

Individualisation of HbA1c targets and treatment strategies in people with diabetes: Real-world observational studies

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Candidate statement

I confirm that the work described here is my own with the following exceptions:

Prof Iskandar Idris, Dr Yana Vinogradova and Dr Jason Gordon designed the basic methodologies and submitted ethical approval and data access requests for both the HbA1c individualisation and electronic frailty index studies; some of the methods used for these were subsequently adapted and finalised by myself during my thesis.

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Prizes, publications, presentations and impact on national policy

Prizes

Association of British Clinical Diabetologists' Rising Star Lecture, Edinburgh, 2023 – awarded for my work on the Association of British of Clinical Diabetologists' audits.

Quality in Care Diabetes Judges Special Award 2023 for the Association of British Clinical Diabetologists' audit of the NHS England Closed-Loop pilot.

Publications

The following were published in peer reviewed journals during my time as a research fellow. I have highlighted those publications included as part of this thesis in **bold.**

1. Crabtree, T.S.J., et al., Flash glucose monitoring: the story so far and the journey ahead. BMJ Innovations, 2023. 9(1): p. 27.

2. **Crabtree, T.S.J., et al., Hybrid Closed-Loop Therapy in Adults with Type 1 Diabetes and Above-Target HbA1c: A Real-world Observational Study. Diabetes Care, 2023. 46(10): p. 1831-1838.**

3. Crabtree, T., et al., The factors predicting glucose and weight response to injectable semaglutide (Ozempic): real-world data from the Association of British Clinical Diabetologists' audit programme. British Journal of Diabetes, 2023. 23(2): p. 94-100.

4. Speight, J., et al., Impact of glycaemic technologies on quality of life and related outcomes in adults with type 1 diabetes: a narrative review. Diabetic Medicine, 2023. 40(1): p. e14944.

5. Aldafas, R., et al., Efficacy and safety of intensive versus conventional glucose targets in people with type 2 diabetes: a systematic review and meta-analysis. Expert Review of Endocrinology & Metabolism, 2023. 18(1): p. 95-110.

6. Griffin, T.P., et al., UK's Association of British Clinical Diabetologist's Diabetes Technology Network (ABCD-DTN): Best practice guide for hybrid closed-loop therapy. Diabetic Medicine, 2023: p. e15078.

7. Patel, R., et al., Safety and effectiveness of do-it-yourself artificial pancreas system compared with continuous subcutaneous insulin infusions in combination with free style libre in people with type 1 diabetes. Diabetic Medicine, 2022. 39(5): p. e14793.

8. Sathyanarayanan, A., et al., Delivering evidence-based interventions for type 1 diabetes in the virtual world–A review of UK practice during the SARS-CoV-2 pandemic. Diabetes Research and Clinical Practice, 2022: p. 109777.

9. Crabtree, T.S., et al., Injectable semaglutide and reductions in HbA1c and weight in the real world in people switched from alternative glucagon-like peptide-1 receptor agonists. Diabetes, Obesity and Metabolism, 2022.

10. Crabtree, T.S.J., et al., Flash glucose monitoring: the story so far and the journey ahead. BMJ Innovations, 2022: p. bmjinnov-2021-000862.

11. Crabtree, T.S.J., et al., Protocol for the Diabetes Technology Network UK and Association of British Clinical Diabetologists' closed-loop insulin delivery audit programme. British Journal of Diabetes, 2022. 22(1): p. 9-13.

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13. Crabtree, T., et al., Intensive glycaemic control and macrovascular, microvascular, hypoglycaemia complications and mortality in older (age ≥60years) or frail adults with type 2 diabetes: a systematic review and meta-analysis from randomized controlled trial and observation studies. Expert Review of Endocrinology & Metabolism, 2022. 17(3): p. 255-267.

14. Crabtree, T., et al., Sodium-glucose link transporter-2 inhibitors in reduced renal function: cross-class comparison from the Association of British Clinical Diabetologists (ABCD) audits. 2022.

15. Crabtree, T., B. Ryder, and E. Wilmot, # We are not waiting-DIY APS Do-It-Yourself Artificial Pancreas Systems: The story so far. British Journal of Diabetes, 2022. 22(Supplement 1): p. S82-S84.

16. Ryder, R., E. Wilmot, and T. Crabtree, Gazing into the future–the next 100 years. Perspectives from diabetologists. British Journal of Diabetes, 2022. 22(Supplement 1): p. S100-S101.

17. Crabtree, T.S.J. and R.E. Ryder, The effect of sodium-glucose link transporter 2 inhibitors on heart failure end points in people with type 2 diabetes mellitus: a systematic review and

meta-analysis. British Journal of Diabetes, 2021. 21(2): p. 186-191.

18. Crabtree, T.S., et al., Effect of empagliflozin on albuminuria, eGFR and serum creatinine: updated results from the ABCD nationwide empagliflozin audit. British Journal of Diabetes, 2021. 21(1): p. 62-66.

19. Alkharaiji, M., et al., Clinical cost evaluation and health benefits of post-bariatric intervention for patients with type 2 diabetes living in the UK. Clinical Obesity, 2021. 11(6): p. e12486.

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25. Crabtree, T.S. and A. Gazis, Insulin pumps and diabetes technologies in pregnancy: an overview for the obstetrician. Obstetrics, Gynaecology & Reproductive Medicine, 2020. 30(4): p. 126-129.

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27. Crabtree, T.S., et al., Reductions in alanine aminotransferase levels with liraglutide treatment are greatest in those with raised baseline levels and are independent of weight loss: real-world outcome data from the ABCD Nationwide Liraglutide Audit. British Journal of Diabetes, 2019. 19(2): p. 118-123.

28. Street, T., T.S. Crabtree, and E.G. Wilmot, Diabetes technology. British Journal of Diabetes, 2019. 19(2): p. 136-140.

29. Crabtree, T.S., T. Sathyapalan, and E. Wilmot, FreeStyle Libre: available on the NHS? British Journal of Diabetes, 2018. 18(1): p. 3-6.

30. Aldafas, R., et al., Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2Is) in Frail or Older People with Type 2 Diabetes and Heart Failure: A Systematic Review and Meta-Analysis. (in press)

Presentations

For the benefit of brevity, I have included only presentations of work contained in this thesis below.

Diabetes Technology Network Conference, 2022

6-month results from the Association of British Clinical Diabetologists audit of the NHS England Closed-Loop pilot (Oral presentation)

European Association for the Study of Diabetes, 2022

Predictors of HbA1c and weight response to semaglutide: results from the Association of British Clinical Diabetologists (ABCD) audit programme (Oral presentation)

Diabetes UK Professional Conference, 2023

Risk of hospital admission in individuals aged≥65 years with type 2 diabetes with and without frailty: The role of electronic frailty index to individualise HbA1c targets (Oral Presentation)

6-month results from the Association of British Clinical Diabetologists audit of the NHS England Closed-Loop pilot (Oral presentation)

American Diabetes Association Scientific Sessions, 2023

All-cause mortality in individuals aged≥65 years with type 2 diabetes with and without frailty: Clinical utility of electronic frailty index to individualise HbA1c targets (Poster presentation)

The impact of age on response to injectable Semaglutide: Insights from the Association of British Clinical Diabetologists' audit programme (Poster presentation)

European Association for the Study of Diabetes Conference, 2023

Composite macrovascular risk and its association with HbA1c in individuals with and without cardiovascular disease: a large UK observational cohort study (Oral presentation)

Impact on national policy

The work contained in chapter 7 has directly informed national policy and fed into the National Institute of Health and Care Excellence technology appraisal of hybrid-closed loop therapy in adults with type 1 diabetes.

Abbreviations

ABCD	Association of British Clinical Diabetologists
ACR	Albumin Creatinine Ratio
ADA	American Diabetes Association
AGE	Advanced Glycosylation End-products
AIC	Akaike's Information Criteria
BMI	Body Mass Index
BNF	British National Formulary
CGM	Continuous Glucose Monitoring
CI	Confidence Intervals
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
DDS2	Diabetes Distress Score 2
DPP4	Dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
EFI	Electronic Frailty Index
eGFR	Estimated Glomerular Filtration Rate
GIP	Glucose-dependent Insulinotropic Peptide
GLP1	Glucagon-like peptide 1
GMI	Glucose Management Indicator
GP	General Practice
GWAS	Genome Wide Association Sequencing
HbA1c	Glycosylated Haemoglobin A1c
HCL	Hybrid Closed-Loop
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD-10	International Classification of Diseases
IDF	International Diabetes Federation
ISAC	Independent Scientific Advisory Committee
isCGM	Intermittently Scanned Continuous Glucose Monitoring
IQR	Interquartile Range
kg	Kilograms
m	Metres

MACE	Major Adverse Cardiovascular Events
MHRA	Medicines and Health Regulatory Authority
MODY	Maturity Onset Diabetes of the Young
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute of Health and Care Excellence
ONS	Office of National Statistics
RCT	Randomised Control Trial
ROC	Receiver Operator Characteristic
rtCGM	Real-time Continuous Glucose Monitoring
SGLT2(i)	Sodium-inked glucose transporter 2 (inhibitors)
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAR	Time above glucose range
TBR	Time below glucose range
TIR	Time in glucose range
UK	United Kingdom
US	United States of America

Abstract

All forms of diabetes are associated with increased risks of vascular complications and all-cause mortality. Although often considered a single condition, it is by its nature heterogenous, even within current type classifications. There is increasing focus on individualising the management of type 2 diabetes with an emphasis on collaborative goal setting and increasing emphasis on the role of real-world observational data to support findings from randomised controlled trials.

Chapter 1 gives a general overview of the pathophysiology of diabetes, with a focus on type 2 diabetes, and explores the heterogeneity of phenotypes within this diagnostic umbrella. It also reviews the current guidelines for treatment. It then goes on to explore the evidence underpinning these recommendations and situations where alternative approaches, including precision medicine, may aid clinicians in future.

Chapter 2 gives a broad overview of observational study methodologies and where they fit in the overall landscape of research evidence. It then details some of the key methods utilised in my main studies (Chapter 3 and 5) and the developmental work that led to their final methodologies.

Chapter 3 presents the results from the HbA1c individualisation study and explores the association between HbA1c, all-cause mortality, and macrovascular complications.

The thesis then moves on to frailty, starting with the systematic review and meta-analysis in chapter 4 which synthesises currently published work on intensive glycaemic control in individuals in older age groups across multiple outcomes and highlights the paucity of research in this area. Chapter 5 then presents data aimed to fill this gap and to my knowledge is the first diabetes study to assess and then utilise electronic frailty index scores within its design. It shares important insights into optimal HbA1c levels using a recognised definition of frailty rather than using age as a proxy – the first study of its kind.

The final two results chapters share outcomes from two real-world observational studies as examples of the impact this work can have in translating randomised control trial evidence into a clinical context. Chapter 6 contains results from a clinical audit assessment of injectable semaglutide and highlights individuals who may benefit the most which may be important information for clinicians in view of medication shortages.

Chapter 7 focuses on hybrid-closed loop therapy in type 1 diabetes. This real-world observational work has had significant impact in informing national policy positions and recent technology appraisals by the National Institute of Health and Care Excellence and is a good example of the power real-world studies can have.

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Chapter 1 – Introduction

Chapter abstract

In this introductory chapter I explore the pathophysiology of diabetes, it's classification and management. I then go on to explore work from a range of "treat to target" trials which form the evidence base to support existing HbA1c targets and examine how these have translated into clinical guidelines.

Frailty and pre-existing cardiovascular disease are then explored as factors which may mediate the optimal HbA1c target and provides the context for the work in subsequent chapters 3-5.

I then move on to assess the place of precision medicine in diabetes care currently and look at how this can be implemented in clinical practice including the potential health economic implications of these approaches.

Finally, I look at new therapeutic options and how these could be targeted towards appropriate populations and individualise care.

Diabetes and its complications: The basics

Diabetes mellitus, literally from the Greek meaning "honey siphon", has been recognised as early as Egyptian times as a condition where excessive urination and thirst are accompanied by the presence of sugar in the urine[1]. Today, it is a well-recognised group of metabolic conditions unified by the presence of elevated blood glucose levels. Diabetes mellitus has several forms but is generally caused by defects in insulin response, release or production leading to a state of relative or absolute deficiency in insulin action[2].

Figures from the World Health Organisation in their most recent 2016 "Global Report on Diabetes" estimated that 422million people globally have a diagnosis of diabetes, equivalent to a prevalence of 8.5% in adults. That year, the mortality rates associated with diabetes were high accounting for an estimated 1.6million deaths globally and, perhaps more worrying, these rates are continuing to increase in comparison to the other most common non-communicable causes of death (i.e. cardiovascular disease, respiratory diseases and cancer) which are all decreasing[3].

In England, data from National Diabetes Audit 2021-22 identified at least 3.5million recorded as living with a diagnosis of diabetes[4]. From a UK wide perspective, Diabetes UK reported 4.9million individuals are currently living with diabetes, with up to 850,000 undiagnosed[5]. This number has more than doubled over 20 years. Diabetes was thought to account for 26,000 premature deaths a year in 2018. The number of

people with diabetes is expected to continue to increase with a total number in the UK of 5.5million expected by 2030[5].

Current Classifications

Diabetes mellitus is classified into various types depending on the underlying aetiology of the disease, a summary of which is shown in **table 1.** The categorisation of diabetes into types is important because, in most cases, it can quickly convey which pharmacological therapies or diabetes technologies may be appropriate, what lifestyle interventions might be needed and the risk of long-term complications. My thesis will mostly focus on type 2 diabetes mellitus, before moving on to examine the real-world outcomes associated with the use of novel technology in type 1 diabetes.

Type 2 diabetes

Epidemiologically, type 2 diabetes accounts for 80-90% of diabetes diagnoses affecting around 5.4% of the total population[6]. It is a broad-brush diagnosis with a high degree of inter-individual heterogeneity[7]. Type 2 diabetes is more prevalent in high and middle-income countries compared to low-income countries[8]. Within high-income countries, those living in social deprivation are much more likely to have type 2 diabetes[9]. Although type 2 diabetes is associated with obesity in all ethnicities, it is more common in those from black and minority ethnic backgrounds across all weight categories, and is likely to occur at a lower body mass index (BMI) in these groups[10]. Some studies estimate that

obesity accounts for 80-85% of the total diabetes risk of an individual[11].

Table 1. The various classifications (or types) of diabetes mellitus, their aetiology and prevalence amongst those with diabetes [2, 4]

Type of diabetes	Proportion	Aetiology
Type 1 diabetes mellitus[12]	8%	Auto-immunity mediated destruction of pancreatic beta-cells; absolute insulin deficiency
Type 2 diabetes mellitus[13]	80-90%	Relative insulin deficiency due to insulin resistance and partially impaired secretion in simplest terms; multiple contributory mechanisms
Gestational Diabetes[14]	0.9-25% of pregnancies dependent on diagnostic criteria	Hormonal changes of pregnancy leading to insulin resistance
Monogenic Diabetes - Maturity Onset Diabetes of the Young (MODY) and neonatal[15]	2%	Due to single gene defects leading to impaired insulin secretion and beta-cell function
Pancreatogenic*[16]	2-10%; often misdiagnosed as type 2	Destruction and complete or partial loss of pancreatic islet cells of all types in the context of other pancreatic disease

**Sometimes referred to as "secondary" or Type 3c, related to disease of the exocrine pancreas i.e. pancreatitis, post-pancreatectomy, also included cystic fibrosis related diabetes*

Type 2 diabetes is one of the leading causes of mortality and reduced quality of life in the UK. Costs of treatment and complications are around £10billion, equivalent to 10% of the total National Health Service (NHS) budget, and this is continuing to increase[5, 17]. Despite no

longer being the leading cause of blindness, it is still one of most common causes of visual loss in those of working age[18]. Furthermore, there are unaccounted for costs to society as a whole with 1 in 4 residential or nursing home residents having the condition[19] and disability rates 82% higher than the rest of the population[20].

Pathophysiology of Type 2 diabetes

In the simplest terms type 2 diabetes is caused by insulin resistance and impaired insulin secretion leading to a state of relative insulin deficiency[13]. However, this does not capture the full complexity of the condition with many different influences, mechanisms and pathways contributing synergistically to hyperglycaemia, with these varying to a greater or lesser extent in every individual[7, 21]. These mechanisms are underpinned by the combination and interplay of genetic and environmental risk factors[22].

Genetics

Although the focus of this thesis is not on the genetic basis of diabetes, it is still important to acknowledge at least in brief, as a significant proportion of precision medicine initiatives in diabetes are directed towards an individual's genetic predisposition. Whilst some types of diabetes are due to very well-established single gene defects, often termed monogenic diabetes or Maturity Onset Diabetes of the Young (MODY), the picture for type 2 diabetes is less clear. There is an apparent underlying genetic influence given there is close to 95% concordance of type 2 diabetes in identical twins[23] and a three-times

increased life-time type 2 diabetes risk is observed in those with one parent with the condition[24]. Additionally, over the years, studies have varied in their estimates of heritability; but some studies estimate that genetic factors may account for up to 80% of an individual's type 2 diabetes risk[25-27]. Single-gene defects have not been clearly identified but current linkage studies or genome wide association studies (GWAS) have identified numerous possible genetic factors which may contribute to type 2 diabetes developing in an individual[28]. Most known genetic loci are related to ß-cell function rather than obesity or insulin action[29]. Resultantly, some of the genes in which polymorphisms have been associated with an increased risk of diabetes are also closely linked to MODY and, although the specific defects and ensuing clinical phenotypes are not consistent with MODY, it suggests some genes may be "key players" common amongst multiple types of diabetes[30].

Other risk factors

In those with a genetic predisposition, environmental exposures and other lifestyle related risk-factors ultimately result in the development of type 2 diabetes. The 2018 review by Bellou et al identifies obesity (metabolically healthy or unhealthy), BMI (obese or overweight) and metabolic syndrome as the most significant risk factors for the development of type 2 diabetes[31]. Other potentially modifiable risk factors include sedentary time, smoking (current or former), educational attainment levels and consumption of some foods such as processed meat or sugar-sweetened beverages. Although these are generally considered to be modifiable, many including smoking, obesity, diet and

levels of physical activity, may be additionally associated with the socioeconomic status, ethnicity or cultural background of an individual and thus be difficult to change[32-35].

Some aspects of an individual's previous medical history (e.g. psoriasis, gestational diabetes, or bipolar disorder) were also found to increase the risk of type 2 diabetes. This may be because they share a common basis in pathophysiology (e.g. insulin resistance in gestational diabetes[36]); because the condition may impact the uptake of other risk factors (e.g. unhealthy diet and inactivity have a much higher prevalence in those with mental health disorders[37]) or finally because the treatments may increase the risk (e.g. steroids in psoriasis[38]).

Diabetes complications

Complications of diabetes can broadly be considered in three categories: acute metabolic, macrovascular, and microvascular complications. The pathophysiology between (and in some cases within) each of these groups differs and are summarised in **table 2.** along with the incidence or prevalence of these in the diabetes population. It is the complications of diabetes which lead to reductions in quality of life and, with macrovascular complications in particular, significant mortality[6]. Most of these complications are mediated via what are termed advanced glycosylation end-products (i.e. glycosylated proteins) (AGEs) which then trigger damage via various mechanisms[39].

When considering what differentiates a microvascular from a macrovascular complication, some complications are the result of pathophysiological processes from both sides of the spectrum, or from other consequences of prolonged elevated glucose exposure. In these cases, they have typically been classified here (as elsewhere) according to the predominant factor.

A good example of the complex interactions between macrovascular and microvascular damage is nephropathy[40]. Nephropathy is typically characterised as being a microvascular complication due to the damage caused by AGEs and other intermediaries to the small capillaries in the renal glomerulus. In addition to this, there is also the effect of prolonged hyperfiltration caused by hyperglycaemia. Its subsequent effects, which include mesangial expansion and damage to the basement membrane lead eventually to albuminuria, proteinuria and finally to reductions in renal function. However, in some people classified as having nephropathy due to diabetes clinically, studies have shown a relatively high prevalence (30.8%) of ischaemic nephropathy due to renovascular disease – in other words, a macrovascular origin for the complication[41]

Table 2. The complications of diabetes categorised by whether they are macrovascular, microvascular, or acute metabolic and including prevalence data and a summary of the underlying pathophysiological process [37]

Group	Complication	Incidence (I)/Prevalence (P)	Pathophysiology
Macrovascular	Any Cardiovascular Disease	(P) 37.2% of people with type 2 diabetes in the UK[42]	Hyperglycaemia and AGEs act via intermediaries (e.g. nitric oxide) to cause endothelial dysfunction, inflammation, and atheroma formation in major blood vessels. This is compounded by a pro-thrombotic state. Ultimately results in complete or partial occlusion of major vessels.
	Myocardial Infarction	(I) 18.03 per 1000/person years in those with type 2 diabetes the UK[43]	
	Congestive Cardiac Failure	(I) 30.9 per 1000/person years in type 2 diabetes in the USA[44]	
	Stroke	(I) 11.91 per 1000/person years in type 2 diabetes in the UK[45]	
Microvascular	Retinopathy	(P) 28.3% of people with type 2 diabetes in the UK[46]	AGEs stimulate endothelial growth factors leading to blood vessel proliferation; microthrombus formation may also cause retinal ischaemia
	Peripheral Neuropathy	(P) 32.1% of people with type 2 diabetes in the UK[47]	Microvascular axonal damage by AGEs and oxidative stress induced apoptosis causing sclerosis and impaired function of the nerves
	Autonomic Neuropathy	(P) 73% of people with type 2 diabetes in a US clinic population[48], but estimates vary (20-70%)[49, 50]	
	Nephropathy	(P) 25% in people with type 2 diabetes after 10 years[51]	Multifactorial – see text
	Erectile Dysfunction	(P) 34% of men with type 2 diabetes reported frequent difficulties[52]	Combined effect of autonomic neuropathy and macrovascular disease
	Foot Disease	(P) Active ulcer in 6.4% of people with type 2 diabetes globally[53]	Combined effect of neuropathy macrovascular disease and impaired immunity leading to ulcer formation, bone infection and possible eventual amputation
Acute metabolic/ Hospital admissions	Hyperglycaemia	(I) 56.3 admissions per 100,000 population[54]	Due to relative or absolute deficiency in insulin action
	Diabetic Ketoacidosis	(I) 0.85 per 1000 person/years in type 2 diabetes in the UK[55]	Lack of insulin causes switch to fat catabolism and ketone production → acidosis
	Hypergylcaemic Hyperosmotic State	Limited data; (I) 1% of diabetes hospital admissions[56]	Prolonged osmotic diuresis due to hyperglycaemia leads to volume loss and severe dehydration
	Hypoglycaemia	(I) 47.1 admissions per 100,000 population[54]	Complication of treatment with some drugs or insulin

Treatment targets in type 2 diabetes

In general terms, treatment of type 2 diabetes is undertaken with the aims of improving quality of life and prolonging life by providing symptom relief from hyperglycaemia and reducing the individual's risk of complications[57]. All major organisations including the National Institute for Health and Care Excellence (NICE) in the UK, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statements are clear that all treatments should be person centred[57-59].

Currently, treatment response is recommended to be monitored using glycosylated haemoglobin A1c (HbA1c) measurements[57]. Other methods, such as fructosamine[60], have occasionally been used in the past despite limited evidence of their correlation to complications or average glucose levels. In the future, newer and yet to be fully validated metrics, such as time-in-range[61], may well be adopted. HbA1c is also used for diagnosis of diabetes, with a HbA1c ≥48mmol/mol [≥6.5%] being the recognised threshold[62].

