13,251)	13.8 (9,231)	

Characteristics of the population

Having presented the differences between the CCA dataset and the incomplete cases, I will move on to compare the characteristics of the CCA dataset with the imputed dataset. It can be seen from the data in table 37 that both datasets were comprised of a majority of males and that the average age was about 61 years of age. Furthermore, other demographic characteristics such as ethnicity and SIMD showed similar proportions for both datasets. The majority of the people were identified as white Scottish/British, 71.0% (62,341), and 70.2% (108,602) for the CCA dataset and the imputed dataset, respectively. In relation to SIMD quintiles, both datasets presented decreasing proportions of people in each quintile. Hence, the majority of the population were in the most deprived quintiles.

Table 37. Comparison of baseline characteristics of people in the CCA dataset and the Imputed Dataset

Variable		CCA Dataset (n= 87,770)	Imputed Dataset (n = 154,660)
Age, years (mean ± SD)		61.3 ± 12.2	61.0 ± 12.5
Age ranges, %	**30 – 44**	10.0	11.2
	45 – 59	41.3	34.9
	60 – 74	34.7	39.8
	≥75	14.0	14.1

Gender, male (%, n)			56.5 (49,589)	55.9 (86,421)
Ethnicity (%, n)	**White Scottish/British**		71.0 (62,341)	70.2 (108,602)
	Other/unknown		29.0 (25,429)	29.8 (46,058)
SIMD quintiles (%, n)	**Most deprived**	**1**	23.9 (20,982)	24.2 (37,495)
		2	23.2 (20,328)	23.0 (35,616)
		3	19.9 (17,506)	20.0 (30,990)
		4	17.9 (15,703)	18.2 (28,077)
	Least deprived	**5**	15.1 (13,251)	14.5 (22,482)

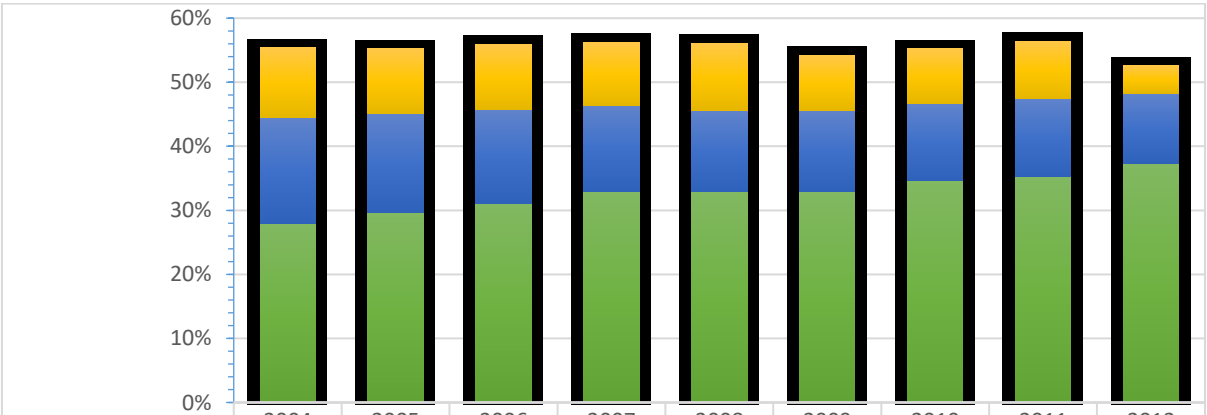
Proportions of people with T2DM with and without GLM prescription and their characteristics

Differences by year of diagnosis

As shown in figure 13, from 2004 to 2012, more than half of the patients received a GLM prescription within two years from the diagnosis of T2DM. Proportions of people who received a prescription ranged from 52.6% in 2012 to 56.4% in 2011.

The majority of the patients who received treatment within 24 months after diagnosis had received GLM by 12 months after diagnosis. Proportions of people receiving GLM prescription within the three first months after T2DM diagnosis increased by index year from 28% in 2004 to 37.3% in 2012). In contrast, a lower proportion of patients were prescribed their first drug within 12 to 24 months after diagnosis.

Figure 13. Proportions of patients in the CCA dataset cohort who received drug treatment, stratified by period of prescription.



	2004	2005	2006	2007	2008	2009	2010	2011	2012
12 to 24 months	10.9%	10.1%	10.2%	9.8%	10.5%	8.6%	8.5%	8.9%	4.3%
3 to 12 months	16.5%	15.5%	14.6%	13.4%	12.6%	12.6%	12.1%	12.2%	11.0%
0 to 3 months	28.0%	29.6%	31.1%	33.0%	33.0%	33.0%	34.6%	35.3%	37.3%

Baseline characteristics of people with T2DM who received GLM prescription vs people with T2DM who did not.

As observed in table 38, GLM-2Y (59.1 years) patients were significantly younger than NM-2Y (64.1 years). Overall, distributions of demographic characteristics such as SIMD significantly differed, a higher proportion of GLM-2Y patients were from the most deprived quintiles.

Mean BMI was significantly higher for the GLM-2Y group than for the NM-2Y. Similarly, GLM-2Y had significantly higher mean HbA1c and mean cholesterol than NM-2Y. Similar results were found when stratified by BMI and HbA1c categories. As shown in table 38, 62.2% GLM-2Y had a BMI ≥30 Kg/m2, and 77.6% had an HbA1c ≥ 53 mmol/mol. Likewise, a higher proportion of GLM-2Y had cholesterol levels > 5 mmol/L. Moreover, GLM-2Y had a significant lower prevalence of pre-existing CVD. Similarly, proportions of people who were actively receiving lipid-lowering and antihypertensive medication were significantly lower among GLM-2Y than NM-2Y.

Table 38. Characteristics of patients in the CCA dataset classified whether they received pharmacological treatment by two years after diagnosis

Variable			Received medication prescription		P values
			Yes (48,468)	No (39,302)	
Age, years (mean ± SD)			59.1 ± 12.1	64.1 ± 11.7	< 0.0001
Gender, male (%, n)			58.0 (28,132)	54.6 (21,457)	< 0.0001
Ethnicity (%, n)	**White Scottish/British**		71.8 (34,790)	70.1 (27,551)	< 0.0001
	Other/Unknown		28.2 (13,678)	29.9 (11,751)	
SIMD quintiles (%, n)	**Most deprived**	**1**	25.7 (12,467)	21.7 (8,515)	< 0.0001
		2	24.3 (11,755)	21.8 (8,573)	
		3	19.9 (9,635)	20.0 (7,871)	
		4	16.8 (8,140)	19.2 (7,563)	
	Least deprived	**5**	13.4 (6,471)	17.3 (6,780)	
BMI	Mean Kg/m2 ± SD		32.7 ± 6.5	31.5 ± 6.0	< 0.0001
	≥ 30 Kg/m2 (%, n)		62.2 (30,139)	55.6 (21,845)	< 0.0001
Systolic Blood Pressure	Mean mmHg ± SD		137.4 ± 14.6	138.5 ± 14.4	< 0.0001
	≥ 130 mmHg (%, n)		68.1 (33,013)	71.6 (28,147)	< 0.0001
Diastolic Blood Pressure	Mean mmHg ± SD		80.6 ± 8.7	79.3 ± 8.6	< 0.0001
	> 80 mmHg (%, n)		49.5 (23,990)	43.9 (17,247)	< 0.0001
HbA1c	Mean mmol/mol ± SD		68.3 ± 18.4	48.6 ± 9.3	< 0.0001
	≥ 53 mmol/mol(%, n)		77.6 (37,624)	19.6 (7,693)	< 0.0001
Cholesterol	Mean mmol/L ± SD		5.0 ± 1.1	4.8 ± 1.0	< 0.0001
	> 5 mmol/L (%, n)		46.6 (22,566)	40.3 (15,836)	< 0.0001

Pre-existing CVD (%, n)	17.5 (8,496)	22.5 (8,842)	< 0.0001
Receiving lipid-lowering medication (%, n)	32.5 (15,761)	43.0 (16,890)	< 0.0001
Receiving antihypertensive medication (%, n)	50.7 (24,578)	66.2 (26,031)	< 0.0001

Analysis by age groups

Overall, in table 39 shows a negative association with between BMI. Thus, people between 30 to 44 years of age had the highest mean BMI, and those of 75 years of age and older had the lowest mean BMI. Similar results were found for baseline HbA1c and cholesterol. Conversely, a positive relationship was observed between age and mean SBP, prevalence of pre-existing CVD and proportions on lipid-lowering medication and anti-hypertensive medication.

For the 30-44 years old group, table 39 shows that although mean BMI was not significantly different by treatment group, the proportion of obese people (BMI ≥ 30 Kg/m2) was significantly higher for NM-2Y. Concerning HbA1c, mean levels and proportion of people with HbA1c ≥ 53 mmol/mol were higher among GLM-2Y.

Among people of 45 to 59 years the GLM-2Y group had higher mean BMI and also a higher proportion of people in the obese category. Moreover, mean HbA1c and the proportion of people with HbA1c ≥ 53 mmol/mol were higher GLM-2Y. In contrast GLM-2Y had lower mean SBP, lower proportions pre-existing CVD, receiving lipid-lowering medication and anti-hypertensive medication.

For the 60 to 74 years old group, GLM-2Y patients had significantly higher mean BMI, mean HbA1c, mean DBP, and mean cholesterol. The GLM-2Y group also had a significantly lower proportion of pre-existing CVD and also lower proportions of people receiving lipid-lowering medication and anti-hypertensive medication.

Among people ≥ 75 years, GLM-2Y patients had significantly higher mean BMI, mean HbA1c, mean DBP, and mean cholesterol.. Conversely, GLM-2Y included a significantly lower proportion with pre-existing CVD and proportions of people receiving lipid-lowering medication and anti-hypertensive medication.