What is HbA1c?

Haemoglobin A1c or HbA1c is a form of human haemoglobin protein. Although its primary function is carrying oxygen, exposure to glucose causes it to become glycosylated[63]. The amount of the protein that is glycosylated is the measure that is reported as a HbA1c value. HbA1c is known to correlate well with an individual's average glucose over the lifespan of the typical red blood cell (i.e. 90 days)[64]. It is a reliable test

but can be affected by conditions in which red blood cell turnover is increased or decreased; or in those with haemoglobin variants such as sickle-cell anaemia[62].

HbA1c was initially shown to correlate with the rate of complications in the Diabetes Control and Complications Trial (DCCT) in people with type 1 diabetes[65]. As a result, it is recognised by the Food and Drug Administration (FDA) in the United States of America (USA) as a validated surrogate endpoint and is used in modern randomised control trials of diabetes therapies, technologies and interventions[66].

Treatment targets – The recommendations

In 2019, NICE in the UK and the ADA in the USA had broadly similar recommendations for treatment targets in type 2 diabetes. The aim, in a non-pregnant adult, was to reduce HbA1c to ≤48mmol/mol [6.5%] if this could be accomplished without introducing significant hypoglycaemia. If this could not be achieved, particularly when sulphonylureas or insulin were used, then the aim should be for a HbA1c ≤53mmol/mol [7%] in the majority of people[57, 67]. Both guidelines emphasised the need for patient centred care and collaborative goal setting. They also highlighted certain situations where the target may need to be altered in view on various individual characteristics. The ADA treatment targets guideline gave clear examples, which include advanced age or limited life-expectancy, multiple long term conditions and disease duration[67]. Although targets were recommended to be adapted considering the above factors, no specific numerical HbA1c values are given. Thus, this

left final target setting to clinician discretion following discussion with the person with diabetes, with any goal being mutually agreed and with a documented underlying rationale. Equally, as an individual approach was clearly the preferred option, it may have been difficult to define target levels clearly across large populations.

In 2022, updated guidelines on the management of hyperglycaemia in people with type 2 diabetes were published jointly by the ADA and EASD[59]. These went much further in their recommendation of a holistic person-centred approach to diabetes care. Firstly, they recognised the importance of individual characteristics in determining ongoing management including both multiple long-term conditions, clinical characteristics such as age, and psychosocial determinants of health. Additionally, shared decision making, individualisation of glucose and weight targets and appropriate use of medications were highlighted as key points within the decision cycle for person-centred glucose management. These guidelines also recommended the use of newer medications, notably sodium linked glucose transporter 2 inhibitors (SGLT2i) and glucagon like peptide receptor agonists (GLP1s), at an earlier stage in view of particular concomitant medical conditions (e.g. atherosclerotic cardiovascular disease in the case of SGLT2i) or individualised goals (e.g. optimising weight loss with GLP1s). Whilst this guideline recognised the importance of individualising care, it did not differ from the earlier guideline in terms of specifying changes to the standard HbA1c goals.

NICE also updated their guidelines in 2022, similarly promoting the earlier use of SGLT2i and GLP1 agonists and increasing the emphasis on individualisation of management approaches to type 2 diabetes[68]. The impact of SGLT2i and GLP1 agonists on cardiovascular outcomes independent of HbA1c has caused a step change away from a glucocentric approach to management[69-71]. In addition, they also produced a patient decision aid for the setting on HbA1c targets which incorporates the views of the individual (concerns regarding hypoglycaemia; concerns regarding side-effects of medications; willingness to take medications) and the presence of other health issues[72]. Again, it does not provide specific HbA1c targets for given individual characteristics, leaving final target setting to clinician discretion.

Treatment targets – The evidence

Following the initial evidence that reductions in HbA1c translated into reduced rates of complications in type 1 diabetes the DCCT trial[65], several large randomised control trials in the late-1990s and 2000s produced evidence that decreasing HbA1c lead to reduced rates of some, but not all, complications in people with type 2 diabetes[73-77]. The main composite outcomes of these trials are summarised in **table 3.** It should be noted that for some sub-outcomes in some trials (for example, incident macroalbuminuria in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[75]) the results were significant (HR 0.71 in the intensive therapy group, P=0.0003) but the composite microvascular outcome failed to reach significance. Meta-analysis of the major trials

summarised in **table 3.** demonstrated reduction in myocardial infarction and coronary heart disease but no statistically significant reductions in all-cause mortality or stroke[78]. In this meta-analysis, however, there was no increased risk of complications noted with intensive glycaemic control – evidence which supports guideline recommendations to reduce HbA1c to a target <48mmol/mol [6.5%].

The risks of "tight glycaemic control"

In February 2008 the first signal that lower HbA1c targets might be associated with increased risk of complications or death arrived when the arm of the ACCORD study targeting a HbA1c <42mmol/mol [<6.0%] was found to have a statistically significantly, albeit numerically small, increased mortality rate[79, 80]. The Action in Diabetes and Vascular disease: Preterax and Diamicron MR controlled evaluation, or ADVANCE, trial was also underway at this point and no such signal had arisen from their data. The decision was made to suspend the ACCORD study at this point. It should be highlighted that the HbA1c target in ACCORD was much lower than in the other major trials in an older population, which may account for some of the findings reported in comparison to other studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), which excluded those aged 65 or older[73, 74].

Table 3. The headline microvascular, macrovascular and mortality outcomes from the major randomised control trials in the late 1990s and 2000s of intensive control in type 2 diabetes (as per HbA1c levels or equivalent fasting glucose level)

	Design	Follow-up	Microvascular	Macrovascular	Mortality
United Kingdom Prospective Diabetes Study (UKPDS)[73]	n=3,867 Intensive group defined by a target fasting plasma glucose <6mmol/L →Intensive therapy [mean Hba1c 7% (53mmol/L)] vs "standard care" [mean Hba1c 7.9% (63mmol/mol)]	10 years	RR 0.75 for intensive group, P=0.0099	Myocardial infarction: RR 0.84 for intensive group, P=0.052 Stroke: RR 1.11 for intensive group, P=0.52	RR 0.94 for intensive group, P=0.44
Action to Control Cardiovascular Risk in Diabetes (ACCORD)[74, 75]	n=10,251 HbA1c <6% (42mmol/mol) vs 7-7.9% (53-63mmol/mol)	Mean 3.5 year	HR 0.95 for <6% group, P=0.4226	HR 0.90 for <6% group, P=0.16	HR 1.22 for <6% group, P=0.04 *Note: trial suspended early*
Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[76]	n=11,140 HbA1c <6.5% (48mmol/mol) vs "standard care" [mean HbA1c 7.3% (approx. 56mmol/mol)]	Median 5 year	RR 0.86 for <6.5% group, P=0.01	RR 0.94 for <6.5% group, P=0.32	HR 0.93 in <6.5% group, P=0.28
Veteran Affairs Diabetes Trial (VADT)[77]	n=1,791 HbA1c difference between groups of 1.5% → Intensive therapy [mean Hba1c 6.9% (52mmol/mol)] vs "standard care" [mean HbA1c 8.4% (68.3mmol/mol)]	Median 5.6 years	Retinopathy & neuropathy Nephropathy: progression of albuminuria reduced in intensive group	HR 0.88 in intensive group, P=0.14	HR 1.07 in intensive group, P=0.62

Subsequent trials have focused more on the potential increases in mortality, as well as other complications such as severe hypoglycaemia and hospital admissions, in both the population as a whole and in specific subgroups of interest.

A meta-analysis of observational studies, including more than 147,000 patients has further supported the view that treating towards lower HbA1c targets is associated with increases in mortality, with a U-shaped or J-shaped curve demonstrating increases in overall mortality at both very high and below target levels of HbA1c[81]. This pattern is seen persistently across multiple studies. Work by Currie et al. demonstrated increased risk of all-cause mortality and cardiovascular events with both high and low HbA1c levels[82]. Observational work by Anyanwagu et al. demonstrated a similar U-shaped association between HbA1c and cardiovascular risk in older individuals with type 2 diabetes treated with insulin[83, 84]. There is a balance that clinicians must achieve between clinical inertia and appropriate de-intensification when appropriate to minimise the risks of complications[85]. Evidence for the most appropriate targets within specific sub-groups is even less clear. Two of these groups, those with frailty and those with pre-existing cardiovascular disease, are of particular interest and were identified as key groups to assess within this thesis.

Frailty and HbA1c targets

Frailty is one obvious example where one might expect a shift in the risk-benefit balance of lower target HbA1c levels, and where that balance may be difficult to achieve.

Frailty has many definitions but is generally considered to be a state of multiple long term conditions, limited physiological reserve and limited resistance to insults or illnesses[86]. It is estimated that 10-20% of individuals aged ≥65years are living with frailty, increasing to 45% in those aged ≥85[86]. Whilst frailty is associated with increasing age, it is also independent of it. There are few studies linking frailty directly, using defined criteria, to diabetes outcomes or targets. Using age as a proxy, we know that with advancing age, diabetes is associated with increased mortality rates as well as the need for social care[87]. It is clear that some of the complications of diabetes, such as retinopathy[88], can still frequently occur in elderly populations due to elevated glucose level. In this group, any subsequent visual impairment may be associated with more pronounced decreases in function, loss of independence and increased frailty than in younger individuals[89]. Furthermore, in the ADVANCE trial, which reported no increased mortality overall with HbA1c values <48mmol/mol [<6.5%] over a 5 year median follow-up period, a prespecified sub-analysis looking specifically at the effect of lower HbA1c targets across age ranges showed no statistically different mortality risk between age groups[76].

Whilst in the overall diabetes population there is an increased risk of mortality associated with of prolonged elevation of glucose levels and suboptimal diabetes management, it is less clear that if the diagnosis is made in later life that intensive glucose management translates into a reduction in mortality[90]. Indeed, one Swedish observational study demonstrated that achieving a lower HbA1c target was only associated with relatively small decreases in mortality rates (HR 0.95, P<0.05)[91]. Finally, attempts to achieve these lower glucose levels in order to prevent complications may be associated with increased rates of both severe hypoglycaemia[92, 93] and falls[94] – both of which can have deleterious on quality of life and increase frailty to a similar extent to the presence of vascular complications from higher glucose levels.

Identifying frailty in practice

Several scoring systems and diagnostic tools exist which can be used to identify individuals with frailty and risk-stratify them once the diagnosis is made. One of the most well established is the Rockwood Clinical Frailty Scale which requires clinicians to subjectively assess the fitness of an individual on a 9-point scale from "very fit" to "terminally ill" with descriptors for each score level[95]. The potential limitation of this method is its dependence on clinical judgement which may lead to variable scoring dependent on the clinician undertaking the scoring. Nevertheless, this score has been demonstrated to correlate well with other scores and has utility in predicting both mortality and admission to an institution (care/nursing home)[95]. More objective measures such as the 4-meter gait speed test, timed up-and-go test and PRISMA-7 have

also been developed and validated for the identification of frail individuals[96, 97]. The NHS in England recommends the use of a more recently developed electronic frailty index (EFI) which utilises the presence or absence of 36 clinical features to identify frailty and risk stratify individuals into fit, mild, moderate of severe frailty, which may be used to target interventions to improve independence, reduce the risk of further functional decline and improve quality of life[98]. Subsequently, EFI has been used in observational studies where it can easily be calculated from diagnostic codes in primary care databases[99, 100].

Guidelines and evidence on frailty and HbA1c targets

The current ADA, EASD and NICE guidelines have already been discussed above[59, 101]. These guidelines all identify that people in older age groups or with frailty may need their HbA1c targets adjusting, but they are not prescriptive in providing recommended targets in these groups. Evidence is limited. A recent statement from a national stakeholder initiative recognised the lack of evidence in this area as a key concern, with many clinical trials excluding older or frail individuals and identified the need for more targeted guidance and the inclusion of these populations in trials as key action points moving forwards[102]. My thesis aims to help provide evidence to support the use of EFI in observational diabetes studies and, moreover, examine the association between EFI, HbA1c levels and outcomes of interest.

The International Diabetes Federation (IDF) published global guidelines in 2020[103]. This echoed the existing principles of personalising

management plans and targets along with amendments to usual exercise and lifestyle interventions which may not be appropriate or impossible to implement in individuals with functional limitations. In addition, this guideline provided more prescriptive glucose targets. It identified three different categories (with two further subcategories) each with a different recommended HbA1c target as follows: functionally independent (HbA1c 53-59mmol/mol; 7.0-7.5%); functional dependent (HbA1c 53-64mmol/mol; 7.0-8.0%); functionally dependent with frailty (HbA1c up to 70mmol/mol [8.6%], avoiding weight loss); functionally dependent with dementia (HbA1c up to 70mmol/mol [8.6%], avoiding hypoglycaemia) and individuals at the end of life (no HbA1c target, minimise symptomatic hyperglycaemia). This has been followed by a further consensus statement with additional glucose targets utilising a healthy, mild, moderate and severe frailty scale (similar to those derived from EFI, though not using this scoring system) which included additional individualised targets for blood pressure, statin therapy, assessment of cognitive decline and fasting plasma glucose readings[104].

Cardiovascular disease and HbA1c targets

Patients with pre-existing cardiovascular disease are another group in which the optimal HbA1c target is less clear. The ACCORD study included 35.6% of participants with pre-existing cardiovascular disease, and a pre-specified sub-group analysis demonstrated significantly increased rates of further cardiovascular disease in those treated towards a lower HbA1c target compared to those who weren't (with the caveat that target of 6% or 42mmol/mol was much lower than in other trials)[76]. There

was also a trend, although not reaching significance, towards an increase in overall mortality in this group compared to those with no history of cardiovascular disease. The Veteran Affairs Diabetes Trials (VADT) included comparable numbers of participants with cardiovascular disease and additionally showed no benefits in attaining HbA1c 53mmol/mol [7%], although no increase in mortality was noted either[77]. A meta-analysis which included all of the above randomised control trials concluded that, in those with cardiovascular disease at baseline, intensive treatment of diabetes to achieve lower HbA1c was of no statistically significant benefit, but equally was not harmful[105].

In contrast to these studies, other observational studies and meta-analyses of non-HbA1c orientated trials have generated a myriad of mixed results demonstrating variably increased or decreased rates of cardiovascular complications and/or overall mortality associated with lower HbA1c targets. The observational study by Bots et al. in 2016 demonstrated an increase in cardiovascular disease risk (HR 1.18, $P<0.05$) for each 1% [approx. 10-11mmol/mol] increase in HbA1c but with no effect on overall mortality[106]. Additionally, a meta-analysis of the recent cardiovascular outcome trials of sodium-glucose linked transporter-2 inhibitors (SGLT2i) and glucagon-like-peptide 1 agonists (GLP1 agonists) by Barer concluded that reductions in HbA1c resulted in additional benefits in reducing risk, additional to the already recognised benefits of these drugs, in those with pre-existing cardiovascular disease[105]. Further supporting this, a Swedish observational study demonstrated that reducing HbA1c <42mmol/mol [<6.0%] reduced

overall mortality risk in those with diabetes and cardiovascular to levels comparable with those without diabetes[107]. Hypoglycaemia in insulin treated type 2 diabetes has also been demonstrated to increase the risk of cardiovascular disease and all-cause mortality; and may be more likely with below target HbA1c levels[108]. Another study has demonstrated increasing incidence of atherosclerotic cardiovascular disease with increasing HbA1c levels and fasting plasma glucose levels[109].

The truth is likely to fall somewhere between the extremes, with benefits of targeting a lower HbA1c likely to be seen up to a certain threshold. However, there may be diminishing returns when targeting a HbA1c level as low as those in the ACCORD trial, with potentially increased risks of all-cause mortality as observed by Arnold et al below this[110]. A recent scoping review published in *Clinical Medicine* summarises the conflicting evidence available when assessing HbA1c targets in people with multiple long term conditions including cardiovascular disease[111].

Guidelines on cardiovascular disease and HbA1c

Despite the evidence indicating no overall effect of HbA1c control on macrovascular and cardiovascular outcomes in this group, guidelines make no recommendations on anything other than the continued use of standard targets for people with pre-existing cardiovascular disease, certainly when the only co-existing conditions are cardiovascular in nature. At the point where an individual may have multiple long-term conditions or subsequent frailty, guidelines relevant to those areas would apply and would advocate for less stringent HbA1c targets[59, 68, 103].

Equally, there is evidence to suggest that some glucose lowering therapies, notably SGLT2i and GLP1 agonists, have significant benefits in reducing the risk of adverse outcomes irrespective of HbA1c, and should be considered as part multi-factor risk reduction approach independent of the individuals current HbA1c level[112].

Research in context

These are two examples of clinical situations where the evidence is grey, and the risk-benefit balance of targeting lower HbA1c levels is likely to be different. Many other situations also exist which include (but are not limited to), baseline obesity, nephropathy or chronic kidney disease, non-alcoholic fatty liver disease, the presence of other medical conditions or malignancy. In any of these situations, which would perhaps fall broadly into the realms of "less likely to benefit from intensive effort to reduce HbA1c to a lower target" in view of the NICE[68], EASD/ADA[58, 59, 67] and other guidelines[103, 104], the recommended target to introduce maximum benefit whilst minimising the risks is not clear and may be difficult to define across broad and diverse diabetes populations.

Beyond HbA1c – newer drugs and risk modification

Over recent years newer pharmacological agents to treat diabetes have been developed which are of significant interest and, in the last 12 months, have been moved up the aforementioned treatment algorithms for type 2 diabetes[59, 68]. The two classes of particular interest are sodium-glucose cotransporter-2 inhibitors (SGLT2i) and incretin-based therapies which includes both single glucagon-like peptide 1 receptor

agonists (GLP1s) and dual agonists which have glucose-dependent insulinotropic peptide (GIP) activity as well as GLP1 activity. Drugs in both pharmacological classes have been demonstrated to reduce HbA1c, reduce weight and improve cardiovascular outcomes beyond that expected from HbA1c reductions alone[112].

The SGLT2i drugs primarily used in the UK include Empagliflozin, Dapagliflozin and Canagliflozin. These medications first came to market in 2013[113]. Antagonism of the SGLT2 receptor prevents the reabsorption of glucose by the kidneys, subsequently causing excretion of glucose in the urine and a lowering of blood glucose levels[114]. Moreover, the loss of glucose in the urine equates to calorie loss which may promote weight loss[114]. Clinical trials across the class have demonstrated consistent HbA1c and weight reductions and were recently summarised by meta-analysis[115].

Both single and dual incretin-based agonists exert their effects on blood glucose by stimulating insulin secretion from the pancreas in a glucose-dependent manner[116]. In addition, their effects in slowing gastric emptying, suppressing appetite and reducing food intake contribute to the significant weight loss often observed[116]. Clinical trials consistently show significant weight loss and HbA1c reductions; meta-analysis comparing these medications to dipeptidyl peptidase-4 inhibitors (an older class of drugs working on the same incretin pathway) demonstrated superior weight loss and HbA1c reductions with GLP1 agonists[117]. Unlike SGLT2i, with GLP1 agonists there is thought to be

differing potency of the various drugs with the newer once weekly injections shown to have superior efficacy in comparative meta-analyses[118] .

In 2008, the Food and Drug Administration (FDA) set a new requirement for diabetes drugs to have proven cardiovascular safety using dedicated clinical trials[119]. Beyond reassuring clinicians there was no negative impact of these drugs on cardiovascular outcomes, these trials demonstrated consistent cardiovascular benefits of both SGLT2i and incretin-based therapies. The cross-class cardiovascular benefits of both SGLT2i and GLP1 agonists have been summarised in meta-analyses[120, 121]. In fact, the beneficial effects of these drugs exceed those expected from HbA1c reductions in isolation[112]. SGLT2i in particular have demonstrated consistent cross-class benefits in reducing composite major adverse cardiac event (MACE) endpoints including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke[120]. Furthermore, SGLT2i have been shown to improve heart failure and kidney outcomes with marked efficacy such that many of these drugs are now licensed and recommended for use in individuals without diabetes for the treatment of heart failure or kidney failure with proteinuria[122, 123].

With older treatments, it’s a different story, with many of the pharmacological options for type 2 diabetes (including metformin, insulin and sulphonylureas) being licensed well before such robust assessment was required. As such, cardiovascular safety data is limited. Analyses

using data derived from clinical trials of newer agents have suggested that insulin use increases the risk of adverse cardiovascular events[124]. A meta-analysis of randomised control trials recently reported reassuring outcomes on the safety of insulin use in type 2 diabetes and no increased risk of MACE or mortality[125]. However, large scale cohort studies have suggested increased risk of multiple diabetes related outcomes associated with insulin use in type 2 diabetes[126]. Whilst clinical trial data on the impact of sulphonylureas on cardiovascular outcomes is sparse, a 2017 meta-regression analysis of observational studies demonstrated a considerable increase in all-cause mortality (HR 1.53; 95% CI 1.43-1.65).

Type 2 diabetes being a heterogenous condition, it is not clear whether all groups experience the same benefits from GLP1 agonists and SGLT2i, however. Notably, there is evidence already to suggest that SGLT2i may have less pronounced benefits on cardiovascular outcomes amongst those with no history of cardiovascular disease[127] – this is something that is reflected within the current UK guidance[68].

The contrast between newer drugs and older agents is stark and incredibly important to highlight. The impact of HbA1c on outcomes in trials from upwards of a decade ago is clear to a point, but these trials were undertaken using only older agents which, as explored above, may independently increase the risk of an adverse outcome. Moreover, there is minimal evidence to suggest either way whether a HbA1c "below target" achieved with a newer agent with recognised cardiovascular

benefits is still associated with the increased risks seen in the ACCORD trial[80, 128]. Large scale randomised control trials to confirm whether the association between HbA1c and outcomes of interest is modified by the use of SGLT2i, or incretin-based medications, are likely to be impractical in the modern era. Instead, we can look to observational study designs to establish associations in the real world (something which will be explored in chapter 2).

Precision medicine in diabetes

One way in which the selection of HbA1c targets or appropriate treatments could be improved in future is by the utilisation of precision medicine techniques.

Precision medicine has multiple definitions and can easily be confused, or erroneously used interchangeably, with the terms individualised or personalised medicine[129]. The United States National Research Council describes precision medicine as "the tailoring of medical treatment to the individual characteristics of each patient" by dividing patients into subpopulations in a healthcare delivery model that, as outlined by Ginsburg & Philips, relies on big data, information and analytics[130, 131]. It may also include the use of biomarkers and genomics; these can be integrated into the clinical picture thus allowing patients to be characterised or stratified into specific subpopulations where treatments may have differing risks or benefits. This differs from personalised or individualised medicine, which again have multiple definitions, and are perhaps orientated more towards selecting treatments in view an

individual's genetic make-up and with due consideration for their beliefs and wishes[130]. Precision medicine is already being used in certain conditions such as cancers and cystic fibrosis to guide therapy[132, 133].

How could it apply to diabetes?

In July 2020, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) released a joint position statement around the use of precision medicine in diabetes which provides a thorough overview of the current state of play and the future plans of their joint precision medicine in diabetes initiative which launched in 2018[134]. They adopt a similar definition for precision medicine and describe personalised or individualised medicine as being the "final step" of management. Adopting their interpretation, "precision medicine" is the stratification of a patient into a subgroup in light of their clinical characteristics, genetics, biomarkers, and other factors and suggest the most appropriate treatment option. After this, "personalised medicine" is the integration of this therapy into the patient's treatment regimen considering their personal beliefs, values and other individual factors.