Table 39. Characteristics of people with T2DM from the CCA, stratified by age groups

Variable		All N= 87,770	Age groups (years)											
			30 to 44 n=8,809			45 to 49 n=30,433			60 to 74 n=36,235			≥75 n=12,293		
			Yes (16,408)	No (2,401)	p-value	Yes (18,966)	No (11,467)	p-value	Yes (18,155)	No (18,080)	p-value	Yes (4,939)	No (7,354)	p-value
Gender, male (%, n)		56.5 (49,589)	64.0 (4,104)	59.2 (1,422)	<0.0001	61.0 (11,577)	59.6 (6,835)	0.013	56.0 (10,172)	55.1 (9,971)	0.092	46.1 (2,279)	43.9 (3,229)	0.015
BMI	Mean Kg/m^2 (±SD)	32.2 (6.3)	34.9 (7.4)	35.2 (7.3)	0.054	33.8 (6.6)	33.4 (6.3)	<0.0001	31.6 (5.7)	31.0 (5.4)	<0.0001	29.1 (4.9)	28.6 (4.8)	<0.0001
	≥30 Kg/m^2, % (n)	59.2 (51,984)	73.5 (4,711)	79.5 (1,822)	0.024	69.8 (13,238)	68.5 (7,855)	0.017	57.0 (10,357)	53.5 (9,664)	<0.0001	37.1 (1,833)	34.0 (2,504)	<0.0001
HbA1c	Mean mmol/mol (±SD)	59.5 (17.9)	70.7 (18.8)	51.4 (12.7)	<0.0001	69.2 (18.5)	49.3 (10.3)	<0.0001	66.9 (18.2)	48.0 (8.4)	<0.0001	66.6 (18.0)	47.9 (7.9)	<0.0001
	≥53 mmol/mol, % (n)	51.6 (45,317)	80.7 (5,170)	29.8 (715)	<0.0001	79.0 (14,978)	22.1 (2,532)	<0.0001	75.4 (13,695)	17.4 (3,140)	<0.0001	76.6 (3,781)	17.8 (1,306)	<0.0001
SBP	Mean mmHg (±SD)	137.9 (14.5)	132.7 (13.8)	133.2 (13.8)	0.082	136.7 (14.4)	137.4 (14.3)	<0.0001	139.0 (14.5)	139.3 (14.2)	0.069	139.8 (14.8)	139.8 (14.8)	0.934
	≥130 mmHg, % (n)	69.7 (61,160)	54.9 (3,516)	56.2 (1,349)	0.269	66.2 (12,564)	68.7 (7,874)	<0.0001	73.1 (13,269)	74.3 (13,425)	0.012	74.2 (3,664)	74.8 (5,499)	0.461
DBP	Mean mmHg (±SD)	80.0 (8.7)	83.0 (9.0)	83.4 (8.9)	0.038	62.7 (8.5)	82.7 (8.3)	0.708	78.9 (7.9)	78.4 (7.9)	<0.0001	75.6 (1.1)	74.9 (7.9)	<0.0001
	>80 mmHg, % (n)	47.0 (41,237)	60.4 (3,872)	61.4 (1,474)	0.408	59.8 (11,339	60.4 (6,924)	0.304	41.3 (7,493)	39.3 (7,114)	<0.0001	26.0 (1,286)	23.6 (1,735)	0.002

Table 3*9* (continued) Characteristics of people with T2DM from the CCA, stratified by age groups

Variable		All N= 87,770	Age groups (years)											
			30 to 44 n=8,809			45 to 49 n=30,433			60 to 74 n=36,235			≥75 n=12,293		
			Yes (16,408)	No (2,401)	p-value	Yes (18,966)	No (11,467)	p-value	Yes (18,155)	No (18,080)	p-value	Yes (4,939)	No (7,354)	p-value
Cholesterol	Mean mmol/L (±SD)	4.9 (1.1)	5.3 (1.2)	5.2 (1.0)	<0.0001	5.2 (1.1)	5.1 (1.0)	<0.0001	4.9 (1.1)	4.8 (1.0)	<0.0001	4.7 (1.1)	4.6 (1.0)	0.001
	>5 mmol/L, % (n)	43.8 (38,402)	57.0 (3,650)	54.7 (1,313)	0.055	53.4 (10,137)	51.1 (5,863)	<0.0001	39.4 (7,154)	35.5 (6,410)	<0.0001	32.9 (1,625)	30.6 (2,250)	0.007
Pre-existing CVD (%, n)		19.8 (17,338)	3.3 (213)	3.4 (82)	0.832	12.4 (2,345)	13.1 (1,507)	0.048	23.8 (4,324)	26.2 (4,734)	<0.0001	32.7 (1,614)	34.3 (2,519)	0.070
Receiving lipid-lowering medication (%, n)		37.2 (32,651)	10.5 (672)	11.5 (277)	0.157	27.0 (5,123)	31.5 (3,608)	<0.0001	42.6 (7,738)	51.0 (9,228)	<0.0001	45.1 (2,228)	51.4 (3,777)	<0.0001
Receiving antihypertensive medication (%, n)		57.7 (50,609)	20.5 (1,314)	27.1 (651)	<0.0001	43.3 (8,211)	54.1 (6,504)	<0.0001	63.1 (11,451)	73.1 (13,215)	<0.0001	72.9 (3,602	81.1 (5,961)	<0.0001

Glycaemic control and GLM prescription initiation

Baseline HbA1c by age groups

Overall, it can be seen that people from the CCA dataset displayed a mean HbA1c of 59.5 mmol/mol, which was slightly lower than the one for the imputed dataset. Furthermore, the table shows that, the 30 to 44 years and 45 to 59 years-age groups presented a higher mean HbA1c than people from the 60 to 74 years and ≥ 75 years age groups.

Table 40. HbA1c closest to diagnosis, stratified by age groups

Age groups	All N= 87,770	30 to 44 n= 8,809	45 to 59 n= 30,433	60 to 74 n= 36,235	≥ 75 n= 12,293
Mean (SD), mmol/mol	59.5 (18.0)	65.5 (19.4)	61.7 (18.6)	57.5 (17.0)	55.5 (15.9)
Median (IQR), mmol/mol	54 (46.5–68.5)	62 (50.3–78)	56.5 (48–73)	52 (46–64.5)	51 (45–60.7)

Differences between people with optimal and sub-optimal HbA1c

As shown in table 41, people with sub-optimal HbA1c consisted of 59.3% (26,878) men. Overall, there was a larger proportion of white Scottish/British and people from the most deprived SIMD quintiles than among people in the optimal HbA1c group. However, ethnicity proportions were not different from people with optimal and sub-optimal HbA1c. Moreover, people with sub-optimal HbA1c were significantly younger than those with optimal HbA1c, mean age of 59.4 years and 63.4 years, respectively.

Furthermore, people with sub-optimal HbA1c Had significantly higher mean BMI and proportion with BMI >=30kg/m2 than people with optimal HbA1c. Likewise, mean cholesterol and mean DBP were higher for people with sub-optimal HbA1c. In contrast, people with optimal HbA1c had a significantly larger proportions of people with SBP ≥ 130 mmHg, pre-existing CVD, people receiving lipid-lowering medication, and people receiving anti-hypertensive medication. Similar results were found in the analysis of the imputed dataset.

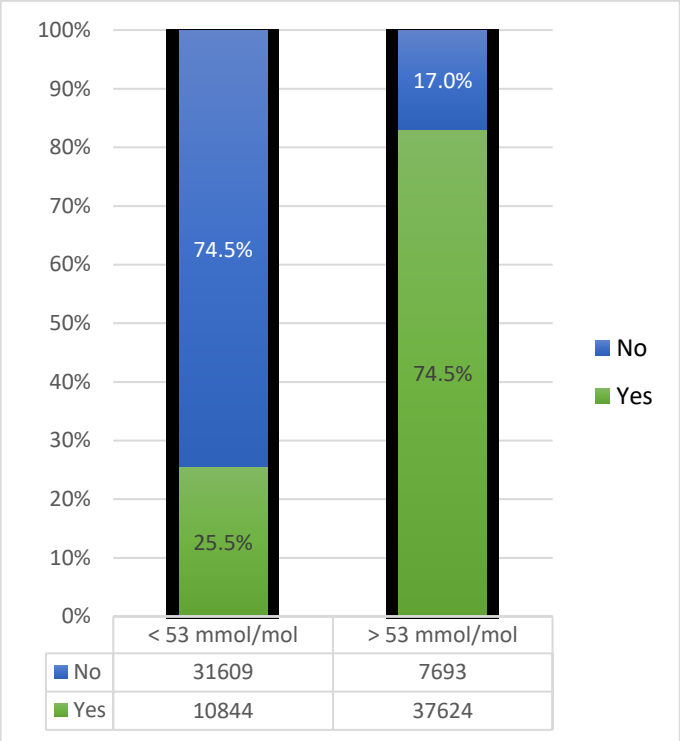
Table 41. Characteristics of people with recently diagnosed T2DM stratified by baseline optimal and sub-optimal HbA1c levels

Variable			Sub-optimal HbA1c		P values
			Yes (45,317)	No (42,453)	
Age, years (mean ± SD)			59.4 (12.2)	63.4 (11.7)	<0.0001
Gender, male (%, n)			59.3 (26,878)	53.5 (22,711)	<0.0001
Ethnicity, White Scottish/British (%, n)			71.0 (32,170)	71.1 (30,171	0.739
SIMD (%, n)	Most deprived	1	24.9 (11,292)	22.8 (9,690)	<0.0001
		2	24.0 (10,895)	22.2 (9,433)	
		3	19.7 (8,930)	20.2 (8,576)	
		4	17.2 (7,809)	18.6 (7,894)	
	Least deprived	5	14.1 (6,391)	16.2 (6,860)	
BMI	Mean Kg/m2 ± SD		32.4 (6.3)	31.9 (6.2)	<0.0001
	≥ 30 Kg/m2 (%, n)		60.5 (27,406)	57.9 (24,578)	<0.0001
Systolic Blood Pressure	Mean mmHg ± SD		137.8 (14.8)	137.9 (14.2)	0.256
	≥ 130 mmHg (%, n)		69.0 (31,249)	70.5 (29,911)	<0.0001
Diastolic Blood Pressure	Mean mmHg ± SD		80.7 (8.7)	79.3 (8.5)	<0.0001
	> 80 mmHg (%, n)		50.1 (22,686)	43.7 (18,551)	<0.0001
Cholesterol	Mean mmol/L ± SD		5.1 (1.1)	4.8 (1.0)	<0.0001
	> 5 mmol/L (%, n)		47.9 (21,706)	39.3 (16,696)	<0.0001
Pre-existing CVD (%, n)			16.8 (7,594)	23.0 (9,744)	<0.0001
Receiving lipid-lowering medication (%, n)			30.4 (13,767)	44.5 (18,884)	<0.0001
Receiving antihypertensive medication (%, n)			48.8 (22,099)	67.2 (28,510)	<0.0001