The consensus statement highlights several areas where precision medicine can clearly be applied to diabetes care moving forwards, as well as where it has been used already. These areas are displayed in **table 4**, alongside a definition and examples of their current use, adapted from the ADA/EASD consensus paper and expanded upon. Further statements

have since been published highlighting the potential benefits across diabetes and multiple long-term health conditions[135, 136].

There are several examples of precision medicine being developed in diabetes already including: precision treatments (and drug discovery) using pharmacogenetics[137], precision monitoring and prognostics in the use of proteomics to predict progression of diabetic nephropathy[138] and, perhaps most wide-spread, the use of genetics and clinical characteristics to aid in precision diagnostics[139].

Palettes and pigeon-holes: Determining types, targeting treatments.
The consensus statement makes one thing clear: that there are plenty of practices that we use routinely in diabetology in order to differentiate types which would already be considered as precision medicine[134], or perhaps more specifically precision diagnostics. These range from the use of autoantibodies and c-peptide in identifying or confirming type 1 diabetes, to the use of genetic testing to identify monogenic forms of diabetes. Identifying these separate diagnoses allows precision therapy or, in those identified at being at risk, precision prevention. There are obvious implications if type 1 diabetes is misdiagnosed and treated without insulin and, perhaps increasingly, if type 2 is misdiagnosed as type 1 and treatment with potential beneficial effects beyond insulin therapy (such as SGLT2i or GLP1 agonists) is contraindicated[140]. In other types of diabetes, it allows for the selection of appropriate therapies including the use of low-dose sulphonylureas and potential avoidance of insulin in HNF1A MODY (a form of monogenic diabetes) or

the avoidance of intervention altogether in glucokinase MODY where there is no lifetime risk of complications due to only very mild hyperglycaemia[141].

Furthermore, the consensus report is clear that there are more opportunities in precision diagnostics that have only recently begun to be realised. For example, with the advent of more advanced genome wide analysis techniques, it may possible to identify those at risk of developing diabetes (type 1 or type 2) and undertake preventative interventions to attempt to halt the development of diabetes in future[142, 143].

The precision medicine of the future is likely to build on the above, and models have recently been put forwards to change the classification systems used for diabetes, further expanding the possibilities of precision diagnostics. One key and widely discussed model, put forward by Ahlqvist et al[144], suggests the stratification of diabetes into 5 clusters using six widely available simple clinical factors: age at diagnosis, body-mass index (BMI), HbA1c, antibody presence and homoeostatic model assessment 2, estimates of β-cell function and insulin resistance. Clusters falling under the umbrella of type 2 diabetes vary from mild-age related diabetes to severe insulin deficient diabetes. One cluster, severe autoimmune diabetes, represents type 1 diabetes. By stratifying individuals into these clusters, the best therapeutic options can be identified and then, following discussion with the patient, these can be implemented in an individualised way.

Table 4. The definitions of different areas of precision medicine within diabetes, along with examples or their current use in clinical practice. Adapted in part from the 2020 American Diabetes Association (ADA) and European Associated for the Study of Diabetes (EASD) precision medicine in diabetes consensus paper [89]

	Definition	**Examples of current use**
Precision Diagnosis	Characterisation of diabetes for therapeutic optimisation or to improve prognostic clarity using information about a person's unique biology, environment and/or context	Auto-antibodies or C-peptide levels Genetics for MODY or neonatal diabetes May include more complex classification systems such as the proposed palette[21] or Ahlqvist models[144]
Precision Therapeutics	Tailoring medical approaches using information about a person's unique biology, environment and/or context to prevent or treat disease	Split into preventative measures and treatment, examples below
Precision Prevention	Using information about a person's unique biology, environment and/or context to determine likely responses to health interventions	Identification of those at high-risk of developing diabetes and attempting to prevent disease from manifesting e.g. NHS Diabetes Prevention Programme[145]
Precision Treatment	Using information about a person's unique biology, environment and/or context to guide choice of an efficacious therapy to achieve the desired therapeutic goals or outcome, minimising side-effects	Sulphonylureas for individuals with specific genetic forms of MODY or neonatal diabetes[146] Hybrid closed loop insulin delivery with algorithmic learning to adjust insulin delivery in type 1 diabetes[147]
Precision Prognostics	Improving the precision and accuracy with which a patient's outcomes are predicted using information about their unique biology, environment, and/or context.	Predicting the risk of complications of mortality using e.g. HbA1c[65] or risk calculators which take into account multiple metrics and specific circumstances[148]
Precision Monitoring	May include the detailed assessment of biological markers, behaviours, diet, sleep, and psychophysiological stress. Used to guide and support other areas within precision medicine	The use of continuous glucose monitoring and adoption of time-in-range[61] The adoption of validated scores to monitor for hypoglycaemia awareness[149] or diabetes distress[150]

The use of this subgrouping model was also able to predict higher rates of metabolic, microvascular and macrovascular associations and complications in certain subgroups[139]. This could be an increased risk, such as the higher risk of retinopathy and neuropathy in severe insulin deficient diabetes or higher rates of nephropathy and fatty liver disease in severe insulin resistant diabetes. Conversely, this could be the lower risk of complications seen with mild age-related diabetes. This model is sometimes described as a pigeon-hole model.

In contrast, McCarthy argues that this model does not go far enough and perhaps over-simplifies the extent of heterogeneity within diabetes[21]. Here it is argued that even where distinctions seem quite clear cut, like that between type 1 and type 2 diabetes, this is not always the case- even here diabetes can exist on a spectrum. This work proposes a palette model as an alternative to the pigeon-hole model. Additionally, it highlights the previously mentioned commonality of some genetic factors, such as polymorphisms in HNF1A derived from genome wide association studies, with various degrees of influence. This model imagines individuals both with and without diabetes having a scale of risk derived of multiple different factors all contributing to their overall clinical condition. It also appreciates how some of these factors, weight for instance, might change over time and ultimately influence whether diabetes becomes overt. This model might be better at recognising the extreme heterogeneity within the type 2 diabetes population but might overcomplicate things and make it harder to target treatments in an evidence-based fashion – if everyone is classified as an individual it may

be much harder to perform studies with enough power to guide future developments.

At present, these models do not include the presence of complications, multiple long-term conditions or frailty in guiding therapy. Whilst they do recognise the importance of precision medicine in being able to select appropriate pharmacological agents for a given individual, they do not include the individualisation of HbA1c targets as a potential precision target. The consensus report puts forwards several research gaps including the need for decision-support tools and the need to demonstrate cost-effectiveness in practice[134]. Additionally, it recognised the important role of real-world observational evidence in supporting the advancement of precision medicine[134].

Health-economics of precision medicine

There are problems with precision medicine in terms of the perceived cost, and these have been acknowledged as a barrier to implementation[151]. Limited evidence exists on the health-economics of precision medicine, although most work acknowledges a net cost due to the expensive nature of genetic testing on which most forms of precision medicine significantly rely[151]. This is also true in diabetes but there are also potential cost-savings. Perhaps most clearly, a person diagnosed as having MODY following genetic testing, instead of type 1 diabetes, may be able to be treated with gliclazide at a cost of £1.65 per month versus a cost of £37.77 for a basal insulin with further costs for bolus insulin[152]. Subsequently, this has been shown to be cost-effective in a

United States based cost-effectiveness analysis[153]. There are other potential savings that can be obtained by reducing the costs of complications in those at highest risk or rationalising the use of expensive medicines use to only those in whom are at the greatest risk and will receive the maximum benefit from the therapy.

Conclusion

Type 2 diabetes is recognised as being an extremely heterogenous disease as well as one which has significant associated costs in terms of long-term complications. Current guidelines suggest that HbA1c targets should be ≤53mmol/mol [≤7.0%] (at least) for most people whilst suggesting some groups, such as those with multiple long-term conditions or frailty, may benefit from higher targets to reduce the potential harms of overtreatment. A handful of randomised control trials, all over a decade old, demonstrated benefits of targeting lower HbA1c levels to prevent some but not all complications. However, it is not that simple – there is also a cautionary tale of increased risk in the ACCORD trial with possible increased mortality from lower HbA1c targets[74, 75]. Furthermore, there is little evidence available for which targets precisely might provide the most benefit with the least risk for specific groups such as those with pre-existing cardiovascular disease or frailty as identified by the guidelines. The approach taken by these studies may, if they used today's newer drugs with proven cardiovascular benefit, have produced different results. These medications stand to benefit many individuals with diabetes and are prominent in current national and international guidelines, although some individuals may respond better than others.

Precision medicine has been applied to diabetes already, but mostly in the form of precision diagnostics and the application of genomics, biomarkers and clinical features allowing clinicians to establish more specific subsets of diabetes phenotypes. These can then be used to stratify the population into those which may benefit from different interventions (whether that be HbA1c targets or medications) to treat or even prevent diabetes. Although the exact system of classification is debated, cost-effectiveness analyses have already shown that in some subsets of diabetes, namely MODY, precision medicine can reduce long-term costs by allowing the use of appropriate cost-effective targeted therapy in the form of sulphonylureas.

My thesis aims utilise observational study approaches to identify optimum HbA1c targets with a focus on individuals with different baseline characteristics, to identify individuals who respond best to newer therapies (GLP1 agonists) and demonstrate the significant impact observational studies can have in informing guidelines and national policy decisions.

In the methods chapter, developmental work which went into these study designs is described, including why the possibility of developing a risk model to calculate optimum HbA1c using an individual's baseline characteristics wasn't successful with the design planned. The thesis then shares some exploratory work from this dataset looking at associations between individuals across various characteristics (e.g. age groups, insulin use, pre-existing cardiovascular disease). The focus then moves

onto frailty, including a systematic review and meta-analysis which highlights significant gaps in evidence, and aims to fill these with results from a large observational study. This study is the first in diabetes, to my knowledge, to incorporate EFI as a marker of frailty, and reports the associations between EFI, HbA1c and the risks of mortality, admission, and complications.

Finally, recent work undertaken using real-world audit data to demonstrate the impact of real-world data in translating randomised control data into practice is shared. Firstly, data analysis which identifies individuals who have more significant response to Semaglutide, a glucagon-like peptide-1 receptor agonist and finally, data from an observational real-world study of hybrid closed-loop therapy in type 1 diabetes which has contributed to a step change in type 1 diabetes management and national policy.

Chapter 2 – Methodologies in observational and real-world Studies

Chapter abstract

In this chapter I discuss the pros and cons of various clinical research trial designs from randomised control trials to observational studies, including the cohort study designs used in several chapters of this thesis. I reflect on the place of observational research in the "big picture" of research evidence and the utility of these types of studies to demonstrate the generalisability of randomised control trial findings to a real-world cohort.

The chapter then moves on to discuss the methodologies used in studies throughout this thesis, with an emphasis on how to test underlying assumptions and correct for missing data – a common problem faced when undertaking observational studies. Cox models are then discussed in detail.

Finally, I share some of the developmental work which eventually led to us deviating from our initial study design, how we established the methodology used eventually, and how this might be improved in future.

Introduction

The aim of this chapter is to discuss the features, advantages and disadvantages of key research study designs encountered in diabetes and medical research in general. It will then explore observational study designs, encompassing both large observational studies and smaller real-world studies, their utility, and their methodologies. This will include methods intended to reduce the risk of bias or address common issues such as missing data and confounding which are important in the studies included in this thesis. It will then discuss the developmental work that went into the methods used for the studies in chapter 3 and chapter 5, with a focus on the HbA1c individualisation study work.

In the practice of evidence-based medicine an evidence hierarchy is frequently used to ascribe value to different study designs in providing high quality, robust and unbiased evidence. The classical pyramid gives most weight to the internal validity of study designs (and thus less likelihood of bias) but also to how filtered the information is – subsequently within this paradigm systematic review and meta-analysis of randomised control trial evidence is considered the best evidence possible[154]. Many variations of this pyramid of levels of evidence exist and are used frequently to assess the quality of evidence in the writing of guidelines or approval of new treatments[155-157]. There are problems with this approach to evidence categorisation as it fails to recognise the impact of study design and potential sources of bias on study outcomes. It may be that a well-designed large observational study is more robust and produces higher quality evidence than a small, poorly designed

randomised control trial. Recognising this, tools have been developed by the Cochrane and Joanne Briggs Institutes to assess for bias in studies, with bias assessment forming a crucial element in the reporting of any systematic review or meta-analysis[158, 159].

To fully understand why some types of study are considered by some to represent higher quality evidence it is important to understand the principles underpinning each design, potential pitfalls, the type of evidence the studies are designed to generate and finally, how this evidence is best used and translated into clinical practice.

Randomised control trials

Randomised control trials (RCTs), whilst cost and resource intensive, are the most robust way of investigating whether an exposure leads to an outcome[160]. Typically, individuals are allocated randomly either to an intervention group or a control group. Ideally, the participants, along with the investigators, should not be aware of which group they are in (i.e. blinded). It is pivotal that this is done on a random basis and as far as practicable all other treatments are matched between the two groups. Matching can also be performed for baseline characteristics such as gender or ethnicity.

There are variations on this standard RCT design. Some RCTs by necessity are unblinded i.e. the participants and investigators know which group they are in. This includes several of the trials discussed in chapter 1, particularly the "treat to target trials" of intensive versus standard glycaemic control such as ACCORD, ADVANCE and UKPDS,

which were not blinded as investigator and participant input was needed to achieve the necessary exposure of lower target glucose levels[73-76, 161]. For RCTs were the intervention is a new therapy this might be called "open-label" – this is not infrequent in the context of diabetes trials especially when investigating technologies and insulin where safety of participants might be at risk otherwise[162, 163]. Others may use "cross-over" study designs where individuals are exposed to both the intervention and control sequentially over the course of the trial, usually with a wash-out period between[164].

RCT design minimises the risk of bias and the impact of unmeasured confounders on the results and leads to high internal validity. Despite these positives, RCTs can be costly, resource intensive and may have ethical considerations that require significant oversight by ethics committees and research governance structures[165]. Furthermore, many RCTs do not include individuals with extreme characteristics or have exclusion criteria which may limit the generalisability of the results into clinical practice. Finally, whilst RCTs are useful and appropriate to investigate interventions, it would be unethical to investigate potential hazardous exposures with this methodology and therefore alternative study designs must be utilised.

Observational study designs

Observational study designs may be employed when interventional trials are either unethical or unfeasible[166]. They may also provide supplementary evidence to complement RCTs and other types of study and improve the generalisability of pre-existing evidence[167, 168].

There are several different types of observational studies. Observational studies can either be cross-sectional (single time point) or longitudinal in nature (over time). Longitudinal studies can be further subdivided, with the two most frequently encountered longitudinal study types being case-control and cohort studies.

Large cohort studies

Cohort studies select participants on the grounds of exposure status and follow them over time to establish whether the outcome of interest develops[169]. This may be done with or without a control group (a group without the exposure) and can be used to assess the impact of multiple covariates at a time within statistical models. This is particularly useful for assessing rare exposures. Cohort studies may be prospective or retrospective in design[170]. Prospective study designs define a cohort, any exclusions, and the data to be collected at each time interval and collect data moving forwards. This can be done in a planned and protocol driven way and recruit participants. Using this methodology, it is possible to perform tests that are outside of routine clinical practice which may be advantageous but may limit the generalisability of findings as only those interested in research may choose to participate. Retrospective designs may involve data collection from existing medical records for individuals with a known exposure over a defined time-period to assess the factors associated with an outcome of interest.

There are many examples of cohort studies, especially within the context of diabetes, where detailed databases of prospectively collected data are readily available. These cover a broad range of diabetes associated

complications and other outcomes of interest, from the risk Parkinson's disease in type 2 diabetes[171] to the risk of cardiovascular disease and mortality with hypoglycaemia[108].

Cohort studies have a varying financial cost depending on the resources required to collect the data and may be labour intensive from a data collection point of view[169]. They are invariably less costly than randomised control trials. Recently, large cohort study designs have become more practical as electronic healthcare records and databases supported by national infrastructure have become accessible to the research community, the Clinical Practice Research Datalink is one example of this in a UK context[172, 173]. Cohort studies also allow for inclusion of a broad range of diverse individuals, increasing the generalisability of any findings, and for the assessment of multiple risk factors at a time. They can also be used to provide evidence of associations between treatments and outcomes, which may compliment pre-existing findings from RCTs and aid in the translation of evidence from clinical trial to real-world practice or even form the groundwork for future RCTs[174].

There are potential disadvantages to cohort study designs. Missing data, especially when using electronic databases or completing retrospective collection, can be an issue[175, 176]. Additionally, findings may be impacted by confounding, selection and other types of bias, although there are measures that can be taken to minimise these[177]. Confounding by indication may be a problem as both exposure and

outcome may be due to a clinician's assessment of the available clinical records.

Smaller real-world studies

Observational studies are, by definition, real-world. But often they include large numbers of individuals and, as already highlighted, often involve the use of large electronic datasets. Alongside these larger studies, there is an increasing emphasis on smaller real-world cross-sectional and cohort studies, utilising data from routine clinical practice. These study designs may allow individuals to assess the impact of new therapeutic options on a national or regional level and evaluate how randomised control trial findings translate into their own clinical practice or report their outcomes locally in comparison to a reported standard[178].

As with larger cohort study designs, real-world data can support the generalisability of randomised control trial findings. They may also allow individuals to assess uptake, tolerance of and adherence to therapies outside of a well-resourced research setting, and report health-economic outcomes in an environment reflecting usual care[174, 179]. Longer-term follow-up may also be possible allowing for surveillance for adverse safety outcomes not identified or trials, especially when these are rarer or when conflicting signals are obtained from RCT data[174, 180]. These studies are invariably more economical than randomised control trials but may require lots of works to collect the data and analyse it appropriately[181].

Generally, because this variation of observational study design often includes fewer patient datasets, the overall power of these studies may be lower and missing data may be more of an issue and harder to correct for using established methods. They may be more prone to confounding or other bias, though methods such as propensity score matching can help to limit this[182]. In the majority of cases, data is only collected during routine care, and investigations or outcomes beyond routine care cannot be assessed without ethical approvals[183]. However, anonymised data use may need to be approved by the Confidential Advisory Group, the local Caldicott Guardian and should adhere to information governance principles[183, 184].

Clinical audit, either retrospectively or prospectively, is often utilised to accrue data for these types of study. This is recognised by the NHS and the Health Research Authority as a vital process in developing services and driving quality improvement within healthcare and is a pillar of clinical governance which all doctors and many allied healthcare staff are required to participate in[183, 185]. This data can therefore be very powerful to assess outcomes locally and drive change but can limit the generalisability and impact of these data outside of the environment in which they were collected[185].

Pragmatic trials, which may include randomisation, also fall within the category of real-world data as they usually deviate from the extensive exclusion and inclusion criteria or randomised control trials and are less

likely to match individuals in the randomisation process[174, 176, 186]. They might be used to assess the impact of an intervention in a specific population or area and aim to recruit a broader range of individuals than a standard randomised control trial[174]. Other aspects of routine care, for example the commencement of other therapies, often continue and are not restricted[174]. Follow-up can be set at intervals with additional investigations or outcomes of interest beyond routine care included within the study design, reducing the amount of missing data[186].

Case-control studies

Case-control studies compare two groups of individuals, which may be matched for other characteristics, with and without a disease or outcome and retrospectively look at exposures to establish correlation[187, 188]. This type of study design is especially useful for assessing correlation between exposures and rare diseases where the availability of data may be sparse or for rare outcomes were conducting an RCT would not be possible.

Although relatively inexpensive compared to other forms of observational study (particularly cohort studies) and RCTs, they may be vulnerable to both selection and recall bias[189].

Cross-sectional studies

Cross-sectional data reports summary statistics for a population at a given time point, whether that be the frequency with which a condition or characteristic is encountered (prevalence) or average measurements for

continuous data[166]. Data collection may be in the form of a survey or single time point data from electronic databases. This type of study might be appropriate to report the prevalence of a condition or characteristic of interest and even compare these across different groups. The yearly report produced by the National Diabetes Audit in the UK is a good example of cross-sectional data[4].

Undertaking this type of study at time intervals may allow for the surveillance of how prevalence or other average measurements change over time but as the population differs at each time point, statistical testing is not possible nor is correcting for confounders. Although simple and usually low-cost, this limits the usefulness of cross-sectional reporting. Ultimately this vulnerability to bias makes it impossible to establish temporal and causative relationships between conditions using cross-sectional studies.

Sources of data for observational studies

In a UK context there are several potential sources of data, many of which can be linked, to facilitate large observational cohort studies.

The Clinical Practice Research Datalink (CPRD) is one example which has already been discussed. This utilises data from general practice electronic records and covers 2,000 practices and around 20% of the UK population in its latest release[190]. The use of primary care data allows for detailed information to be collected on individuals over a prolonged period. Information included in CPRD includes medications, diagnoses, demographics, and other health-related data. Data collection is ongoing

and the data available for research is updated periodically. CPRD has been demonstrated to be representative of a UK population[172]. Moreover, a subset of practices with data held within CPRD allow for linkage with other datasets. There are two parts of CPRD, Gold and Aurum, containing data from different groups of practices and data received from each is in a different format[191]. CPRD is compared to other UK data sources in **table 5.**

Primary care data can be linked to Hospital Episode Statistics (HES), Office of National Statistics (ONS) and other datasets. This may improve reporting of some demographics (such as ethnicity[192]) but also allows for the identification for hospital admissions and death, as well as the causes of these[193].

Table 5. UK electronic healthcare record research databases[194]

Research Database	**Number of individuals**	**Number of practices**	**Coverage of UK population**
Clinical Practice Research Datalink	60 million (18 million active)	2000+	Approx. 20%
The Health Improvement Network	11.1 million (3.7 million active)	562	Approx. 6.2%
QResearch	13 million (unknown active)	754	Approx. 7%
ResearchOne	30 million "records"	Unknown	Unknown
British Heart Foundation Data Science Centre[195]*	Unknown	Unknown	Unknown
OPENSafely[196]**	24 million	Unknown	42.6%

**This dataset merges data from all 4 UK Nations, although exact numbers are not reported it is likely this contains close to UK wide coverage of cross-sectional data*

***Primarily used for COVID-19 research*

Data is completely anonymised, and researchers must adhere to strict data control requirements. Data for medications, diagnoses, demographics, and other clinical measurements are coded. A vital step in any research using a large-database is therefore the cleaning of the data and the identification and translation of codes in order to identify the relevant population, outcomes and covariates of interest[197].

Although initial work such as power calculations and feasibility counts can be conducted prior to ethical approval, all studies performed using CPRD, THIN, HES or ONS data must undertake ethical approval with prospective submission and review of the study protocol by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA)[198].

There are limitations to use of large databases in a UK context. Firstly, they depend on reliable coding by patient-facing clinicians in clinical practice. For some studies, it might be prudent to take additional measures to ensure data is coded correctly or that the correct population has been identified. For example, in a type 2 diabetes context, it is not uncommon for studies to exclude individuals with younger age of onset or rapid progression to insulin due to the risk of this being miscoded type 1 diabetes[199]. This might be termed as a phenotyping algorithm. As studies rely on coding, free-text entries are inaccessible, and any data

contained in them cannot be seen. Additionally, information scanned into the system or medications prescribed outside of primary care, by hospital outpatients or on discharge, are not captured here nor by the linkage data. Missing data can be problematic and can introduce bias but there are methods to manage this to help mitigate this risk.

Managing missing data in Cohort studies

Altman and Bland outlined three key ways of managing missing data that are commonly utilised: omitting variables with missing values; omitting individuals without complete data and the imputation of missing vales[200]. It has been reported that the most common approach to missing data (in 2/3 of cases) is to omit individuals with incomplete data and perform complete-case only analysis[201] but this can introduce bias and limit the power of the study[202]. Frameworks exist for the management of missing data which are recommended to be adhered to by observational researchers[202-204].