GLM prescription among people with optimal and sub-optimal HbA1c

Approximately one-third of people (25.5%) with optimal HbA1c received medication prescription by two years after diagnosis. Conversely, for those with sub-optimal HbA1c, the majority in the CCA dataset (74.5%) received a pharmacological prescription for glucose control within two years after T2DM diagnosis.

Figure 14. Proportions of people with T2DM in the CCA, with optimal and sub-optimal HbA1c with and without prescription for pharmacological treatment within 2 years of diagnosis of diabetes.

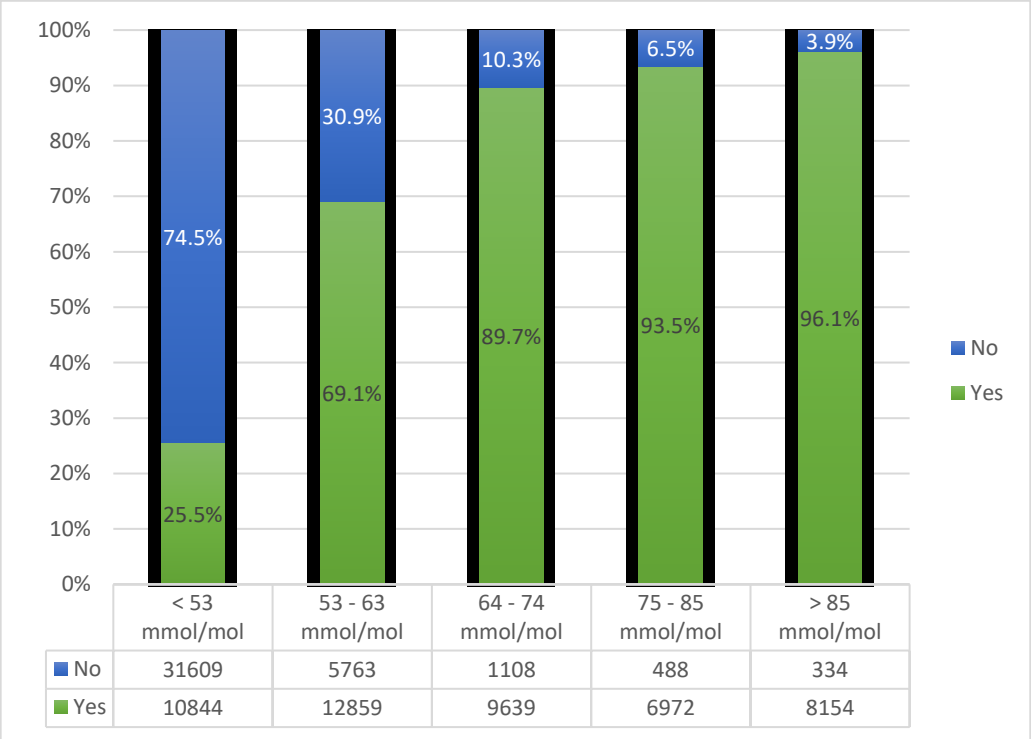


Proportions of people who received and did not receive GLM prescription stratified by different ranges of sub-optimal HbA1c

Figure 15 below illustrates the breakdown of people with and without GLM prescription stratified by different groups of sub-optimal HbA1c. In general, the majority of people with HbA1c ≥ 53 mmol/mol received medication prescription, ranging from 69.1% (12,859) for those with an HbA1c of 53 – 63 mmol/mol to 96.1% (8,154) for the people with an HbA1c > 85 mmol/mol.

In the figure, it can be observed a clear trend of decreasing proportions of people without medication prescription. Thus, the higher the HbA1c group, the larger the proportion of people who received GLM prescription by two years after diagnosis. Overall, proportions were similar to the ones found for the imputed dataset.

Figure 15. Proportions of people with T2DM in the CCA dataset with optimal and sub-optimal HbA1c with and without pharmacological treatment, stratified by ranges of sub-optimal HbA1c



Sub-optimal HbA1c by age groups

Table 42 shows that across all age groups there was a decreasing trend of people without medication prescription the higher HbA1c, which is in accordance to data previously shown in figure 15. It is also shown that the 30 to 44 years group had a high proportion of people with HbA1c >63 mmol/mol. Conversely, people ≥75 years had the lowest proportions of people with HbA1c in the highest categories.

Table 42. Proportions of patients in the CCA with sub-optimal glucose control who did not receive pharmacological treatment by two years after diagnosis, stratified by age groups and HbA1c sub-optimal ranges.

Variable	All	Age group (years)			
	N= 7,693	30 to 44 n= 715	45 to 59 n= 2,532	60 to 74 n= 3,140	≥ 75 n= 1,306
53 – 63 mmol/mol (%, n)	74.9 (5,763)	58.6 (419)	67.9 (1,719)	80.0 (2,511)	85.3 (1,114)
64 – 74 mmol/mol (%, n)	14.4 (1,108)	21.4 (153)	17.6 (445)	12.1 (381)	9.9 (129)
75 – 85 mmol/mol (%, n)	6.3 (488)	11.2 (80)	8.6 (219)	4.9 (153)	2.8 (36)
> 85 mmol/mol (%, n)	4.3 (334)	8.8 (63)	5.9 (149)	3.0 (95)	2.1 (27)

Time to GLM prescription

Time to GLM initiation by age group

Kaplan Meier

The results of the Kaplan-Meier survival analysis are presented in figure 16. For the CCA dataset cohort, 32.9%, 46.2%, and 55.2% of the cohort initiated drug treatment within 30 days, 1 year, and 2 years of diagnosis, respectively. Furthermore, figure 16 shows that the proportion of patients who had received drug treatment for T2DM within two years of diagnosis decreased with increasing age, proportions of people who received GLM prescription by two years after diagnosis were 72.7%, 62.3%, 50.1%, and 40.2% for patients in the 30 to 44, 45 to 59, 60 to 74, and ≥ 75 age groups, respectively (p<0.0001).

Figure 16. Kaplan-Meier curves for the CCA for time to glucose-lowering treatment initiation after diagnosis of T2DM by age group

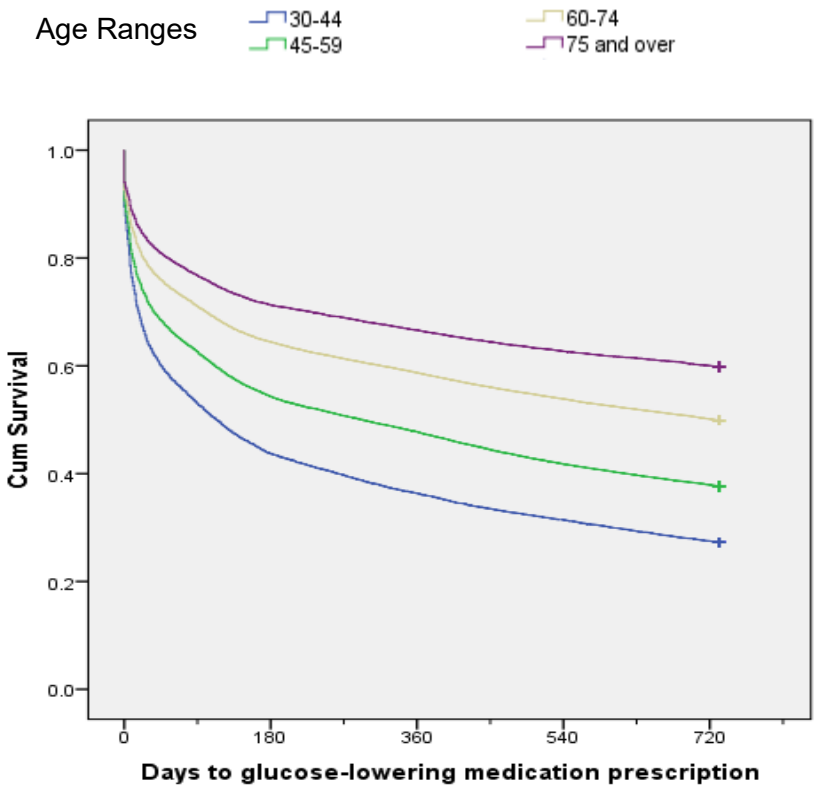


Table 43 below presents the comparison of proportions of people who received GLM prescription by two years after the diagnosis of T2DM and the median time to pharmacological prescription (25th, 75th percentile). Results are presented before and

after stratifying by age groups. Overall, mean and median days were higher for the older age group and lower for the youngest group.

Table 43. Time to pharmacological treatment initiation by age group among patients over 30 years of age in Scotland 2004-2013 with complete data available who started drug treatment within two years after diagnosis

Variable	All N= 87,770	Age group (years)			
		30 to 44 n= 8,809	45 to 59 n=30,433	60 to 74 n=36,235	≥ 75 n= 12,293
Patients with drug treatment within 2 years after diagnosis, n (%)	48,468 (55.2%)	6,408 (72.7%)	18,966 (62.3%)	18,155 (50.1%)	4,939 (40.2%)
Median days to time to treatment initiation (IQR)	46 (7 – 210)	31 (6 – 159)	43 (7 – 201.2)	53 (7 – 233)	55 (7 – 235)
Mean days to time to treatment initiation	143.3	121.8	140.7	151.9	149.7