Multiple imputation is the generally recommended approach and is increasingly used to account for missing data without loss of data or power[202, 205]. Multiple imputation relies on the assumption that data are missing at random and normally distributed (although data may be transformed to account for this)[206]. It utilises linear regression (for continuous covariates) or ordinal logistic regression (for categorical covariates) to derive missing variables from available data and generates multiple variations of potential datapoints. These multiple datasets can then be analysed but must be combined using Rubin's rules[207]. For

example, in the studies in this thesis, 5 imputed sets were generated each containing different imputed values for missing variables. Analysis must be performed on each set individually and then averaged across all the sets – it is not sufficient to analyse the data as one single larger set.

There are disadvantages to multiple imputation. It is computationally intensive, because datasets are multiplied in size by the number of imputations added, and this can require significant computer power and analyses can take a long-time to perform. Errors in analysis can therefore be costly. There is also a risk, because imputation introduces a "random" element, that expected associations may not appear. QRISK was highlighted by Sterne et al. as an example of this[206] – in the imputed dataset there was counterintuitively no association observed between cholesterol levels and cardiovascular risk, whilst an association was observed using complete-case data only[208].

Addressing other types of bias

Missing data as a source of bias in cohort studies has been discussed, but other types of bias can exist. Confounding bias can exist and known potential confounders must be corrected for – this can be done using statistical models such as a Cox model[209]. With larger datasets with a broad range of accessible covariates it is likely that data for known confounders will be available, and therefore perhaps this is less of an issue, but for small studies or studies with retrospectively collected data, unavailable confounders may significantly impact the results. Unknown confounders may also exist and cannot be corrected for. Selection bias

may occur if a study is performed on a smaller sample of the population and subtypes of selection bias are well recognised including sampling bias (not using representative populations), attrition bias (loss to follow-up over time) and confounding by indication[210, 211]. Information bias, in the context of large health databases, may be introduced by inaccurate coding (by the clinical team) or inaccurate identification of codes by the research team[197]. Using recognised lists of codes and collaborative working may minimise this risk and efforts are ongoing to publish recognised code lists and phenotyping algorithms[212].

Cox models

The Cox model was developed in 1972 as a proportional hazards model to be used in survival (or time-to-event) analysis in clinical trials[213]. It has subsequently been adopted in cohort and case-control studies. This differs from other means of exploring survival following a given exposure, such as Kaplan-Meier plots, because it allows for the inclusion of confounders which may impact the results[214]. The model is described as semiparametric. It makes no assumption about the distribution of survival times but instead relies on the assumption that the impact of a particular covariate is constant over a given time-frame[215].

The Cox model reports the ratio of the hazard in exposed versus unexposed individuals, or hazard ratio, and its confidence interval[216]. The interpretation of hazard ratios was framed nicely in a minireview by Spruance et al. as representing the odds that, for a randomly selected pair of individuals in a study, one exposed and one non-exposed, that the exposed individual reaches the outcome first[217].

The standard Cox model assumes that covariates do not change over time and in reality, this is unlikely. Many variables, such as weight or HbA1c in a diabetes context, will vary regularly. This will likely have an impact on the results and can be accounted for using a Cox model with time-varying covariates[218].

Cox models can be used to report the difference between exposed and unexposed individuals in survival analysis but may also be used to develop predictive models and has been used widely in the past for models such as QRISK, which is employed widely in clinical practice in the UK[208]. Models can be developed by the selection of covariates in a step-wise fashion and statistical testing can be undertaken to ensure the addition of a covariate to the model is adding information – Akaike's Information Criteria (AIC) is an example of one such test[219]. This method penalises the inclusion of extraneous covariates which add no additional information; for the studies in this thesis a change in AIC of -2 has been considered as being significant. In a diabetes context, an example of this might be HbA1c and fasting glucose, individually these may be both associated with an outcome but, because the two are linked themselves, including both within the same model may not be beneficial.

The selection of covariates is performed in a stepwise manner and can be forwards (adding to *a priori* selected variables) or backwards (including all available covariates and removing one at a time).

In the development predictive models, it is common practice to hold out a proportion of the dataset. The model will be developed on a large proportion of the data and then tested for its ability to predict outcomes accurately on the remaining dataset[220]. Alternatively, one could select and fit a model using one database (e.g. CPRD Gold) and the test its performance in a different one (e.g. CPRD Aurum). Model performance is determined by both calibration and discrimination[221].

Discrimination is the ability of the model to classify individuals correctly into the outcome. In the context of the studies in this thesis, this might be the ability of the model to classify the population correctly into those who had a myocardial infarction and those who didn't and is important when generating predictive models[221]. Receiver operator characteristic curves (ROC) are commonly used to report discrimination[221], though this has limited relevance to Cox models outside of predictive models. Calibration reports numerically how close the predicted probabilities to observed probabilities for the outcome of interest[221]. There are two methods used in the studies in this thesis to report calibration: Royston-Sauerbrei D-Statistic[222] and Harrell's C index[223, 224]. Royston-Sauerbrei D-Statistic reports a number between 0 and 1 and represents the amount of observed variation in outcome is explained by the model. For example, a value of 0.27 would mean 27% of the observed variation is explained by the model. Harrel's C-index also generates a value between 0 and 1 but with 0.5 representing non-concordance between model and outcome, 1 representing perfect concordance and 0 representing perfect anti-concordance[224, 225].

The main limitation of Cox models is their reliance on hazards being proportional over time[226]. This should be assessed graphically or statistically before undergoing Cox model analysis. If for a covariate the hazards are found to violate this assumption, then data may be transformed to assess whether this resolves the issue. For continuous covariates, this may be as simple as a logarithmic transformation but increasingly fractional polynomials are used[227]. Fractional polynomials involve the transformation of a variable from a single term into multiple terms[228]. As an example, for a given variable x, this might transform x into $x + 2x^{-1} + 3x^{2}$…. The multiple terms generated can then be included within the model. This may however make the hazard ratios hard to translate clinically as a hazard ratio is generated per term and significant transformations will distort these within the model. For binary or categorical covariates, violation of the proportional hazards assumption can be addressed by including the variable as a strata[229].

Cox models have a well-established history and are recognised for their validity but in future may be replaced by machine learning or artificial intelligence models[230, 231].

Method development

To address the identified unmet need of individualising HbA1c targets, the initial plan was to develop a predictive model that could be used as a near-patient tool to aid in collaborative discussions and goal setting. This proved challenging (as explained below) and eventually the methodology transformed into a more exploratory approach reporting the associations

between HbA1c, key factors (e.g. frailty, specific medications, baseline cardiovascular disease) and important outcomes.

Cleaning the data

The process first involved the selection of appropriate Read codes and variables that would be needed. Much of this involved the use of clinical knowledge to identify variables which we know, in practice, impact on our pre-determined outcomes of interest as well as key demographics including age, gender, and ethnicity.

Clinical measurements such as blood pressure (systolic and diastolic), weight (kg), height (m) and BMI were used as these are known to influence risk of certain outcomes, for example, the risk of myocardial infarction which increases in those who are more overweight or have higher blood pressure[232]. Family history of young (age<60 years) cardiovascular disease, smoking status and alcohol consumption were used as all are recognised to increase the risk of cardiovascular disease[233, 234]. For lipid profiles (high density lipoprotein, low density lipoprotein and total cholesterol) numerical continuous data were identified as important and included as a covariate given its recognised association with several outcomes[235, 236].

Renal function (eGFR) and urine albumin creatine ratios (ACR) are important additional factors that can increase mortality and the risk of cardiovascular disease[237, 238]. Due to the nature of laboratory reporting, the available data were expected to contain a significant

number of qualitative values for both eGFR and ACR (e.g. >60ml/min/1.73m^2). To ensure consistency, eGFR data was assessed alongside Read Codes for chronic kidney disease diagnoses, and a new covariate was generated to indicate the highest stage of CKD derived from Read code or available eGFR data. Similarly, an ACR covariate was generated and categorised using recognised definitions[237] into normoalbuminuria (<2.5 [male] or 3.5mg/mmol [female] or less than lower reference limit), microalbuminuria (3-30mg/mmol) or macroalbuminuria (>30mg/mmol).

The duration of diabetes and age at diagnosis were included by using age at baseline and the quarter of follow-up in a time-varying Cox analysis. This was important because longer durations of diabetes and younger age at diagnosis are both known to increase the risk of adverse diabetes outcomes[239, 240].

Data on prescribed medications were extracted. Firstly, the type of anti-diabetes drugs prescribed were captured. This was important as many pharmacotherapies have additional beneficial effects beyond HbA1c in reducing cardiovascular risk or nephropathy – notably sodium-glucose link transporter 2 inhibitors (SGLT2i)[112, 241, 242] and glucagon like-peptide 1 (GLP1) agonists[70]. Additionally, one group, the thiazolidinediones (or "-glitazones") potentially increase cardiovascular disease risk[243]. Other medications included any antihypertensives, lipid lower drugs, antipsychotics or steroids – all of which may modify the

risks of cardiovascular disease[244-246] and/or adverse microvascular outcomes[247, 248].

Data were extracted for concomitant conditions which can modify the risk of an outcome or death occurring including hypertension, atrial fibrillation, migraine, systemic lupus erythematosus, severe mental illness (including psychosis, schizophrenia and bipolar), human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS) and erectile dysfunction. Depression was not collected as it had not previously been used in studies by our group and has been flagged as an omission for consideration of inclusion in future studies. Finally, a Charlson Comorbidity Index, which is demonstrated to predict one year survival, was calculated for each patient to include as a covariate, to encompass multiple long-term conditions[249, 250]. This was eventually excluded due to its overlap with many of the key concomitant medical conditions selected during the model selection phase.

Clinical measurements were converted to standard units to ensure standardisation across the cohort and were considered missing if conversion is not possible or units were not reported.

The Read codes for the HbA1c individualisation study were developed by myself, updating codes from previous work by Dr Vinogradova[251]. For the frailty study, alongside these codes, access to the codes used by

Bottle et al. for their study linking electronic frailty index and heart failure admission was granted and these were updated accordingly[99].

Delineating the cohort

Individuals for the HbA1c individualisation study were identified at diagnosis of type 2 diabetes and followed from this point. Individuals in the EFI study were included with any prevalent diagnoses of type 2 diabetes at the origin of the study.

For the HbA1c individualisation study, the initial protocol suggested that individuals with less than one year's follow-up should be excluded. The rationale for this being that from our clinical experience it is unlikely they would develop complications as a direct consequence of their diabetes alone in this short timeframe, or that their diabetes diagnosis may represent an acute deterioration in health otherwise. This would be outside of the study aim of assessing the impact of HbA1c on outcomes in otherwise clinically stable individuals.

This assumption was assessed by examining the characteristics of the two groups (those with more or less than 12-months follow-up) and demonstrated high rates of hospital admission and mortality in the group with less than one year follow-up suggesting a more acute course. There is no direct comparator for this (as the rates would by definition by zero in the >12-month follow-up cohort). The number of individuals who died during the study who were included (i.e. >12-month follow-up) was only 11.7% compared to 40.02% in just a 12-month period in those excluded.

Differences in baseline characteristics, notably an older skew of age distribution and higher proportion of white British individuals, were also noted. This data is shown below in **table 6** and **appendix 1.**

Table 6. Mortality and admission percentages of the cohort with <1yr data available in the HbA1c individualisation study

	n=	%
Total	24,504	
Admitted during time period	**9,532**	**38.90**
of which died	6,973	73.15
Died during time period	**9,807**	**40.02**

Subsequent to this, the cohort was divided into roughly 75% derivation (training) cohort for model development and a 25% validation (testing) cohort for assessing model calibration, by GP practice, in a similar fashion to other studies including QRISK[252]. Further developmental work was performed using the validation cohort only.

Assessing the rates of identified outcomes.

As an external validation step, rates of our outcomes within our validation dataset were assessed and compared them to those reported in the literature to ensure there were no obvious coding errors for these, and that the results were similar to published research. This was undertaken for both the HbA1c individualisation and EFI studies. **Table 7** shows this for the primary outcomes of the HbA1c individualisation study.

Assessing Cox model assumptions

The next step was to assess the assumptions necessary for appropriate implementation of a Cox model were met. Firstly, univariate associations for the risk of each outcome and continuous covariates were explored and the use of fractional polynomials assessed where the risk was not linear. This was done both graphically and with statistical testing. An example of this is shown below in **figure 1.** for HbA1c and all-cause mortality. The significant change in deviance with additional fractional polynomial terms ($P<0.001$) and clear non-linearity graphically would prompt the use of fractional polynomials for HbA1c, which would be transformed using the powers suggested into two terms.

Structuring the data

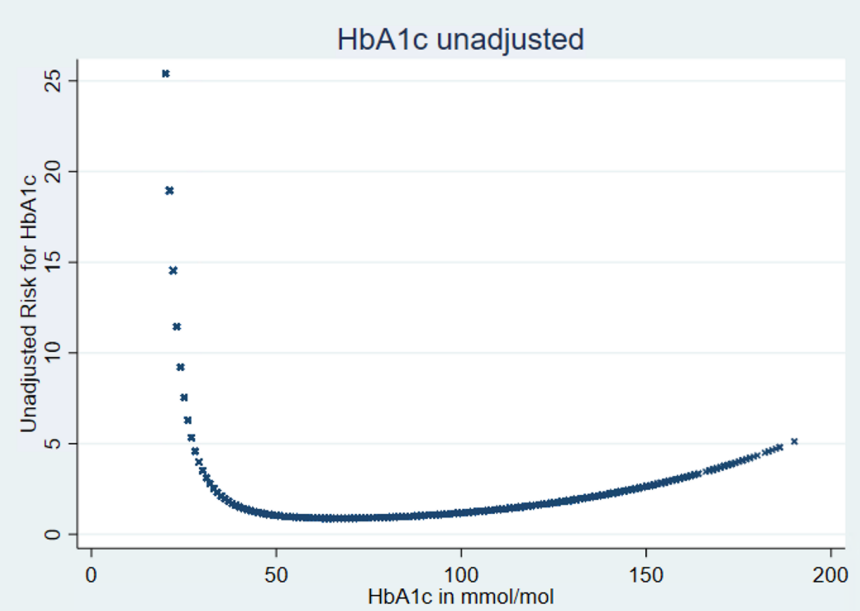
For the HbA1c individualisation study, a time-varying analysis was used with the aim of allowing this to account for the change in HbA1c values over time. For this, data was captured at 91-day (quarterly) intervals and structured in a "long" format. The EFI study utilises data from baseline only and has methodologies similar to other studies such as QRISK[208].

Table 7. Comparison of event rates in the HbA1c individualisation study with published event rates. n/r=Not recorded/reported

Overall rates							
Outcome	Study	Total n=	Person-years	Events n=	rate (95%CI)	per person-years	Comments
Macrovascular	Our Study	172,869	687,074	24,239	3.53 (3.48- 3.57)	100	
	Wright et al. 2020[253]	432,641	n/r	129,262	4.79 (4.71-4.31)	100	Rates in this study are from CPRD plus SCI-Diabetes and are likely to be higher due to not including those with baseline cardiovascular disease which we are doing at present.
	Khunti et al., 2015[108]	9,161	n/r	740	1.62 (15.1-17.4)	100	Study primarily looking at hypoglycaemia and association with cardiovascular risk. Reports overall cardiovascular event incidence rate.; additionally, was only looking at insulin treated. This figure is for those with no baseline cardiovascular diagnosis i.e. similar to our cohort
	Shah et al., 2015[254]	n/r	162,756	6137	3.77	100	This study included peripheral arterial disease in its counts of macrovascular disease which fall under microvascular in our protocol. Additionally, they did not exclude the cohort with less than 12-months data which in our cohort have significant amounts of cardiovascular disease
Mortality	Our Study	172,869	753,667	20,151	2.67 (2.63-2.71)	100	
	Wright et al., 2017[253]	n/r	n/r	n/r	4.27	100	Higher than ours using CPRD but did not exclude the cohort with less than 12-months data with the relatively high associated mortality this probably accounts for the discrepancy
	Stratton et al., 2015[255]	n/r	n/r	n/r	1.61	100	These values tended towards higher rates. UKPDS excluded anyone over age 65 which makes exact comparisons difficult but this likely accounts for the relatively lower rates of mortality in the study compared to ours
	Yun et al., 2019[256]	1,568,097	n/r	153,036	1.73	100	Looking at hypoglycaemia and incident rates of cardiovascular disease and mortality but does report overall mortality rate. Korean study, so cultural factors might reduce this compared to our cohort

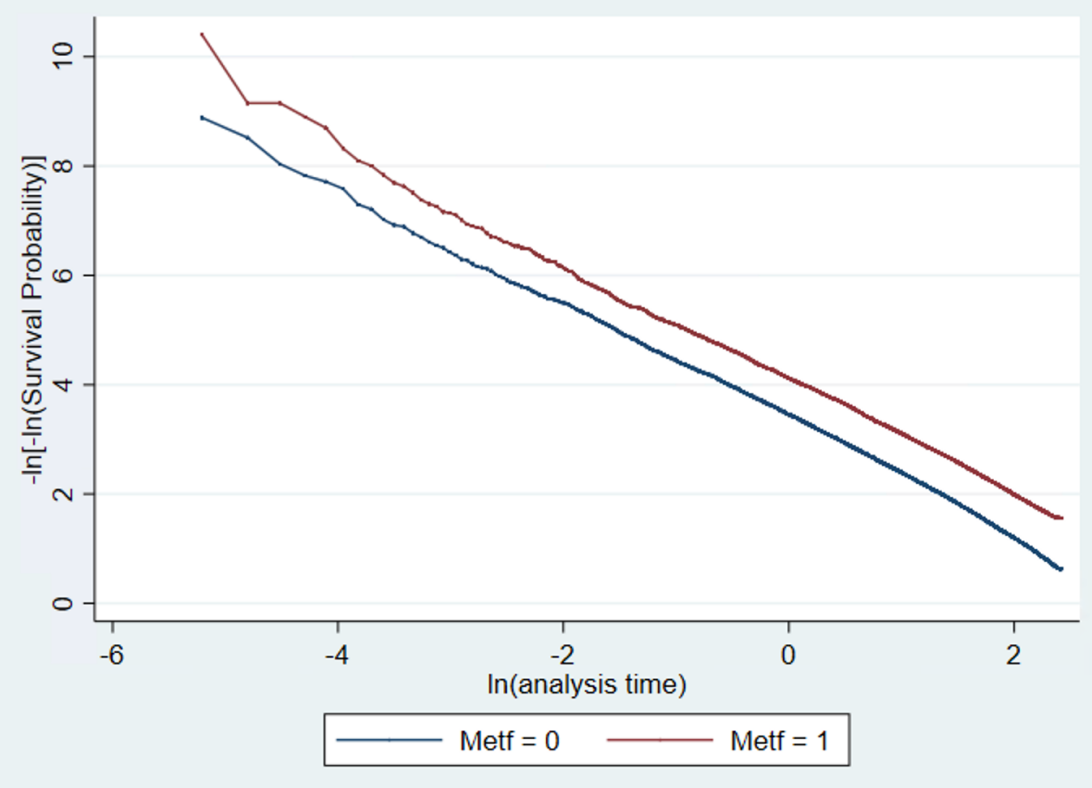
Figure 1. Univariate association of HbA1c level with risk of all-cause mortality displayed graphically and statistically.

HbA1c	df	Deviance	Dev. dif.	P(*)	Powers
omitted	0	156320.77	579.463	0.000	
linear	1	156211.07	469.757	0.000	1
m = 1	2	155878.59	137.274	0.000	-2
m = 2	4	155741.31	0.000	--	-.5 0



For binary or categorical covariates, the proportional hazards assumptions were assessed graphically. To meet this assumption the hazards should be proportional, with parallel log(-log) survival plots over time and should not cross[257]. **Figure 2.** gives an example using the log(-log) survival plot for Metformin use and all-cause mortality. Here the lines are clearly parallel, the same shape and do not cross, therefore the assumption is met.

Figure 2. log(-log) survival graph for Metformin users and all-cause mortality use to assess proportional hazards assumption.



Model selection

Model selection was performed using Akaike's Information Criteria (as mentioned above) and a reduction of 2 was considered significant. Base *a priori* covariates included age, gender and HbA1c. Three different methods of model selection were undertaken: forward step-wise selection, backwards step-wise selection and forward step-wise selection but including a broader range of *a priori* covariates similar to the UKPDS risk engine[258]. The same model was selected by all 3 methods and therefore the forwards stepwise method was utilised for all model selection moving forwards.

Shift in study design

For the HbA1c individualisation study, model calibration was assessed in both the derivation and validation cohorts. At this point, potential problems were identified with the study design for the development of a predictive model. These included:

- The use of time-varying covariates in model development which has not, to our knowledge, been done previously and led to sub-optimal model performance with low Royston-Sauerbrei D-statistics (<0.2) and Harrell's C (approaching 0.5) which would not be acceptable for clinical decision making.
- The use of data from diagnosis meant that diabetes duration may not be accounted for properly and, additionally, the model may not apply to those with durations of diabetes beyond 11 years (the maximum follow-up of the study)

Following much work, discussion, and exploration of the data further, it was decided to adopt a more exploratory approach to HbA1c by examining the association between key characteristics and HbA1c levels and outcomes within the same cohort followed from diagnosis. The characteristics of interest were age (as groups), previous cardiovascular disease, insulin use and sulphonylureas use (due to risk of hypoglycaemia). Although developing predictive models that could be used in clinical practice was not possible, the data produced will still be useful and novel for clinicians in collaborative goal settings in individuals with varying baseline characteristics.

If this work were to be undertaken in future it might be that newer methods such as machine learning might be more appropriate once they are more widely established.

Conclusion

This chapter has discussed the advantages and disadvantages of various study designs with a focus on cohort studies and an exploration of the journey that led to the methods eventually used in subsequent chapters of this thesis.

Observational studies provide a cost-effective alternative to randomised control trials and can supplement and support results from studies in assessing how RCT findings translate into real-world practice. Furthermore, they are often more generalisable including individuals from a broader population than selected participants in clinical trials. For some rarer exposures or conditions, they may be the only ethical means to conduct research.

Access to large electronic healthcare records has improved the opportunities for observational research and the power of the results of such studies. Current databases in use, including CPRD used in this thesis, have been demonstrated to be representative of a UK population. However, there may be limitations due to the dependence on accurate coding from clinicians in their day-to-day working and the potential impact of missing data. Some information is lacking from these databases at present, and free-text responses are inaccessible.

Smaller cohort studies might be useful for exploring local outcomes and clinical audit may be a means utilised in a UK context to accrue data for such reports which can provide valuable insights.

Cohort studies provide a useful means of exploring associations between exposures and outcomes over time, and Cox models allow for the reporting of hazard ratios with adjustments for confounders. They may also be used to develop predictive models, such as QRISK, which are widely used in practice. It is important that with Cox models the assumptions are tested and addressed if violated and the approaches to this are discussed. In future, newer approaches may arrive that make Cox models obsolete.

The methods developed for the studies in this thesis took time and reflection. Unfortunately, the initial study protocol did not perform as expected and changes had to be made. The rationale for this is explained and suggestions of how future researchers may want to take this forward have been suggested – perhaps using machine learning or artificial intelligence. As a result, the methods used became more exploratory, but the insights gained will still have value in aiding clinicians in their decision making.

Finally, observational studies at present continue to only allow us to explore associations. Causation and efficacy or new treatments must be established by randomised control trials. But, especially in diabetes research, it can be argued there is a place for both to complement each

and that outcomes from either, or both, will continue to support clinicians in their decision making and improving patient care.

Chapter 3 – Individualisation of HbA1c targets using data from electronic healthcare records

Chapter abstract

Introduction: Type 2 diabetes is associated with increased risk of adverse cardiovascular outcome and all-cause mortality. Management of glucose levels, and reducing HbA1c, remains a pillar of risk reduction alongside multifactor interventions to improve blood pressure, cholesterol, and lifestyle adjustment. Some evidence to date has suggested potential increased risk of adverse outcomes with lower HbA1c level. The aim of this study was to explore the association of HbA1c with mortality, a composite macrovascular outcome, and different cardiovascular events across a type 2 diabetes population and within subgroups of individuals with different characteristics or treated with therapies with a risk of hypoglycaemia.

Method: Individuals with an incident diagnosis of T2DM within a UK primary care electronic database (the Clinical Practice Research Datalink) and linkage data from Hospital Episode Statistics from 2007-17 were included. Time-varying multivariate Cox regression models were developed for each outcome: all-cause mortality, a composite macrovascular outcome (MACE), myocardial infarction heart failure and stroke. Subgroup analysis exploring the association between HbA1c and outcomes in individuals aged ≥60 years, with pre-existing cardiovascular disease or using insulin or sulphonylureas for each outcome was

performed. Five HbA1c categories at approximately 11mmol/mol intervals (mapped to guidelines) were used. The reference group was defined as individuals with HbA1c 48-57.9mmol/mol [6.5-7.4%] (in the non-exposed subgroup if relevant, e.g. no pre-existing cardiovascular disease).

Results: 172,869 individuals were included and followed for a maximum duration of 11.2 years. A "U-shaped" association between HbA1c and all-cause mortality was observed with increased risk observed at HbA1c<48mmol/mol [<6.5%] and the lowest risk observed at HbA1c 48-57.9mmol/mol [6.5-7.4%]. For MACE, risk was increased in higher HbA1c groups but was similar across both the HbA1c<48mmol [<6.5%] and 48-57.9mmol/mol [6.5-7.4%] groups. Linear associations were noted for myocardial infarction and stroke with the lowest risk at HbA1c<48mmol/mol [6.5%], but for heart failure a "U-shaped" association was again noted, with an optimal HbA1c of 48-57.9mmol/mol [6.5-7.4%]. Across multiple outcomes, insulin use was found to modify the risk such that it was similar across all HbA1c groups.

Conclusion: This evidence suggests that whilst for some outcomes HbA1c reductions are important, there may be a point of diminishing returns and for other outcomes, such as all-cause mortality and heart failure, HbA1c targets should be higher to minimise the risk. This may have implications in the context of current guidelines and support the de-escalation of therapies in some situations when HbA1c<48mmol/mol [6.5%].

Introduction

Macrovascular complications are those caused by damage to large blood vessels. This manifests as ischaemic heart disease, strokes and myocardial infarctions and ultimately contributes to both the significant impact on quality of life and mortality. As already discussed, large randomised control trials such as the United Kingdom Prospective Diabetes Study (UKPDS)[73], Action to Control Cardiovascular Risk in Diabetes (ACCORD)[74] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[76] studies demonstrated potential benefits in reducing the risk of microvascular complications; the evidence to support intensive glucose control to prevent macrovascular complications and reduce risk of all-cause mortality is less clear. Furthermore, the ACCORD study was stopped early due to increased risk of mortality observed with intensive control[74]. Subsequent observational studies have demonstrated "U-shaped" associations between HbA1c and mortality and macrovascular risk in some cohorts, particularly in older individuals or insulin users[83, 84].

The evidence from these studies underpins much of the guidance produced nationally, by the National Institute of Health and Care Excellence (NICE)[68], and internationally, by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD)[59]. To recap, these guidelines support a target HbA1c ≤48mmol/mol [6.5%] if this can be achieved without risk of hypoglycaemia; if hypoglycaemia is a concern, then HbA1c ≤53mmol/mol [7.0%] should be the desired goal. In addition, they advocate for patient centred care and a collaborative goal

setting approach to HbA1c targets taking a view on the individual's other co-existing medical conditions, lifestyle, and frailty status. No prescribed targets are given for individuals with different characteristics and evidence to support any specific target in subgroups according to other concomitant conditions, therapy or other characteristics is limited. It has been argued that there are potential risks of over-treatment, and a careful balance to be struck between clinical inertia and de-intensification[85].

The aim of this study is to explore the associations between HbA1c and macrovascular outcomes and all-cause mortality according to patient characteristics (such as age, other long-term conditions, and medications) and determine the optimum HbA1c level in different cohorts of adults with type 2 diabetes.

Methods

Data Source

Data for this study was sourced from UK general practices contributing to the Clinical Practice Research Datalink (CPRD) database, with linked data from the Hospital Episode Statistics (HES) and Office of National Statistics (ONS) databases as available. The utilised part of CPRD, GOLD, contained data from 674 primary care practices, and more than 17.1 million patient datasets[190, 259]. CPRD has previously been validated to be representative of the overall UK population[172]. Data from HES and the ONS used for linkage purposes allowed for consideration of hospital activity and mortality of individuals identified in the study population from the CPRD data.

Study population

An open cohort of adults aged ≥18 years with a diagnosis or prescription record indicating incident T2DM during the 11-year index period from 1st January 2007 to 31st December 2017 was defined. Data was available for look-back purposes from 1st January 1997. Individuals with type 2 diabetes were identified via Read codes or prescriptions in CPRD data and International Classification of Diseases 10th edition ICD-10 codes in HES data[260].

Exclusion criteria

Individuals with a concomitant diagnosis of T2DM or any other type of diabetes (e.g. steroid induced, type 1 diabetes), or evidence of a BNF product code indicating a potential treatment for diabetes in the pre-index look back period were excluded. Individuals with less than 12-months follow-up data from diagnosis were excluded. Patients aged <18 years old at the index date or anyone commencing insulin within 12-months of diagnosis were deemed to have a higher risk of being misdiagnosed type 1 diabetes and were therefore be excluded from the analysis. This is consistent with similar works performed using CPRD data[261]. Individuals with existing cardiovascular disease of any type were not excluded from the composite outcome, as they were identified as being a particular group of interest. Individuals with previous myocardial infarction, stroke or heart failure were excluded from the respective individual outcome.

Outcomes and covariates

A composite macrovascular outcome (MACE) was used as the primary outcome. This was defined as any event of, or death due to, myocardial infarction, stroke, and heart failure. Secondary outcomes included all-cause mortality, and individual myocardial infarction, stroke, and heart failure outcomes.

Patient characteristics and measurements included age, gender, body mass index, blood pressure, ethnicity, alcohol consumption and smoking status. Clinical diagnoses included known history of atrial fibrillation, ischaemic heart disease, previous stroke, heart failure, chronic kidney disease, peripheral arterial disease, Parkinson's disease, rheumatological conditions, hypertension, severe mental health problems, HIV/AIDS, and family history of heart disease. Medications included lipid lowering drugs, antihypertensives, metformin, sulphonylureas, thiazolinediones, dipeptidyl peptidase-4 inhibitors (DPP4), sodium glucose linked transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1). Laboratory values included HbA1c, urinary albumin creatinine ratio, estimated glomerular filtration rate and lipid profile (triglycerides, total cholesterol, high-density and low-density lipoprotein levels),

The complete list of potential covariates for which data was obtained is outlined in **appendix 2.**

Statistical analysis

Incidence rates for the composite and each individual outcome were calculated by dividing the number of patients with the outcome by the number of person years. Kaplan-Meier curves have been used to present this information.

Multiple chained equations using a model containing key demographics, outcomes of interest and follow-up time were used for imputation of missing data. The degree of missing data for key covariates in the baseline quarter are shown in **table 8.** All analyses were performed using Rubin's rules to combine effect estimates and standard errors across 5 imputed sets[206]. Data were assumed to be missing at random.

A time-varying multivariate Cox regression analysis was used to assess the associations between covariates and outcomes of interest. Data were captured at quarterly (91-day) intervals. All variables that could vary over time (e.g. other than gender, ethnicity) were included as time-varying covariates. Proportional hazard assumptions and the distribution of all potential covariates were assessed - any variable violating these assumptions were included as a strata or transformed into fractional polynomials if they were selected for inclusion within the model. Continuous variables were assessed for distribution and linear risk associations and included in the model as fractional polynomial terms if deemed necessary. Some continuous covariates were included as categorical covariates (e.g. HbA1c) to aid in the interpretation of the data.

The model for each outcome was developed using forwards stepwise selection. The model was deemed to be optimal once Akaike's Information Criteria (AIC)[262] reduced by less than 2 with the addition of new variables. Royston-Sauerbrei's D-statistic[222] and Harrell's C index[263] statistics are reported as measures of model calibration. Age at diagnosis and HbA1c group were included in the model as *a priori* covariates, and pre-existing cardiovascular disease was included as an *a priori* strata.

Pre-specified sub-analyses were undertaken to explore patient level characteristics where it was suspected that these may impact the optimal HbA1c level and thus inform clinical decisions. These included: pre-existing cardiovascular disease, insulin use, sulphonylurea use and age group at diagnosis.

HbA1c levels were categorised into 5 groups aligned with current guidelines (<48mmol/mol [6.5%]; 48-57.9mmol/mol [6.5-7.4%]; 58-69.9mmol/mol [7.5-8.4%], 70-80.9mmol/mol [8.5-9.4%] and ≥81mmol/mol [≥9.5%]). Age at diagnosis was used as a continuous covariate in all other circumstances but was used a categorical covariate (<60 years, ≥60 years) for the purposes of exploring the association of HbA1c and age with outcomes. All outcomes are reported using hazard ratios (HR) and 95% confidence intervals within each HbA1c group; the HbA1c 48-57.9mmol/mol [6.5-7.4%] was defined as the reference group and for sub-analyses the non-exposed group was considered as the reference (e.g. non-insulin user, no pre-existing cardiovascular disease).

Ethics and funding

The study was approved by the Independent Scientific Advisory Committee (ISAC) of CPRD and the Medicines and Health products Regulatory Authority (Protocol 19_202) and is funded by the University of Nottingham.

Results

Cohort characteristics

A total of 215,772 with an incident diagnosis of T2DM during the study period were identified. After applying the exclusion criteria, 172,869 individuals remained in the study for the MACE and all-cause mortality outcomes. For the individual macrovascular event outcomes, 160,013 individuals were included for myocardial infarction, 159,739 for stroke and 171,638 for heart failure. **Figure 3** demonstrates the numbers are each stage and reasons for exclusion and **table 8** summarises the baseline characteristics of the overall cohort.

During the study 20,151 (11.7%) of individuals died and 24,239 (14.0%) experienced a MACE event. The mortality rate was 2.61 (95% CI 2.58-2.65) per 100 person-years and the rate of MACE was 3.53 (95% CI 3.48-3.57) per 100 person-years. The median follow-up time for the mortality outcome was 4.0 years and for MACE was 3.4 years, the last observed exit from the study for both outcomes was at 11.2 years. The total analysis time at risk was 770,996.5 years for mortality and 687,073.5 years for MACE. The Kaplan-Meier graphs for event rates, by HbA1c group, are shown in **figures 4a and 4b.**

Figure 3. Flowchart demonstrating the numbers included and reasons for exclusion at each stage for mortality and macrovascular composite outcomes, and myocardial infarction, heart failure and stroke sub-outcomes.

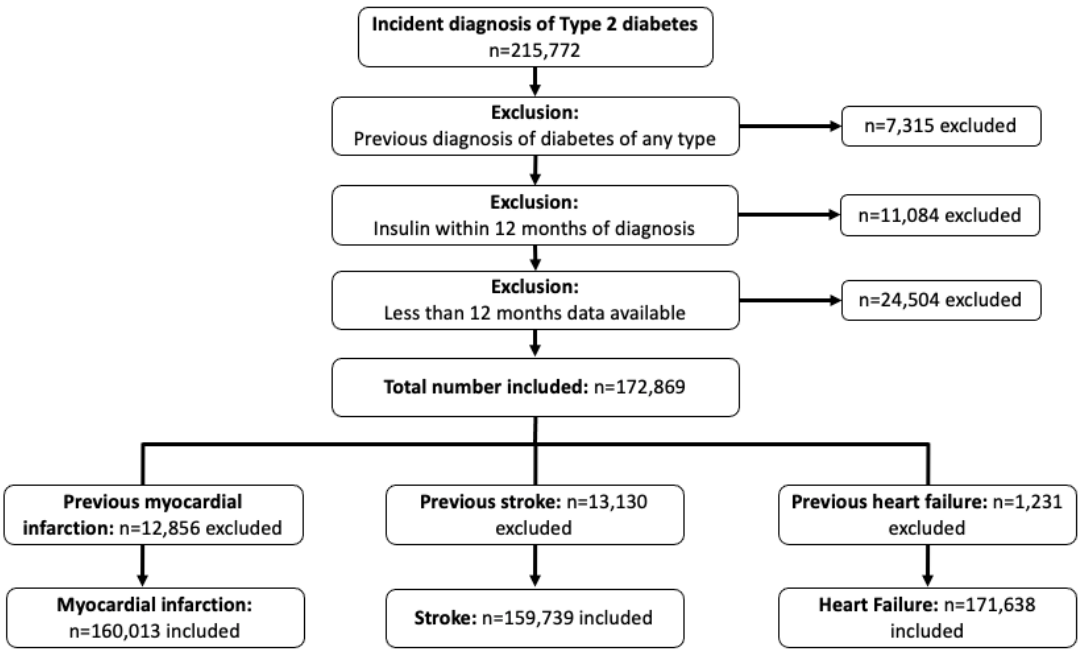


Table 8. Baseline characteristics of the cohort

Baseline characteristics	n=172,869	Non-missing at baseline - n (%)
Age (Years), mean (SD)	62.6 (14.0)	172,869 (100.0)
Weight (kg), mean (SD)	90.9 (20.9)	95,498 (55.2)
BMI (kg/m2), mean (SD)	31.9 (6.6)	95,222 (55.1)
Systolic BP (mm/Hg), mean (SD)	133.7 (15.1)	127,265 (73.6)
Diastolic BP (mm/Hg), mean (SD)	76.9 (9.5)	127,240 (73.6)
Total Cholesterol (mmol/L), mean (SD)	4.5 (1.1)	89,847 (60.0)
HDL Cholesterol (mmol/L), mean (SD)	1.2 (0.4)	78,887 (45.6)
LDL Cholesterol (mmol/L), mean (SD)	2.5 (1.0)	59,076 (34.2)
HbA1c (mmol/mol), mean (SD)	52.6 (13.3)	106,120 (61.4)
Gender, Female, n (%)	92,271 (54.6)	172,869 (100.0)
Ethnicity, White British, n (%)	106,267 (62.9)	118,513 (68.6)
Smoker, Current, n (%)	14,508 (8.4)	80,433 (47.6)

For the sub-outcomes, myocardial infarction occurred in 4,502 individuals (2.8%), an event rate of 0.65 (95% CI 0.63-0.67) per 100 person-years, 6,190 (3.9%); stroke events occurred with a rate of 0.90 (95% CI 0.87-0.92) per 100 person-years and for heart failure 2,852 (1.7%) events occurred with an event rate of 0.38 (95% CI 0.37-0.39) per 100 person-years. The event rates for the sub-outcomes by HbA1c group are illustrated in the Kaplan-Meier plots, **figures 4c-e.** The total analysis time at risk of each of the outcomes were: myocardial infarction 695,132.0 person-years, stroke 691,272.0 person-years and heart failure 751,882.9. The last observed exit was 11.2 years for all sub-outcomes. The median follow-up time for each outcome was: 6.2 years for myocardial infarction, 6.1 years for stroke and 6.2 years for heart failure.

Figures 4a-e. Kaplan-Meier survival plots for mortality (a), macrovascular composite outcome (b), myocardial infarction (c), stroke (d) and heart failure (e)

Fig 4a.

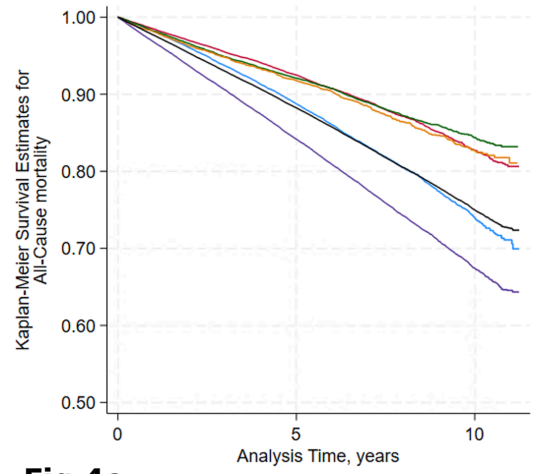


Fig 4b.

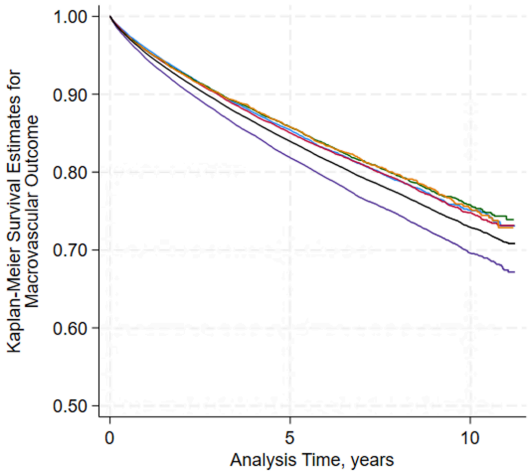


Fig 4c.

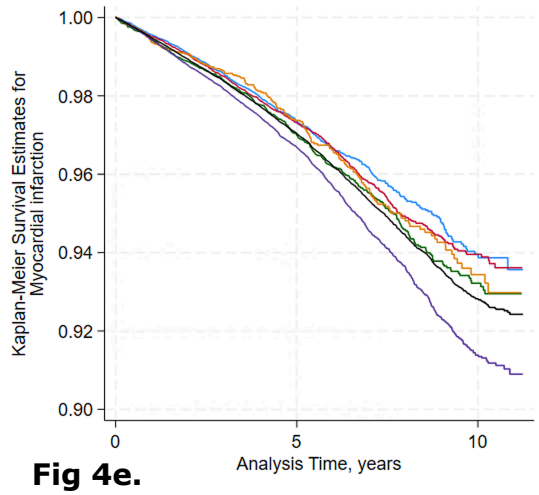


Fig 4d.

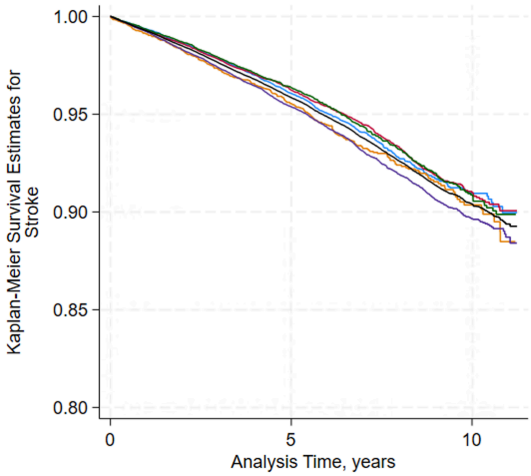
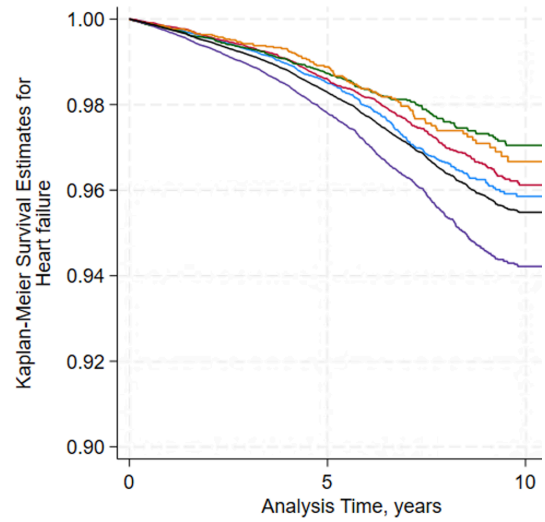
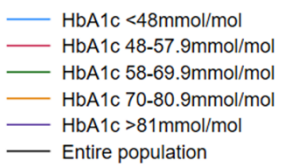


Fig 4e.





HbA1c dual report

<48mmol/mol	<6.5%
48-57.9mmol/mol [6.5-7.4%]	6.5-7.4%
58-69.9mmol/mol	7.5-8.4%
70-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Models

The model selected for the risk all-cause mortality is shown in **appendix 3a**, and for MACE is shown in **appendix 3b**. The all-cause mortality model had a Royston-Sauerbrei D-Statistic of 0.495, a Harrell's C index of 0.824. The MACE model had a D-statistic of 0.739 and Harrell's C Index of 0.739. For the secondary outcomes of myocardial infarction, stroke, and heart failure the D-statistics were 0.232, 0.261 and 0.486 respectively and the Harrell's C Indexes were 0.702, 0.736 and 0.820 respectively. The models are outlined in **appendices 3c-e.**

All-cause mortality outcome

The lowest risk of call-cause mortality was observed in the reference group (HbA1c 48-57.9mmol/mol [6.5-7.4%]), increased in the lower HbA1c<48mmol/mol [<6.5%] group (HR 1.18 [95% CI 1.08-1.29]) and was highest with a HbA1c≥81mmol/mol [≥9.5%] (HR 1.36 [95% CI 1.18-1.56]). This is illustrated in **figure 5a.** For the overall mortality outcome, and in sub-analyses by age, pre-existing cardiovascular disease and insulin or sulphonylureas use, a "U-shaped" association between HbA1c and mortality was demonstrated.