Factors associated with time to drug treatment initiation

In this section, the results of the Cox regression analysis, the univariate and the four adjusted models are presented. As explained in the results section, the first column *"Univariate model"* indicates the results from the one variable to the left side of the table. The following column *"Adjusted model 1"* presents the results the model adjusted by demographic characteristics of the patients, variables included in the model were age, sex, ethnicity, and SIMD. Next, the column *"Adjusted model 2"* provides the results from the model, which adjusted for the demographic characteristics included in the previous model plus baseline HbA1c. Then, the column *"Adjusted model 3*" presents results from the model included the ones in model 2 plus other metabolic factors such as BMI, SBP, DBP, cholesterol and pre-existing CVD. Finally, the last column *"Adjusted model 4"* provides the results of the model, including demographics, HbA1c, BMI, pre-existing CVD and the use of other drugs such as lipid-lowering medication and antihypertensive medication.

CCA dataset: Hazard ratios for GLM prescription

Table 44 provides the results obtained from the Cox regression analysis. In general, increased age was associated with longer time to drug treatment initiation. Moreover, HbA1c ≥53 mmol/mol was associated with shorter time to drug prescription.

The adjusted model 1 shows an association between increased age and longer time to medication prescription. Likewise, being female compared to male, identified as having other/unknown ethnicity compared to white ethnicity and from the least compared to the most deprived SIMD quintiles were associated with longer time to medication prescription. In the adjusted model 2, where HbA1c was taken into account, age, other/unknown ethnicity and the least deprived SIMD quintiles were associated with increased prescription time. However, being female compared to male and having HbA1c ≥53 vs <53 mmol/mol were associated with shorter times to treatment.

Furthermore, in the fully adjusted models 3 and 4, it can be seen that from the demographic factors, increased age, other/unknown ethnicity, and the least deprived SIMD quintiles were associated with longer time to GLM prescription. Moreover, HbA1c ≥53 mmol/mol was associated with shorter times to pharmacological prescription. However, no significant association was found for BMI ≥30 Kg/m2.

In relation to other metabolic factors, model 3 indicates that raised blood pressure; SBP ≥130 mmHg and DBP >80 mmHg; was associated with longer time to drug treatment prescription. Likewise, cholesterol >5 mmol/L and pre-existing CVD were associated with longer time to GLM prescription. Moreover, the adjusted model 4 shows that receiving antihypertensive medication was associated with longer time to medication prescription. However, receiving lipid-lowering medication was associated with shorter times to medication prescription.

Table 44. Hazard ratios for time to initiation of glucose-lowering medication for people with T2DM in the CCA dataset

Variable		Univariate model		Adjusted model 1		Adjusted model 2		Adjusted model 3		Adjusted model 4	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age at diagnosis		0.98 (0.98-0.98)	<0.0001	0.98 (0.98-0.98)	<0.0001	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001
Sex	Male	1.00	<0.0001	1.00	<0.0001	1.00	0.001	1.00	0.001	1.00	<0.0001
	Female	0.91 (0.89-0.92)		0.95 (0.93-0.97)		1.03 (1.01-1.05)		1.03 (1.01-1.05)		1.04 (1.02-1.06)	
Ethnicity	Scottish/British	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001	1.00	<0.0001
	other/unknown	0.99 (0.99-0.99)		0.96 (0.94-0.98)		0.94 (0.92-0.96)		0.94 (0.92-0.96)		0.94 (0.92-0.96)	
SIMD	Most deprived 1	1.00		1.00		1.00		1.00		1.00	
	2	0.97 (0.94-0.99)	0.005	0.99 (0.97-1.02)	0.634	0.99 (0.96-1.01)	0.324	0.99 (0.97-1.02)	0.404	0.99 (0.97-1.02)	0.332
	3	0.89 (0.87-0.91)	<0.0001	0.93 (0.90-0.95)	<0.0001	0.94 (0.91-0.96)	<0.0001	0.94 (0.92-0.97)	<0.0001	0.94 (0.91-0.96)	<0.0001
	4	0.81 (0.79-0.84)	<0.0001	0.85 (0.83-0.88)	<0.0001	0.87 (0.85-0.90)	<0.0001	0.88 (0.85-0.90)	<0.0001	0.87 (0.85-0.90)	<0.0001
	Least deprived 5	0.75 (0.72-0.77)	<0.0001	0.79 (0.77-0.81)	<0.0001	0.82 (0.80-0.85)	<0.0001	0.83 (0.80-0.85)	<0.0001	0.82 (0.80-0.85)	<0.0001
HbA1c	<53mmol/mol	1.00	<0.0001			1.00	<0.0001	1.00	<0.0001	1.00	<0.0001
	≥53 mmol/mol	6.01 (5.88-6.14)				5.70 (5.58-5.83)		5.72 (5.60-5.85)		5.65 (5.53-5.78)	
BMI	<30 Kg/m^2	1.00	<0.0001					1.00	0.290	1.00	0.156
	≥30 Kg/m^2	1.17 (1.15-1.19)						1.01 (0.99-1.03)		1.01 (0.99-1.03)	
SBP	<130 mmHg	1.00	<0.0001					1.00	<0.0001		
	≥130 mmHg	0.88 (0.86-0.89)						0.93 (0.91-0.95)			
DBP	≤80 mmHg	1.00	<0.0001					1.00	0.048		
	>80 mmHg	1.15 (1.13-1.17)						0.98 (0.96-0.99)			
Cholesterol	≤5mmol/L	1.00	<0.0001					1.00	0.001		
	>5mmol/L	1.17 (1.15-1.19)						0.97 (0.95-0.99)			
CVD	No	1.00	<0.0001					1.00	0.013	1.00	0.793
	Yes	0.79 (0.77-0.81)						0.97 (0.95-0.99)		1.01 (0.98-1.03)	
Lipid-lowering medication	No	1.00	<0.0001							1.00	0.008
	Yes	0.73 (0.72-0.75)								1.03 (1.01-1.06)	
Antihypertensive medication	No	1.00	<0.0001							1.00	<0.0001
	Yes	0.64 (0.63-0.65)								0.90 (0.89-0.92)	