For those age <60years at diagnosis, when compared to those ≥60 years, there was a lower risk of mortality at all HbA1c levels. For both groups, the optimum HbA1c was 48-57.9mmol/mol [6.5-7.4%] (age ≥60 years, HR 3.29 [95% CI 2.94-3.67]). An increased HR was observed in both the younger (HR 1.24 [95% CI 1.06-1.45]) and older group (HR 3.70 [95% CI 3.33-4.12]) at HbA1c<48mmol/mol [<6.5%]. The highest

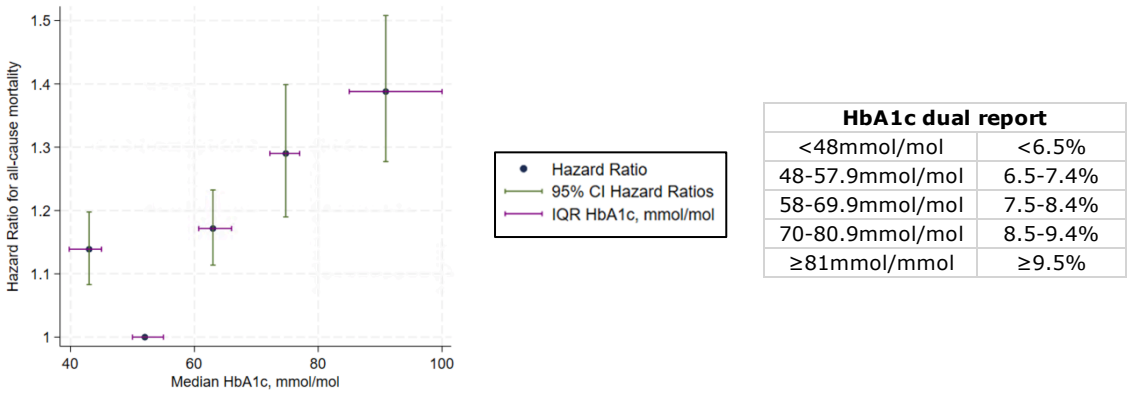
risk in both age groups was at HbA1c≥81mmol/mol [≥9.5%] (HR 1.40 [95% CI 1.17-1.66] in age<60 years vs HR 4.34 [95% CI 3.78-4.99] in age≥60 years). This is shown in **figure 5b.**

Individuals with pre-existing cardiovascular disease had higher all-cause mortality at all HbA1c levels. In keeping with the overall results for mortality, the optimum HbA1c in both groups was 48-57.9mmol/mol [6.5-7.4%]and increased with HbA1c<48mmol/mol [<6.5%] and at higher HbA1c levels. The maximum observed HR for those with cardiovascular disease was in the HbA1c 70-80.9mmol/mol [8.5-9.4%] group (HR 1.70 [95% CI 1.52-1.91]), the lowest at HbA1c 48-57.9mmol/mol [6.5-7.4%] (HR 1.32 [95% 1.23-1.42]) and increased again in the HbA1c<48mmol/mol [<6.5%] group (HR 1.44 [95% CI 1.33-1.56]). This is illustrated in **figure 5c.**

The results for insulin and sulphonylureas users and shown in **figures 5d. and 5e.** For insulin users, the minimum risk of all-cause mortality occurs in the HbA1c 58-69.9mmol/mol [7.5-8.4%] group with a HR 1.52 (95% CI 1.20-1.94) and the highest risk was observed in the HbA1c <48mmol/mol [<6.5%] group (HR 2.42 [95% CI 1.79-3.27]. For sulphonylurea users the lowest risk of mortality was at HbA1c 48-57.9mmol/mol [6.5-7.4%] (HR 1.15 [95% CI 1.06-1.23]) and the highest at HbA1c ≥81mmol/mol [≥9.5%] (HR 1.52 [95% CI 1.33-1.72]). Insulin and sulphonylurea use were both associated with a higher risk of mortality at all HbA1c levels. The confidence intervals between users and

Figures 5a-e. Graphs demonstrating the association between HbA1c and all-cause mortality across the entire cohort (a) and within subgroups of interest as follows: b) age group, c) pre-existing cardiovascular disease, d) sulphonylureas use and e) insulin use. Vertical bars/shaded area representing 95% confidence intervals.

Fig 5a.



HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-69.9mmol/mol	7.5-8.4%
70-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 5b.

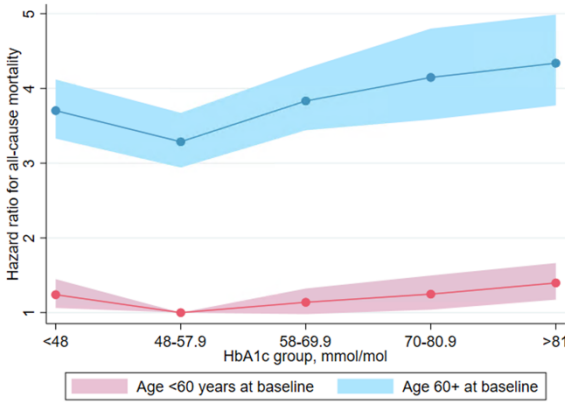


Fig 5c.

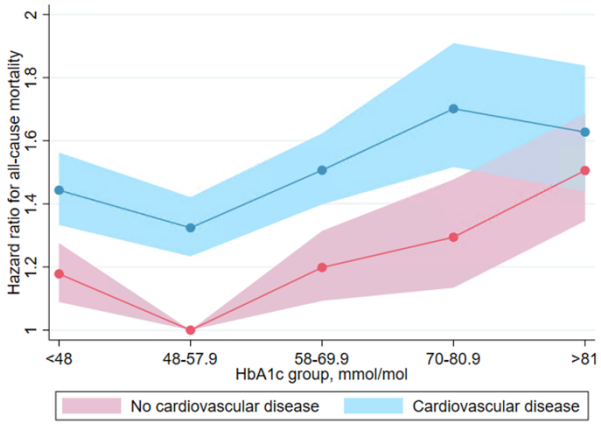


Fig 5d.

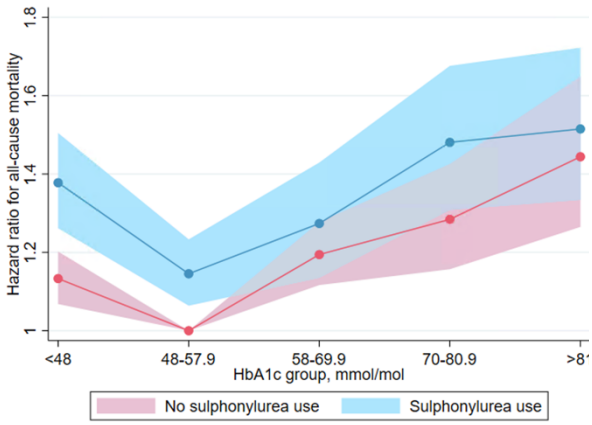
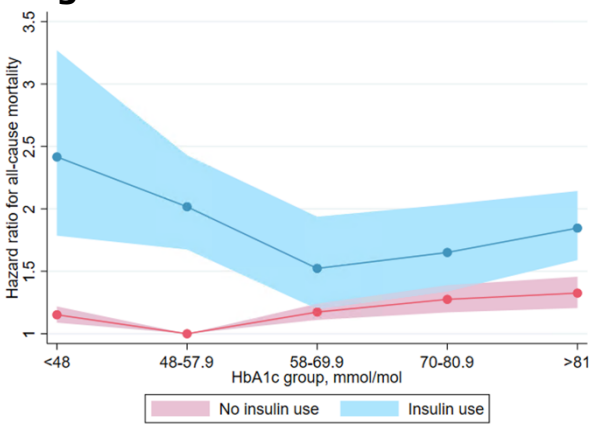


Fig 5e.



non-users at higher HbA1c levels are overlapping, suggesting difference between these groups do not exist at higher HbA1c levels.

Macrovascular composite outcome

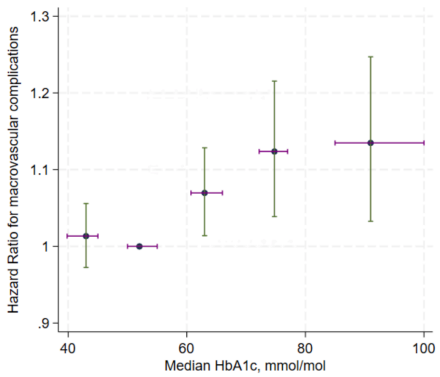
For the macrovascular composite outcome, the lowest risk was observed in the reference group, HbA1c 48-57.9mmol/mol [6.5-7.4%]. The hazard ratios were similar in the lower HbA1c <48mmol/mol [<6.5%] group (HR 1.01 [95% CI 0.97-1.06]) but increased at higher HbA1c levels; the highest hazard for MACE was observed in the HbA1c ≥81mmol/mol [≥9.5%] group (HR 1.13 [95% CI 1.03-1.25]). This is illustrated in **figure 6a.**

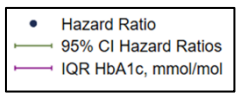
When looking at the different age groups, the lowest risk of MACE in those aged <60 years was in the HbA1c <48mmol/mol [<6.5%] group (HR 0.90 [95% CI 0.83-0.97]). In those aged ≥60 years the lowest risk was in the HbA1c 48-57.9mmol/mol [6.5-7.4%] group (HR 1.62 [95% CI 1.52-1.72]) and rose at both lower and HbA1c levels; the highest MACE hazard was observed in the 70-80.9mmol/mol [8.5-9.4%] group (HR 1.78 [95% CI 1.58-2.02]). The older group had a higher risk of MACE at all HbA1c levels, as demonstrated in **figure 6b.**

Pre-existing cardiovascular disease was associated with a higher risk of MACE at all HbA1c levels. The lowest risk in those with pre-existing cardiovascular disease was observed at HbA1c 48-57.9mmol/mol [6.5-7.4%] (HR 3.07 [95% CI 2.89-3.26]) and was highest with a HbA1c 58-69.9mmol/mol [7.5-8.4%] (HR 3.26 [95% CI 2.99-3.55]).

Figures 6a-e. Graphs demonstrating the association between HbA1c and macrovascular composite outcomes across the entire cohort (a) and within subgroups of interest as follows: b) age group, c) pre-existing cardiovascular disease, d) sulphonylureas use and e) insulin use. Vertical bars/shaded area representing 95% confidence intervals.

Fig 6a.





HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-69.9mmol/mol	7.5-8.4%
70-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 6b.

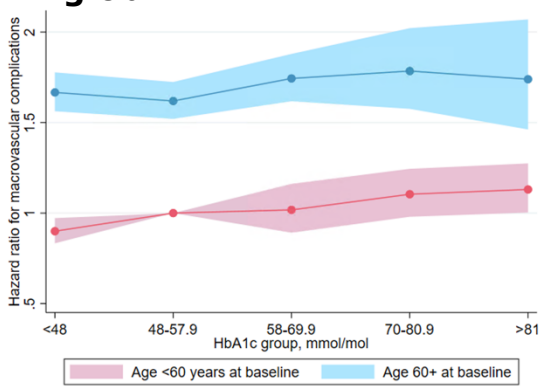


Fig 6c.

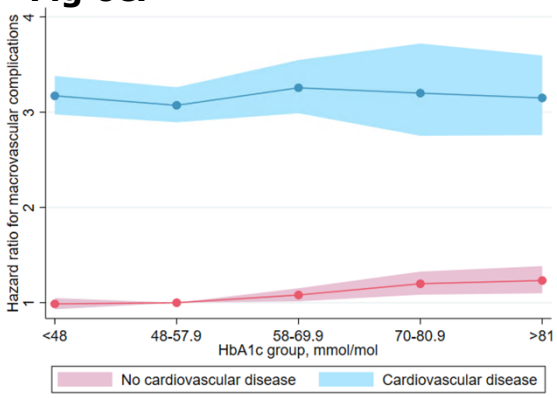


Fig 6d.

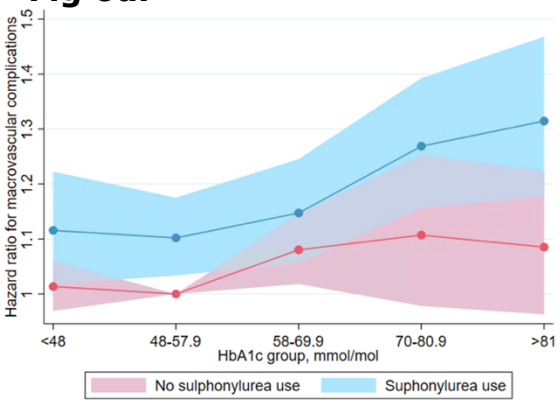
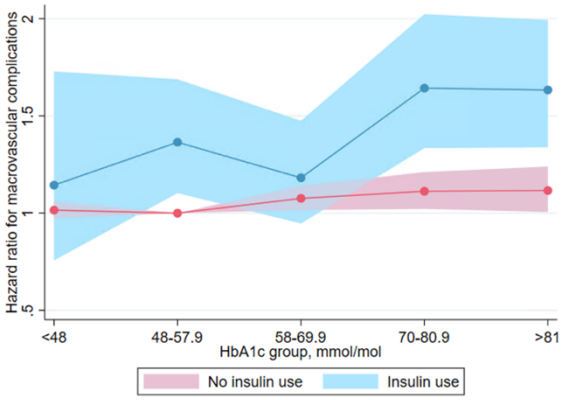


Fig 6e.



Risk also increased in the lowest HbA1c <48mmol/mol [<6.5%] group (HR 3.17 [95% CI 2.98-3.38]). In those without cardiovascular disease, the HbA1c <48mmol/mol [<6.5%] group had the lowest risk of MACE (HR 0.99 [95% CI 0.93-1.05]) and this rose across the groups and was highest with HbA1c≥81mmol/mol [≥9.5%] (HR 1.23 [95% CI 1.10-1.38]). This is illustrated in **figure 6c.**

Both insulin and sulphonylurea use were associated with a higher risk of MACE at all HbA1c levels. The lowest risk of MACE for insulin users was in the HbA1c <48mmol/mol [<6.5%] (HR 1.18 [95% CI 0.95-1.48]) but was similar across all HbA1c groups with wide confidence intervals. The lowest risk of MACE in sulphonylurea users was in the HbA1c 48-57.9mmol/mol [6.5-7.4%] group (HR 1.10 [95% CI 1.03-1.18]) and was highest in the HbA1c >81mmol/mol [≥9.5%] group (HR 1.31 [95% CI 1.18-1.47]). The confidence intervals are broad and overlapping suggesting the differences between insulin users and non-insulin users and sulphonylureas users and non-sulphonylureas users are not significant. The results for sulphonylureas and insulin users are demonstrated in **figures 6d. and 6e.**

Myocardial infarction

The lowest hazard ratio for myocardial infarction was observed in the HbA1c<48mmol/mol [<6.5%] group (HR 0.84 [95% CI 0.78-0.91]) and increased with increasing HbA1c levels; it was highest in the HbA1c

≥81mmol/mol [≥9.5%] group (HR 1.59 [95% CI 1.40-1.81]). This is shown in **figure 7a.**

The sub-analysis by age group demonstrated a higher risk of myocardial infarction at all HbA1c levels in individuals age≥60 years at diagnosis. The lowest hazard was observed at HbA1c<48mmol/mol [<6.5%] in both groups (age ≥60 years, HR 1.17 [95% CI 1.50-1.98]) and the highest was observed in the HbA1c≥81mmol/mol [≥9.5%] group (age ≥60 years, HR 2.94 [95% CI 2.37-3.64]) as demonstrated by **figure 7b.**

A similar pattern was noted amongst individuals with pre-existing cardiovascular disease, who had a higher risk of myocardial infarction at all HbA1c levels with the lowest risk at HbA1c<48mmol/mol [<6.5%] (HR 1.98 [95% CI 1.75-2.24]) and highest risk at HbA1c≥81mmol/mol [≥9.5%] (HR 3.33 [95% CI 2.58-4.29]) as illustrated by **figure 7c.**

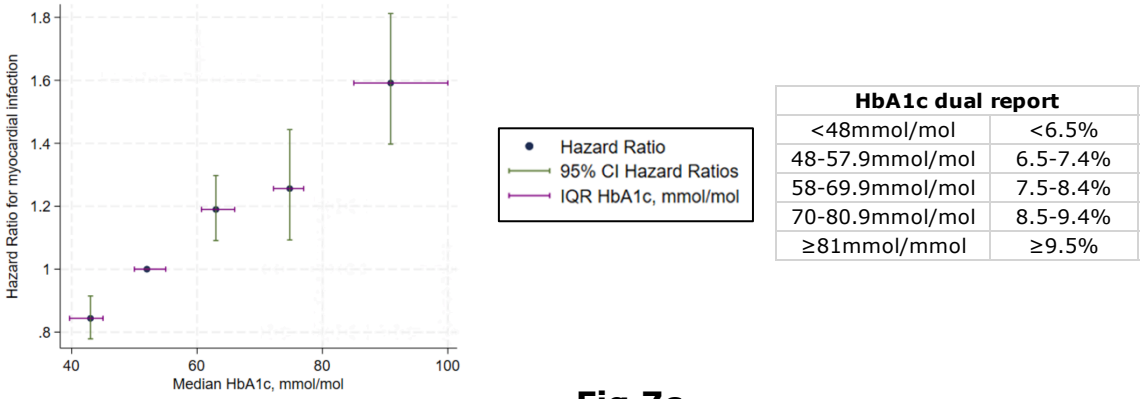
Suphonylurea users had a similar risk of myocardial infarction to non-users at all HbA1c levels. In both groups the hazard was lowest at HbA1c<48mmol/mol [<6.5%] (sulphonylurea use, HR 0.84 [95% CI 0.66-1.08]) and rose with increasing HbA1c; risk was highest in the HbA1c≥81mmol/mol [≥9.5%] group (sulphonylureas use, HR 1.46 [95% CI 1.89-1.79]). This is shown in **figure 7d**.

Insulin use was associated with a similar risk of myocardial infarction to non-users at all HbA1c levels. The lowest hazard of myocardial infarction in insulin users was observed in the HbA1c<48mmol/mol [<6.5%] group

(HR 0.42 [95% CI 0.11-1.58]) but with notably wide confidence intervals across all HbA1c categories. In individuals not using insulin the lowest

Figures 7a-e. Graphs demonstrating the association between HbA1c and myocardial infarction across the entire cohort (a) and within subgroups of interest as follows: b) age group, c) pre-existing cardiovascular disease, d) sulphonylureas use and e) insulin use. Vertical bars/shaded area representing 95% confidence intervals.

Fig 7a.



HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-69.9mmol/mol	7.5-8.4%
70-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 7b.

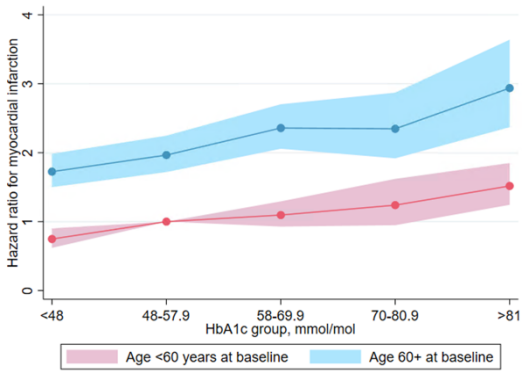


Fig 7c.

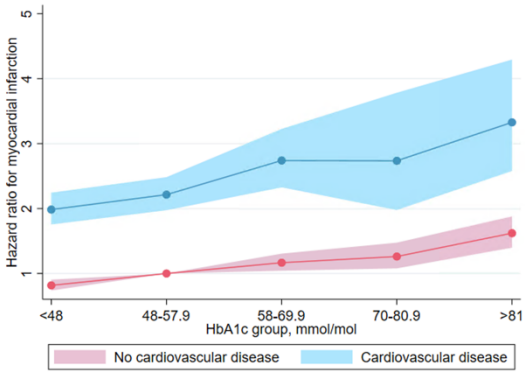


Fig 7d.

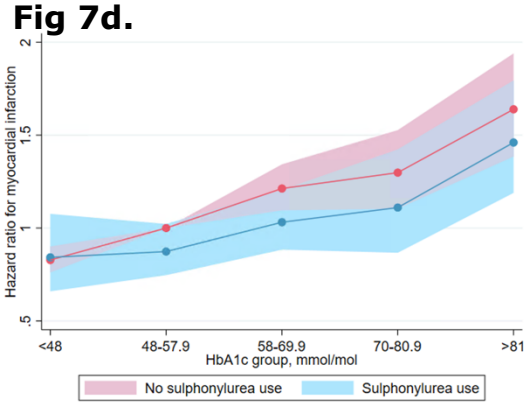
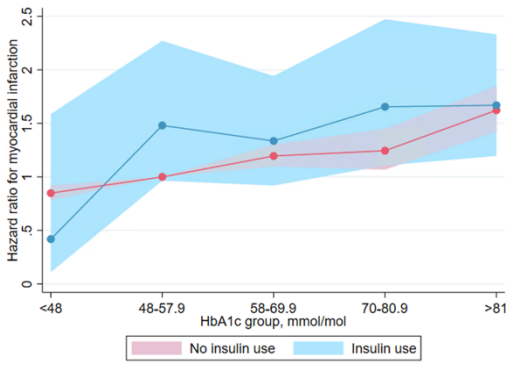


Fig 7e.



risk was also in the HbA1c<48mmol/mol [<6.5%] (HR 0.85 [95% CI 0.78-0.92]) and highest in the HbA1c≥81mmol/mol [≥9.5%] group (HR 1.62 [95% CI 1.42-1.85]). This is demonstrated in **figure 7e.**

Heart failure

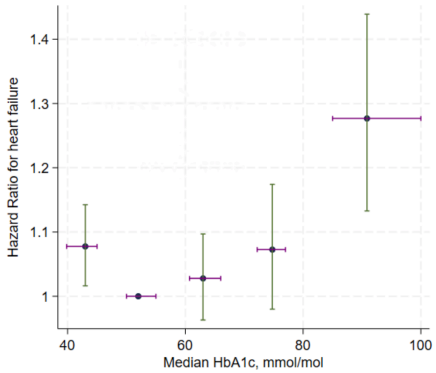
The hazard for heart failure was lowest in the reference group, HbA1c 48-57.9mmol/mol [6.5-7.4%]. The HbA1c<48mmol/mol [<6.5%] group was associated with increased risk of heart failure (HR 1.08 [95% CI 1.02-1.14]). The highest risk was observed in the HbA1c≥81mmol/mol [≥9.5%] (HR 1.28 [95% CI 1.13-1.44]). **Figure 8a.** demonstrates this graphically and appears to be a ”U-shaped” associated with risk increasing at both lower and higher than 48-57.9mmol/mol [6.5-7.4%].

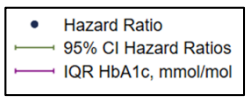
The sub-analysis by age group demonstrated an increased risk of heart failure across all HbA1c levels in the ≥60-year age group. In those aged <60 years, the risk was similar across the three lowest HbA1c groups, being lowest in the HbA1c <48mmol/mol [<6.5%] group (HR 0.90 [95% CI 0.74-1.09]). In this age group the highest risk was observed at HbA1c≥81mmol/mol [≥9.5%] (HR 1.39 [95% CI 1.08-1.80]). In the age ≥60 years group, the risk was similar across all HbA1c levels with wide confidence intervals, though was numerically lowest in the HbA1c 70-80.9mmol/mol [8.5-9.4%] group (HR 5.25 [95% CI 4.23-6.51]). This is demonstrated in **figure 8b.**

In individuals without pre-existing cardiovascular disease the reference HbA1c group of 48-57.9mmol/mol [6.5-7.4%] was associated with the

Figures 8a-e. Graphs demonstrating the association between HbA1c and heart failure across the entire cohort (a) and within subgroups of interest as follows: b) age group, c) pre-existing cardiovascular disease, d) sulphonylureas use and e) insulin use. Vertical bars/shaded area representing 95% confidence intervals.

Fig 8a.





HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-69.9mmol/mol	7.5-8.4%
70-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 8b.

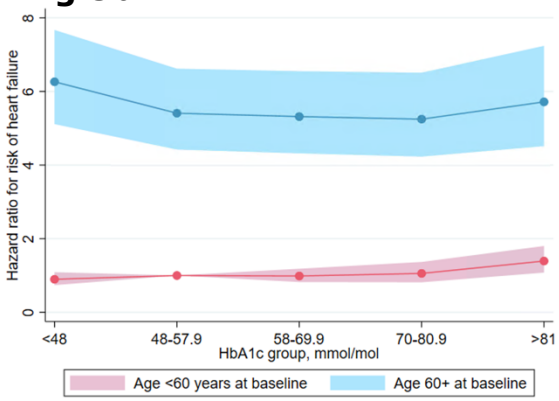


Fig 8c.

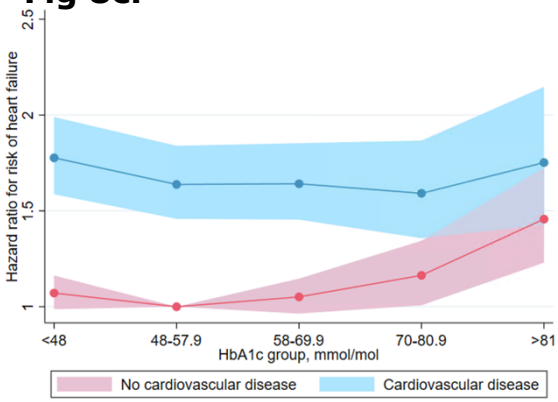


Fig 8d.

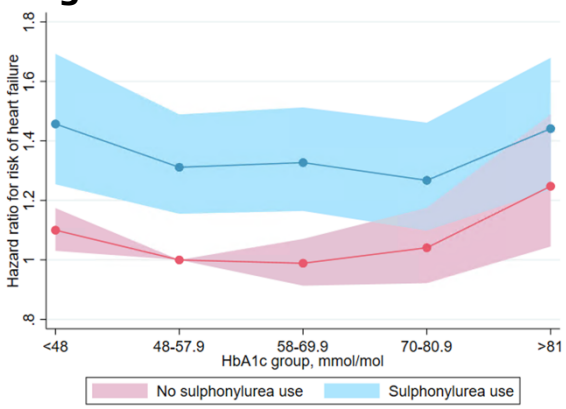
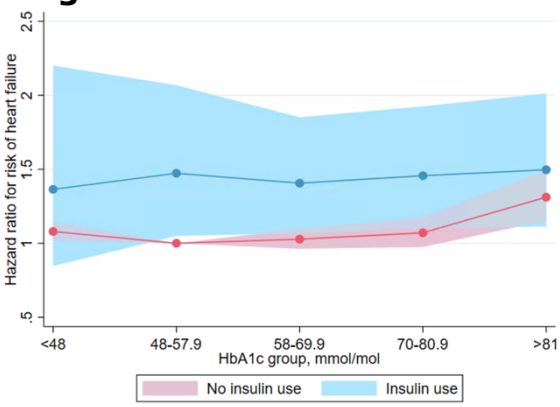


Fig 8e.



lowest risk of heart failure. The risk of heart failure was significantly higher at all HbA1c levels apart from HbA1c >81mmol/mol [≥9.5%]. The risk was not significantly different at <48mmol/mol [<6.5%] (HR 1.07 [95% CI 0.99-1.16]) or at 58-69.9mmol/mol [7.5-8.4%] (HR 1.05 [95% CI 0.96-1.15]). In those without pre-existing cardiovascular disease, the highest risk was observed at >81mmol/mol [≥9.5%] (HR 1.46 [95% CI 1.23-1.73]). In those with pre-existing cardiovascular disease the hazard was numerically lowest in the HbA1c 70-80.9mmol/mol [8.5-9.4%] group (HR 1.59 [95% CI 1.36-1.87]) but was not significantly different to all other groups. These results are shown in **figure 8c.**

Figures 8d and 8e. show the hazard ratios for HbA1c and risk of heart failure in suphonlyurea and insulin users respectively. For both drug classes, risks were similar across all HbA1c levels with no significant differences. In individuals not using the drug the lowest risk was in the reference group, HbA1c 48-57.9mmol/mol [6.5-7.4%].

Stroke

The risk of stroke was lowest in the HbA1c <48mmol/mol [<6.5%] (HR 0.97 [95% CI 0.90-1.05]), though this was not significantly lower than the reference group of 48-57.9mmol/mol [6.5-7.4%]. The risk of stroke increased with higher HbA1c and was highest in the HbA1c 70-80.9mmol/mol [8.5-9.4%] group (HR 1.46 [95% CI 1.30-1.63]) and HbA1c ≥81mmol/mol [≥9.5%] group (HR 1.45 [95% CI 1,27-1.65]) which were not statistically different from each other. These results are shown in **figure 9a.**

Figure 9b. shows the hazard ratios for risk of stroke by patient age group. In individuals aged <60 years old at diagnosis, the lowest risk of stroke was observed with HbA1c<48mmol/mol [<6.5%] (HR 0.89 [95% CI 0.72-1.11]) and HbA1c 48-57.9mmol/mol [6.5-7.4%] (reference) with no statistically significant difference between the two groups. The hazard ratio increased with rising HbA1c and was highest in the HbA1c ≥81mmol/mol [≥9.5%] group (HR 1.49 [95% 1.20-1.84]). In the older age group, the lowest risk numerically was associated with HbA1c 48-57.9mmol/mol [6.5-7.4%] (HR 3.07 [95% CI 2.66-3.53]) though with wide confidence intervals there were no statistically significant differences between any of the HbA1c groups. Older age at diagnosis was associated with an increased risk of stroke at all HbA1c levels.

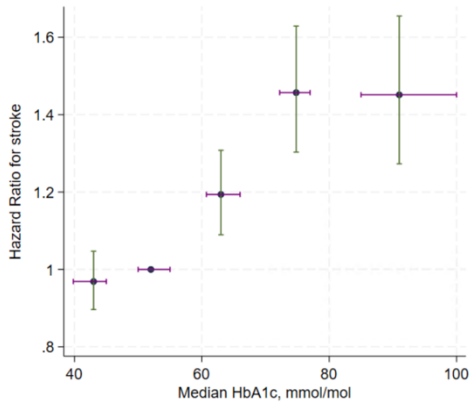
As demonstrated by **figure 9c.**, the risk of stroke decreased with lower HbA1c levels in individuals both with and without pre-existing cardiovascular disease. The risk was lowest in the HbA1c<48mmol/mol [<6.5%] in both instances (pre-existing cardiovascular disease, HR 1.28 [1.15-1.42]). The risk of stroke was higher in those with pre-existing cardiovascular disease compared to those without at lower HbA1c levels but was not significantly higher in the HbA1c 70-80.9mmol/mol [8.5-9.4%] and >81mmol/mol [≥9.5%] groups.

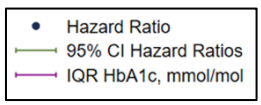
Individuals taking insulin or sulphonylureas did not have a significant increased risk of stroke compared to those not taking them at any HbA1c level, as demonstrated graphically with the broad overlapping confidence intervals. The lowest risk of stroke in insulin users was observed at

HbA1c<48mmol/mol [<6.5%] (HR 0.88 [95% 0.31-2.51]), though with wide confidence intervals, the difference in stroke hazard at different HbA1c levels was not significant. For sulphonylurea users, the lowest risk of stroke was also at HbA1c <48mmol (HR 1.03 [0.85-1.25]) and was similar at HbA1c 48-57.9mmol/mol [6.5-7.4%] (HR 1.06 [95% CI 0.93-1.20]). The highest risk was at HbA1c 70-80.9mmol/mol [8.5-9.4%] (HR 1.64 [95% CI 1.36-1.98]) and at 81mmol/mol [≥9.5%] (HR 1.62 [95% CI 1.37-1.91]). These results are shown in **figure 9d.** (for sulphonylureas users) and in **figure 9e.** (for insulin users).

Figures 9a-e. Graphs demonstrating the association between HbA1c and stroke across the entire cohort (a) and within subgroups of interest as follows: b) age group, c) pre-existing cardiovascular disease, d) sulphonylureas use and e) insulin use. Vertical bars/shaded area representing 95% confidence intervals.

Fig 9a.





HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-68.9mmol/mol	7.5-8.4%
69-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 9b.

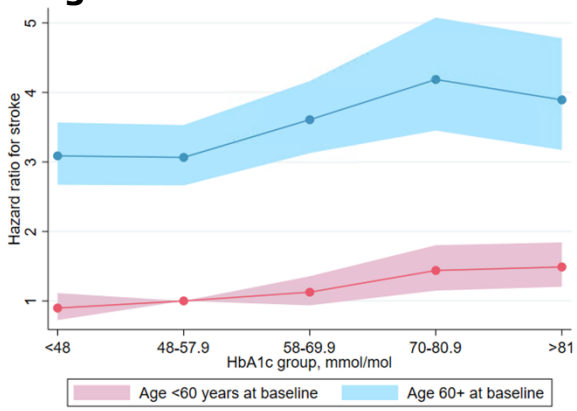


Fig 9c.

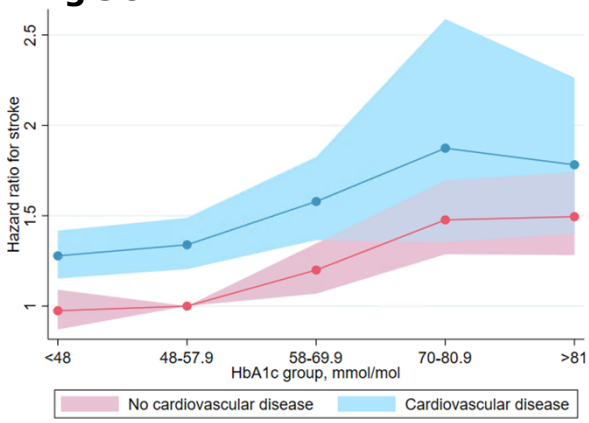


Fig 9d.

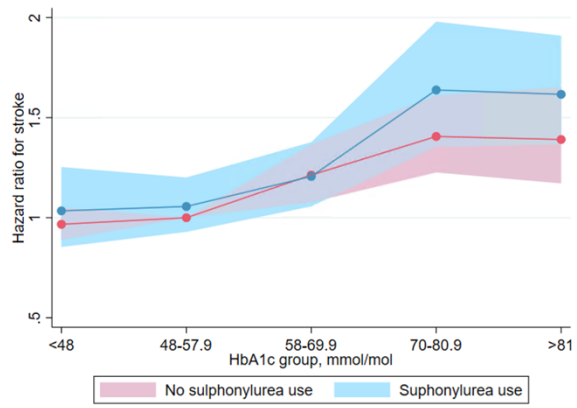
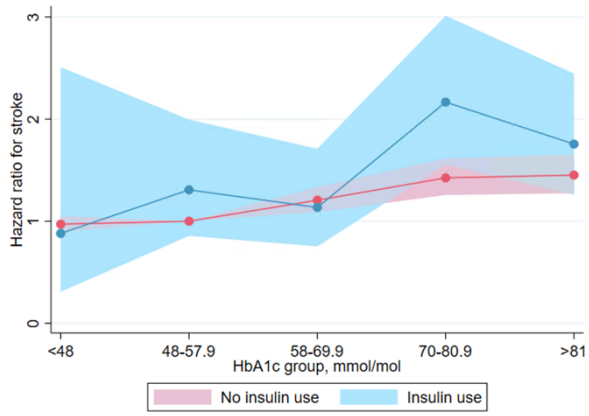


Fig 9e.



Discussion

This study provides additional evidence to support the individualisation of HbA1c in view of patient characteristics or the choice of therapy. It supports the current ADA/EASD hyperglycaemia and NICE NG28 guidelines for the management of type 2 diabetes in adults in recommending collaborative goal setting and taking a broad view of the patient's global health and their priorities[59, 68]. However, this study additionally identifies risks associated with HbA1c levels below target that should prompt clinicians to consider de-escalation of treatments to prevent risk of complications.

For all-cause mortality, risk increased at with both higher and lower HbA1c levels which we described as a "U-shaped" association with the optimal HbA1c level being 48-57.9mmol/mol [6.5-7.4%]– notably higher than recommended by most guidelines. This persisted across all sub-analyses performed, notably in both younger and older age groups irrespective of therapy. Whilst current UK guidelines suggest a target of <53mmol/mol for individuals using therapies with a risk of hypoglycaemia (sulphonylureas and insulin)[68], this study suggests that the lowest risk of all-cause mortality was associated with a HbA1c 58-69.9mmol/mol [7.5-8.4%] and increased at lower HbA1c level. This may have implications for target setting in insulin treated individuals with type 2 diabetes.

The HbA1c levels associated with the lowest risk of MACE were observed in the <48mmol/mol [<6.5%] and 48-57.9mmol/mol [6.5-7.4%] groups.

On the one hand, this is in keeping with current guidelines and existing studies[59, 68, 73, 264]; however, it may also be viewed that this demonstrated no additional benefits in MACE risk reduction from reducing HbA1c level beyond 57.9mmol/mol. When assessing the results from the subgroup analyses, individuals aged <60 years old at diagnosis were observed to have small but additional benefits from reducing HbA1c to <48mmol/mol [<6.5%] (HR 0.90 [95% CI 0.8-0.97]). Individuals with pre-existing cardiovascular disease had similar risk of further MACE irrespective of glucose levels; suggesting the adoption of multifactor risk reduction rather than a glucocentric approach may be beneficial. Similarly, to the association between all-cause mortality and HbA1c levels in insulin users, both insulin and sulphonylureas use had similar risk across all HbA1c levels with broad confidence intervals with a trend towards use of these medications increasing the overall risk. Again, this could suggest that reducing HbA1c with these medications confers no additional benefit in MACE risk reduction or may represent more difficult diabetes management associated with insulin resistance the presence of other cardiometabolic risk factors[265, 266].

For risk of myocardial infarction, a more linear association between adverse outcome and HbA1c levels was observed with the lowest risk in the HbA1c<48mmol/mol [<6.5%] group, a target that mirrors guideline recommendations[59, 68]. This persisted for the sulphonylureas, age group and pre-existing cardiovascular disease sub-group analyses. For insulin users, due to wide confidence intervals, this association was less

clear. Notably, insulin and suphonylurea use was not associated with increased with of myocardial infarction compared to non-use.

A ”U-shaped” association between HbA1c and risk of heart failure was observed, with the lowest risk in the HbA1c 48-57.9mmol/mol [6.5-7.4%] group. In individuals aged >60 years old, with pre-existing cardiovascular disease and those using insulin or sulphonylureas the risk was similar across all HbA1c levels and did not significantly increase at lower or higher levels. This is further evidence that suggests a glucose management may be less relevant in reducing HbA1c levels in these groups. In younger individuals a more linear association was noted, though with similar hazard ratios across all three lower HbA1c groups (<48, 48-57.9 and 58-69.9mmol/mol [7.5-8.4%]). This suggests benefits to lowering glucose levels, but that this may have limited incremental benefit beyond 69.9mmol/mol. Similar “U-shaped” associations to the overall analysis for the heart failure outcome were demonstrated in individuals without pre-existing cardiovascular disease and those not using insulin and sulphonylureas. Comparing these results to guidelines, we observe that the optimal HbA1c levels to prevent heart failure exacerbation may be higher than recommended and at the 48-57.9mmol/mol [6.5-7.4%] level[59, 68]. This is contrary to published reviews that suggest HbA1c is a poor predictive marker of heart failure exacerbation[267], but mirrors other published works which have demonstrated clear “U-shaped” associations between HbA1c and heart failure outcomes[268].

The two lowest HbA1c groups (<48 and 48-57.9mmol/mol [6.5-7.4%]) were associated with the lowest risk of stroke in both the overall analysis and in the sub-analyses of individuals aged <60 years, without pre-existing cardiovascular disease and not using insulin or sulphonylureas. This demonstrates benefits of HbA1c reduction to a level <58mmol/mol with limited benefits from further reduction and could have implications in the context of current guidelines[59, 68].

In insulin users, there were similar risks of stroke irrespective of HbA1c level. Insulin use and sulphonylureas use did not increase the risk of stroke at any HbA1c level compared to non-use. This differs to published work which demonstrated "U-shaped" associations between HbA1c and stroke, notably in a smaller cohort with a larger proportion of non-white individuals or in individuals with concomitant atrial fibrillation[269, 270].

Strengths

The strengths of this study included the use of a large patient dataset, robust time-carrying Cox model methodology to account for change in covariates overtime and is one of the first to assess the association between HbA1c and multiple macrovascular outcomes, in multiple different clinically relevant subgroups of patients, in the real-world. It supplements existing knowledge from randomised control trials like ACCORD[74] and ADVANCE[264]. Our study emphasises the need the consider key characteristics and choice of treatment to achieve targets to minimise risk of adverse outcomes, as well as the potential risks of over-

treatment, even with HbA1c levels considered acceptable within existing guidelines[59, 68].

Limitations

This study utilises data from diagnosis though with a long follow-up over 11.2 years, it is possible that that for some individuals this was not enough time for risk to accrue and complications to develop. Additionally, given the time-period of the study, relatively few individuals would have been using sodium glucose-link transporter 2 inhibitor or glucagon-like peptide-1 receptor agonists drugs which are now recommended earlier in treatment algorithms and have recognised cardiovascular benefits[59, 68, 69, 271]. If a higher proportion of individuals were using these medications with a long length of follow-up, it is feasible that the risk of achieving lower HbA1c levels may differ from those demonstrated in this study if they could be achieved with these drugs over other therapies. The use of HbA1c prevents the quantification of hypoglycaemia – future studies could consider including time-in-range as a newer metric of glycaemic control and better correlate outcomes with glucose levels[61].

Future work

This work should be repeat in future to assess how the risk benefit of achieving certain HbA1c levels modifies mortality and cardiovascular risk in the era of newer therapies. Additionally, work is needed to explore the association between HbA1c and other important outcomes including risk of hypoglycaemia, hospital admission, acute metabolic and microvascular complications.

Conclusion

There is a complex relationship between HbA1c and key outcomes. For some outcomes, or in some situations, achieving lower HbA1c levels does not significantly reduce the risk, or further risk reduction beyond a certain level confers no additional benefits. In addition, for some outcomes a HbA1c <48mmol/mol [<6.5%] may increase the risk of adverse outcome. Guidelines continue to advocate for an individualised and collaborative approach to target settings and we provide evidence to support both the appropriate adjustment of HbA1c targets in some sub-groups and supports existing arguments around the appropriate de-escalation of therapy in others.

Chapter 4 – Frailty and HbA1c targets: A Systematic Review and meta-analysis

Chapter abstract

Background: Current guidelines for type 2 diabetes (T2DM) recommend individualized HbA1c targets to take into account patient age or frailty. We synthesized evidence derived from randomised controlled trials (RCT) and observational studies for intensive treatment towards lower HbA1c targets (HbA1c target ≤58mmol/mol) versus standard care, in elderly (age ≥60years) or frail adults with T2DM.

Methods: Data were from medical literature using a modified Cochrane data extraction, utilizing recognised terms for T2DM, frailty, older age and HbA1c and outcomes of interest. Where hazard ratios (HR) were available, the log-hazard ratios were pooled by meta-analysis, otherwise a narrative synthesis was performed. Primary outcomes of interest were all-cause mortality, severe hypoglycaemia, and hospital admission rates. Secondary outcomes were falls and fracture, hypoglycaemia, and cognitive decline.

Results: 7,528 studies were identified of which 21 manuscripts covering 15 different clinical studies were included in the final review: 9 in meta-analysis and 6 in narrative. No significant difference was noted in all-cause mortality when targeting lower HbA1c levels (pooled hazard ratio 0.96, 95% confidence interval 0.90-1.03) but was associated with increased risk of for severe hypoglycaemia (2.45, 2.22-2.72), which was

further supported by narrative evidence from two additional studies. In contrast, lower HbA1c targets were associated with reduced risk of micro-vascular (0.73, 0.68-0.79) and macro-vascular complications (0.84, 0.79-0.89). Outcome data for risk of hospitalization, decreased cognition and falls and fractures were limited.

Conclusion: In elderly or frail patients with T2DM, targeting lower HbA1c levels was associated with reduced rates of complications but with a statistically significant increased risk of hypoglycaemia. Minimal evidence is available for the effect of targeting lower HbA1c levels on risk of hospitalization, falls, fractures, or cognition. Much heterogeneity exists and the impact of different drug regimens is unclear. Caution is therefore needed when setting glycaemic targets in elderly or frail people with diabetes.

Please note: a version of this chapter has been published in Expert Review of Endocrinology & Metabolism, 2022[272]

Crabtree, T., et al., Intensive glycaemic control and macrovascular, microvascular, hypoglycaemia complications and mortality in older (age ≥60years) or frail adults with type 2 diabetes: a systematic review and meta-analysis from randomized controlled trial and observation studies. Expert Review of Endocrinology & Metabolism, 2022. 17(3): p. 255-267.

Introduction

As discussed in Chapter 1, diabetes and frailty are increasingly coinciding in our aging population. The impact of diabetes on elevating the risk of frailty is therefore recognised and represented in frailty scoring systems such as the electronic frailty index[98, 273, 274].

To recap, the current management of type 2 diabetes (T2DM), irrespective of age or the presence of other long-term conditions is centred on the management of glucose levels, assessed by HbA1c. The National Institute for Health and Care Excellence (NICE) in the UK and the American Diabetes Association (ADA) in the USA have broadly similar recommendations for HbA1c targets in T2DM of <48mmol/mol [<6.5%] (6.5%) if this can be accomplished without introducing significant hypoglycaemia or HbA1c <53mmol/mol [<7.0%] in the majority of people at high risks of hypoglycaemia [67, 275]. Although HbA1c targets are recommended to be adapted in view of patient specific factors, until recently no specific numerical values are given - this leaves final target setting to clinician discretion following discussion with the person with T2DM, with any goal being mutually agreed and with a clear underlying rationale. Other guidelines, such as the 2014 International Diabetes Federation (IDF) meanwhile, adopt less glucose centric approaches and advocate strongly for holistic care, consideration of non-pharmacological management where appropriate and the setting of individualised goals to reduce the risks of hospitalisation and minimise hypoglycaemia[276, 277]. Newer guidelines and consensus statements have provided more prescriptive targets using frailty categories broadly

aligned to recognised scoring systems to support clinicians in adjusting treatment to account for differing levels of physical dependence, dementia and end of life care[102, 277]. Glucose control, however, remains to be an important consideration in the consensus statement by the European Diabetes Working Party for Older People (EDWPOP) which advocated for a HbA1c target of 53-59mmol/mol [7.0-7.5%] for those with mild functional impairment at one end of the frailty spectrum to >70mmol/mol in those with advanced dementia, with an emphasis on avoiding hypoglycaemia and more holistic care[278].

Although consensus and experience tell us that lower HbA1c targets are likely to introduce additional risks, evidence to support this is lacking. Where present, it is heterogenous and uses variable definitions of frailty and differing treatment regimens to achieve glycaemic targets.

Although age is independent to frailty, and not all people of aged>60-years are frail, we can examine this as a proxy to try and unify current studies and their varied outcomes. It has been established that advancing age with T2DM is associated with increased mortality and need for social care[87]. In addition, complications of T2DM due to sub-optimal glycaemic management can cause significant functional limitations and frailty, often more so than in younger or less frail counterparts. For example, significant eye disease [88] in an elderly or frail person is associated with more profound decreases in function or loss of independence and which further increased frailty compared with younger individuals[89]. Despite this, attempts to achieve this tight

glycaemic control in an elderly cohort, and prevent such complications, were associated with increased rates of both severe hypoglycaemia[92, 93] and falls[94] – both of which can have similar derogatory impacts on quality of life. Thus, although glucose centric approaches may not be completely appropriate in frail or elderly individuals, the understanding of the role of glycaemia in the prevention of complications and possible worsening frailty, whilst minimising the risk of hypoglycaemia, is an increasingly important area for study[278]. Given the conflicting evidence for tight glycaemic control, especially in an elderly or frail cohort, this systematic review was undertaken to explore and synthesise the current available RCT and observational evidence assessing the risk versus benefits of tight glycaemic control on multiple relevant outcomes in a frail and/or elderly population.

Aims

This systematic review is being undertaken in order to examine the relationship between intensive treatment targeted towards glucose lowering, as defined by target HbA1c levels, and various outcomes of interest in a frail and/or elderly populations of people with type 2 diabetes mellitus. The outcomes of interest will include macrovascular complications; microvascular complications, metabolic complications; healthcare utilisation; cognition and memory and mortality.