Variables included in each model: ***Model 1*:** sex, ethnicity, and SIMD. ***Model 2:*** age at diagnosis, sex, ethnicity, SIMD, and HbA1c. ***Model 3:*** age at diagnosis, sex, ethnicity, SIMD, HbA1c, BMI, SBP, DBP, cholesterol and CVD. ***Model 4****:* age at diagnosis, sex, ethnicity, SIMD, HbA1c, BMI, CVD, receiving lipid-lowering medication and receiving antihypertensive medication

Appendix 5 – Interview topic guide

Introduction

- Thank participant and explain the PhD study
- Remind them that their participation is voluntary
- Ask if there is any question and inform about the consent form.

Topic guide

1. I would like to start by asking you about your practice. Could you tell me more about your work please?
    - Compared to other practices in the area, how big is this practice?
    - What kind of area is the practice in?
    - What kind of patients does the practice serve?
        - Are there a lot of people from ethnic minority groups?
    - How the practice has change in the last years?
    - How is the practice structured? How many GPs and nurses work in the practice?
    - How is the workload divided within the healthcare team?
    - How is diabetes care organised in the practice? Is there anyone else responsible for care of people with diabetes? How do you divide the workload?
2. I would like to know more about you role in the practice. Could you tell me a little bit about yourself and your role in your practice?
    - What is your job title?
    - How long have you been practising? Do you usually get to see the same patients?
    - How long have you been working in this practice?
    - How long have you been working in this position?
3. How, and when, did managing people with diabetes become part of your role?

- Do you feel you have received appropriate training for the role? Do you have the opportunity to keep up to date? If so, how do you do this?
- How hard/easy is to keep updated with new policies/guidelines?

4. What is a typical patient pathway when a patient is diagnosed with type 2 diabetes?
   - Is it possible for all or some newly diagnosed patients to be referred to a structured diabetes education course? Where? What sort of education? Who is in charge of this? Are there any alternatives – for example can you refer people to a dietician?
   - How long does it take to be seen?
   - What happens if the patient is not motivated or is reluctant to go? Are they put on medications?
   - Does education affect their motivation? How useful have you found this programme/course? What patients say about this programme/course? Do they find it useful?
   - Do you think it is possible to predict who will do well using lifestyle/dietary management? What makes you decide how long to let people attempt lifestyle change. How patient's motivation is assessed?
   - How frequently do you review patients? In the first year after the diagnosis of diabetes in your practice?
   - How frequently do you review people in terms of their diabetes in the second and subsequent years after a diagnosis of diabetes?
   - Does it help to reduce hba1c if the patient is motivated?
5. How do you decide when is appropriate or necessary to prescribe pharmacological treatment for glucose control?
   - What kinds of factors and considerations influence your decision? Can you talk me through some examples?
     - Is patient's age important? Is patient's history of weight management important?
     - Are there differences between genders?

- How much are patients usually involved in the decisions about when to initiate pharmacological treatment? How continuity of care is related to these decisions?
- The side effects of the medications are usually discussed with the patient?
- What kind of patients tend to be reluctant or resistant to starting pharmacological treatment? What kind of patients tend to push for pharmacological treatment?
- What medications, other than for glucose control, are typically provided to newly diagnosed patients? What are the most common types of treatment?
- Are there any reasons about why your decisions about when to initiate pharma treatment might have changed over time?
- Do you think you manage patients differently?

6. Does the guidelines and targets influence your practice?
   - Have past and present guidelines been useful?
   - Is there anything that can be done different to better help and enable support for people with T2DM?
   - Do you think the decommissioning of QOF has had any impact on the treatment and care given to patients with T2DM? In particular do you think it might affect decisions about when to initiate treatment
7. Is there anything else you would like to talk about today which would help us to understand when and why people with T2DM in your practice are prescribed pharmacological treatment?

Thank participant for their time. Explain dissemination activities and how and when they can access the findings from the study. Ask participants if they can pass on an invitation pack to potentially interested colleagues and explain processes for doing so.