Ultimately, the aim of the study is to establish what the current evidence suggests is the optimum HbA1c target in a frail and/or elderly

populations to minimise the risk of complications, admissions or mortality whilst preventing adverse events or potential increased mortality.

Table 9. A summary of the PICO (population, intervention, comparison, and outcome) model used for this systematic review and meta-analysis.

	Description
P (Population)	Adults aged ≥60 years or with frailty AND a diagnosis of type 2 diabetes mellitus
I (Intervention)	**Intensive glycaemic control:** as defined by HbA1c levels reduced to a pre-specified target level of at least ≤59mmol/mol (≤7.5%), irrespective of treatment used
C (Comparison)	**Standard care**
O (Outcomes)	**All-cause mortality** **Hypoglycaemia** **Hospital admissions** **Macrovascular:** rates of myocardial infarction or stroke **Microvascular:** rates of foot disease or amputation, nephropathy, neuropathy, or retinopathy **Cognition and memory:** rates of dementia, other measures of cognitive decline including mini-mental state examinations. **Falls and fractures:** rates of falls or fractures

Methods

Protocol and registration

A protocol for this systematic review and meta-analysis was prospectively registered with PROSPERO (registration number: CRD42020175114). The final version deviates, as speculated in the initial protocol[279], by the inclusion of observational studies, due to a paucity of RCT data for some of the outcomes. The reporting of this review has been undertaken in the format recommended by the PRISMA guidelines[280]. A summary of the PICO (population, intervention, comparison, and outcome) model for this systematic review is shown in **table 9.**

Eligibility criteria

RCT and observational data (cohort, case-control, and cross-sectional designs) comparing intensive versus conventional glycaemic control, as defined by treatment to a pre-specified HbA1c level, in adults aged ≥60 years or with frailty (as defined by study design) were eligible for inclusion. Sub-group analyses focussing on frail or elderly cohorts from studies including a broader range of patients were eligible for inclusion. Studies published prior to 1990 were excluded, as to our knowledge research in this area began after this date following the Diabetes Control and Complications Trial in type 1 diabetes and any research before this using HbA1c would not have been robust[281]. Additionally, studies published in a non-English language were excluded. Other forms of publication or study design, such as case-series, reviews, or opinion pieces, were excluded.

Studies included had a population with age ≥60 years or specifically included frail individuals irrespective of age, using a recognised definition or assessment tool, in their design. Although those aged ≥60 may not be frail, the lack of studies identified during an informal scoping review and preparatory work meant that criteria had to be widened from the initial age of ≥65. Only studies involving individuals with T2DM were included. Studies including people with type 1 diabetes mellitus or other forms of diabetes (maturity onset diabetes of the young, type 3c diabetes, gestational diabetes) were excluded, unless outcomes for those with T2DM were reported separately.

Studies were selected if their primary intervention was treatment, using any therapy, to a pre-specified HbA1c level irrespective of the eventual target attained. The pre-specified HbA1c target must have been less than 59mmol/mol [7.5%]. The comparison group of usual care should have "standard care" with or without a pre-specified level of HbA1c.

The primary outcomes of interest were all-cause mortality, severe hypoglycaemia (i.e., that requires third party assistance, paramedic callout or admission) or hospital admission for any reason. Secondary outcomes of interest included the following:

- Macrovascular complications: myocardial infarctions, stroke, or heart failure
- Microvascular complications: nephropathy, retinopathy, foot disease (including amputations) or neuropathy.
- Cognitive decline: assessed by mini-mental state examination or similar, dementia.
- Falls and fractures.

Data sources and search strategy

The following electronic databases were searched for English language papers, within the date limits of 01/01/1990 and 25/01/2021: Cumulative Index to Nursing & Allied Health Literature (CINAHL); The *Cochrane Central* Register of Controlled Trials (CENTRAL); EMBASE; MedLine and PubMed.

The search terms used in OVID: Medline are displayed in **table 10.** as an example of the terms used. These were adapted if needed for each database. Language and date limits were applied during the search, but no others were use.

Study screening and selection

Studies were imported into EndNote v9.3 for reference management purposes. Reference lists of any secondary literature found were hand-searched and cross-referenced to ensure no relevant studies were excluded. Titles were screened for irrelevance, following which abstracts were reviewed prior to full-text screening. Full-text studies were selected for inclusion providing they met the pre-specified criteria. Where full-text versions were not available for access, the authors were contacted to obtain results. If this was not possible then the study was excluded from the analysis. All studies were reviewed independently by two reviewers (TC and JJO). Any disputes regarding inclusion/exclusion were adjudicated by a third reviewer (II).

Data extraction

An adapted version of the Cochrane's data collection form for RCTs and non-RCTs was used, tailored specifically to the outcomes of this review[158]. The adapted form is available as **appendix 4.** Key data to be extracted included HbA1c targets, outcomes of interest and participant characteristics including age, frailty, baseline HbA1c, duration of diabetes, weight, BMI, ethnicity, relevant co-existing conditions, and medications (specifically insulin use). Outcomes were captured as hazard ratios (HR)

with 95% confidence intervals to facilitate meta-analysis if possible. If this data was not available, then available outcomes were summarised in a narrative format for subsequent synthesis.

Table 10. Example of search terms for retrieval of studies, in this case from Ovid: Medline electronic database at: http://ovidsp.ovid.com/

1. exp Diabetes Mellitus/
2. diabet*
3. 1 or 2
4. "Type 2" or "type-2" or "type-II" or "type II" or "type two" or "type 2" or "noninsulin dependent" or "non-insulin dependent" or "non insulin dependent"
5. 3 and 4
6. exp Diabetes Mellitus, Type 2/
7. "NIDDM" or "DMT2" or "T2DM" or "T2 DM" or "DM T2" or "TIIDM" or "DMII" or "TII DM" or "DM TII" or "DM2" or "DM" or "DMTII"
8. 5 or 6 or 7
9. exp Frailty/ or exp Frail Elderly/ or exp Health Services for the Aged/ or exp Aged/
10. exp Geriatrics/
11. ag?ing or elder* or senior* or veteran* or retir* or sexagen* or centa* or old* or frail* or octogen* or nonagen* or septugen*
12. old* adj2 (age* or adult* or female* male* or m? n or patient* or people or person* or population* or subject* or wom?n)
13. late* adj2 (life or year*)
14. 9 or 10 or 11 or 12 or 13
15. exp Glycated Hemoglobin A/
16. "HbA1c" or "A1c" or "haemoglobin A1c" or "hemoglobin a1c" or "glycoh?emoglobin" or (h?emoglobin adj3 gly*)
17. (tight* or strict* or agressiv* or rigorous or stringent* or low or optim* or good or excell* or best or better) adj3 (control* or treatment* or target* or intervention* or therap* or manag*)
18. 15 or 16
29. 17 and 18
20. 8 and 14 and 19

Bias assessment

Risk of bias assessments were conducted using the Cochrane's Collaboration bias assessment tool for RCTs[282]. For observational studies, the relevant version (e.g. cross-sectional, cohort) of the The

Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used[283]. Bias was assessed both within studies and across each individual outcome. Bias studies were not excluded from narrative synthesis or narrative review, however, to reduce the risk of introducing further bias into this review. The bias of included studies is one potential limitation of the study design.

Synthesis of results

Data presented as hazard ratios were synthesised by meta-analysis using generic inverse variance with log[HR] and standard errors in Stata 16 SE. A random-effects model was utilised to reflect the broad base from which the search was conducted and the desire to broaden the generalisability of the findings, as has been suggested as good practice by Borenstein et al[284]. Inter-study heterogeneity and variation was assessed and reported using Q and I^2 statistics[285, 286]. Where data were available from a combination of RCT and observational data for the impact of HbA1c levels on outcome of interest, an overall estimate of effect using hazard ratios from both randomised control trials and cohort studies complemented by subgroup analysis by study design. This was undertaken due to a lack of RCT studies and the relative observational nature of many of the RCT extensions. Data of interest from other types of study, such as cross-sectional or case-control, have been synthesised in narrative. For outcomes with an extreme paucity of study data or inter-study heterogeneity or where data was not in an appropriate format to include in meta-analysis, a narrative synthesis of the results have been presented or included alongside meta-analysis.

Results

Literature search and study selection

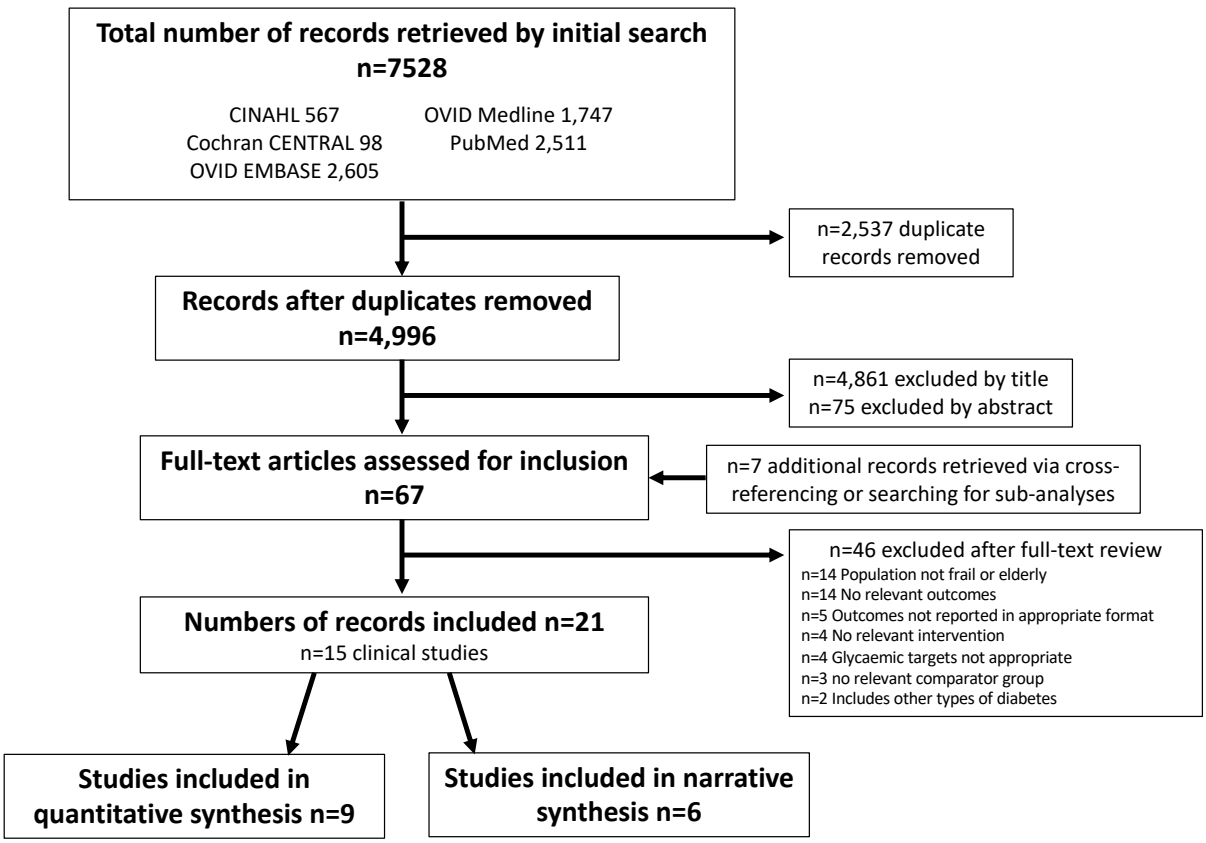
A total of 7,528 records were identified. Of which 567 records were identified through CINAHL, 98 records from Cochrane CENTRAL, 2,605 records from OVID: EMBASE, 1,747 records from OVID: Medline and 2,511 records identified through PubMed. 2,537 were immediately excluded as duplicates. Initial screening of the remaining 4,996 records titles and abstracts resulted in the further exclusion of 4,936 records which did not meet the inclusion criteria. Hand searching of the bibliographies of secondary literature or relevant sub-analyses not identified by the search but included on clinicaltrials.gov yielded an additional 7 records of potential relevance.

67 records were assessed for eligibility by examining full-text content, of which 21 papers reporting the results of 15 different clinical studies with outcomes of interest were identified for final inclusion. Whilst 6 of the studies had outcomes relevant to the review, the data presented was not in a format suitable for meta-analysis and therefore the results of these have been discussed in a narrative format. For the remaining 9 studies, at least some outcome data was available for synthesis by meta-analysis. However, for some outcomes within these studies, data may have been explored or synthesised narratively either due to a general paucity of data for that outcome across the included studies or within the study itself. Two of the studies identified for inclusion – the ACCORD trial[74, 75] and ADVANCE trial[76, 287] – required the assessment of multiple manuscripts (6 and 3 respectively) to fully ascertain and assess the

relevant results, trial design and risk of bias. Reasons for exclusion are demonstrated in the flowchart **Figure 9.**

12 of the identified studies were observational studies – either cohort, cross-sectional or case-control by design and only three were RCTs. The study characteristics for the included observational studies are shown in **table 11** and for the RCTs in **table 12.**

Figure 9. Flow chart showing the systematic review process and the numbers excluded at each stage, with reasons where appropriate.



Risk of bias assessment

Bias assessment concluded potential sources of bias in all but one study. However, much of this was due to lack of clarity in the reviewed manuscripts. Additionally, of the 5 studies with the highest risk of potential bias, 3 of these (Puar et al.[288], van Hateren et al.[289], Davis et al.[290]) are included in narrative synthesis only. The RCT with the highest risk of bias, Chen et al.[291], has significantly smaller numbers than the ADVANCE[76, 287] and ACCORD[74, 128] trials, so will unlikely influence the outcome of meta-analysis significantly. The full results of the bias assessment as included in **table 13** (RCT) and **tables 14a, 14b and 14c** (observational studies) below.

Table 11. Study characteristics of the observational studies included in this review

Study name or reference	Study Design	Study region	Setting	Age or Frailty	Treatments	Numbers in intensive arm (n)/total (N)	Duration	HbA1c target Intensive vs Standard (mmol/mol)	Outcomes of interest
Anyanwagu et al.[83]*	Cohort	United Kingdom	Primary Care	Age>65	Any & on insulin	1,657/4,589	5 years	≤58 vs >58	Macrovascular Mortality
Davis et al.[290]‡[1]	Cross-sectional	United Kingdom	Nursing homes	Age>65	Any & on insulin	n/583[1]	n/a	<53 vs intervals up to >75	Hypoglycaemia
GERODIAB[292]*	Cohort	France	Outpatient	Age>70	Any	178/987	5 years	≤50 vs >50	Mortality
Hamada et al.[293]*	Cohort	United Kingdom	Primary Care	Age>80	Any	11,826/25,966	Unclear	≤53 vs >53	Mortality
Huang et al.[294]*	Cohort	CA, USA	Outpatient	Age>60	Any	43,046/71,092	4 years	≤53 vs >53	Macrovascular Microvascular Mortality Hospitalisation[2]
Lee et al.[295]	Cohort	USA	Outpatient	Age>65	Any	n/652,901[3]	Unclear	<48 vs >58	Falls/Fracture
Ling et al.[296]	Cohort	UK	Primary care	Age>70	Insulin or sulphonylureas	6,288/22,857	Up to 17 years	≤53 vs >53	Mortality[4] Hypoglycaemia
Oliver et al.[297]†[5]	Cross-sectional	NY, USA	Outpatient	Dementia, Age>65	Any & on insulin[5]	221/448	n/a	≤53 vs >53	Hospitalisation
Puar et al.[288]‡[6]	Cross-sectional	Singapore	Hospital	Frailty	Any	n/129[6]	n/a	<48 reported	Falls/Fracture
Schwartz et al.[298]‡[7]	Cohort	USA	Outpatient	Age>70	Insulin and non-insulin[7]	n/2641[7]	Unclear	<42 vs >64	Falls
van Hateren et al.[289]‡[8]	Cohort	Netherlands	Primary Care	Age>75	Any	n/374[8]	Unclear	≤53 vs >53	Hospitalisation
Ying et al.[299]‡*	Case Control	Hong Kong	Primary Care	Age>65	Any	271/688	n/a	<48 vs 48-64	Mortality

*Multiple sub-groups pooled together to facilitate comparison; † Odds ratios calculated by hand using data extracted from the study (therefore narrative synthesis only); ‡ included in narrative synthesis only

1. Number in each group not cited, results reported as rates per 100person/months; 2. Hospitalisation due to hyperglycaemic complications only; 3.Total number available, but data not clear on numbers with HbA1c <6.5%; 4. Separate reports for cardiovascular and non-cardiovascular mortality; 5. Only data for those on insulin was presented in a suitable format; 6. Study reported % of fractures with HbA1c <6.5%; 7. Numbers involved not clear and multiple models used; 8. Group sizes not reported for this result, which is a sub-analysis of those with diabetes duration <5 years

Table 12. Study characteristics of the randomised controlled trials included in this review

Study name or reference	**Study region**	**Setting**	**Numbers in intensive arm (n)/total (N)**	**Duration**	**HbA1c target Intensive vs Standard (mmol/mol)**	**Outcomes of interest**
ACCORD[80, 128, 300-302]	North America	Outpatients	Age >65: 1,732/3,475	3.7 years	<42 vs 53-64	Macrovascular Microvascular (*neuropathy only*) Mortality Hypoglycaemia Falls[1]
ADVANCE[76, 287, 303]	Global	Outpatients	Age >65: 3,296/6,613	5 years	≤48 vs >48	Macrovascular Microvascular Memory Mortality Hypoglycaemia
Chen et al.[291]‡	China	Outpatients	30/60[2]	3 years	≤53 vs "usual care"	Memory Hypoglycaemia

‡Included in narrative synthesis only due to small numbers unclear design.
1. Falls outcomes include patient aged<60 year, but due to paucity of other data this has been extracted for discussion
2. n=30 in intermediate group excluded, comparisons between "usual care" and tight glycaemic control arm

Table 13. Risk of bias assessment for included randomised controlled trials (RCTs), assessed using the original Cochrane Collaboration Risk of Bias assessment tool[282]

Bias Assessment - RCTs	ACCORD[74, 128]	ADVANCE[76, 287]	Chen et al.[291]
1. Random sequence generation	Low	Low	Low
2. Allocation concealment	Unclear	Low	Unclear
3. Blinding of participants and personnel	Unclear	Unclear	High
4. Blinding of outcome assessment	Low	Low	High
5. Incomplete outcome data	Unclear	Low	Unclear
6. Selective reporting	Low	Low	Low
7. Other sources of bias	Low	Low	Low

Table 14a. Risk of bias assessment for included observational cohort studies, as assessed using The Joanna Briggs institute Critical Appraisal Checklist[283] for analytic cohort studies

Bias Assessment - Cohort Studies	Anyanwagu et al.[83]	GERODIAB[292]	Hamada et al.[304]	Huang et al.[294]	Lee et al.[295]	Schwartz et al.[298]	van Hateren et al.[289]
1. Were the two groups similar and recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were confounding factors identified?	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
5. Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	Yes	Unclear	Yes	No
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear
7. Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
10. Were strategies to address incomplete follow up utilised?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
11. Was appropriate statistical analysis used?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Table 14b. Risk of bias assessment for included observational case-control studies as assessed using The Joanna Briggs institute Critical Appraisal Checklist[283] for analytic case-control studies

Bias Assessment - Case-Control Studies	Ling et al.	Ying et al.
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Yes	Yes
2. Were cases and controls matched appropriately?	Yes	Yes
3. Were the same criteria used for identification of cases and controls?	Yes	Yes
4. Was exposure measured in a standard, valid and reliable way?	Yes	Yes
5. Was exposure measured in the same way for cases and controls?	Yes	Yes
6. Were confounding factors identified?	Yes	Unclear
7. Were strategies to deal with confounding factors stated?	Yes	Unclear
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	Yes	Yes
9. Was the exposure period of interest long enough to be meaningful?	Yes	Yes
10. Was appropriate statistical analysis used?	Yes	Yes

Table 14c. Risk of bias assessment for included observational cross-sectional studies as assessed using The Joanna Briggs institute Critical Appraisal Checklist[283] for analytic cross-sectional studies

Bias Assessment - Case-Control Studies	Davis et al.	Oliver et al.	Puar et al.
1. Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes
2. Were the study subjects and the setting described in detail?	Yes	Yes	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
4. Were objective, standard criteria used for measurement of the condition?	Yes	Yes	Yes
5. Were confounding factors identified?	No	No	No
6. Were strategies to deal with confounding factors stated?	No	No	No
7. Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
8. Was appropriate statistical analysis used?	No	Yes	Yes

All-cause mortality

Of the identified studies, eight had outcome data for mortality (six observational studies and two RCTs). The meta-analysis of the data from these studies demonstrated in **figure 10.** suggests that tight HbA1c targets were not associated with any significant change in all-cause mortality rates (HR 0.96; 95% CI 0.90-1.03, random effects). Findings were similar in the CPRD based study by Ling et al., which could not be included in meta-analysis as it sub-divided cardiovascular and non-cardiovascular mortality without reporting a hazard ratio for all-cause mortality and without elaborating on which causes were included[296]. In this study, no clear increased risk of mortality was noted for a HbA1c of ≤53mmol/mol [≤7.5%] for both cardiovascular mortality (HR 0.98; 95% CI, 0.91-1.06) and non-cardiovascular mortality (HR 1.05; 95% CI 0.99-1.11).

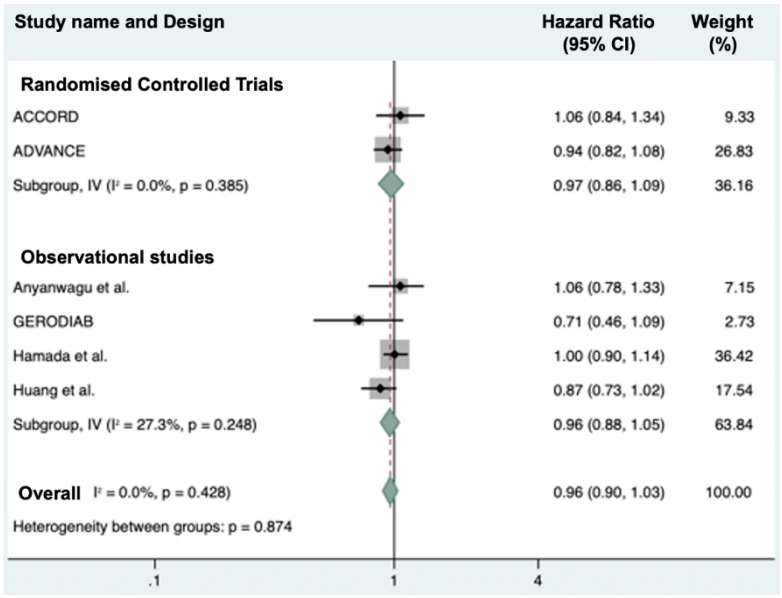
In contrast, the 2020 study by Ying et al. reported an odd's ratio for all-cause mortality of 1.94 (95% CI 1.41-2.68) for tight glycaemic control (HbA1c<48mmol/mol [<6.5%]). This is an outlier compared to the other outcomes of the other included studies which are otherwise homogenous in their outcomes with a Q statistic of 4.91 (5 degrees of freedom [d.f.]) and I^2 0.00%.

Severe hypoglycaemia

Five studies had outcome data for severe hypoglycaemia, including three RCTs. The three studies included in meta-analysis are shown in the forest plot **figure 11**. There was a significant increase in the rate of

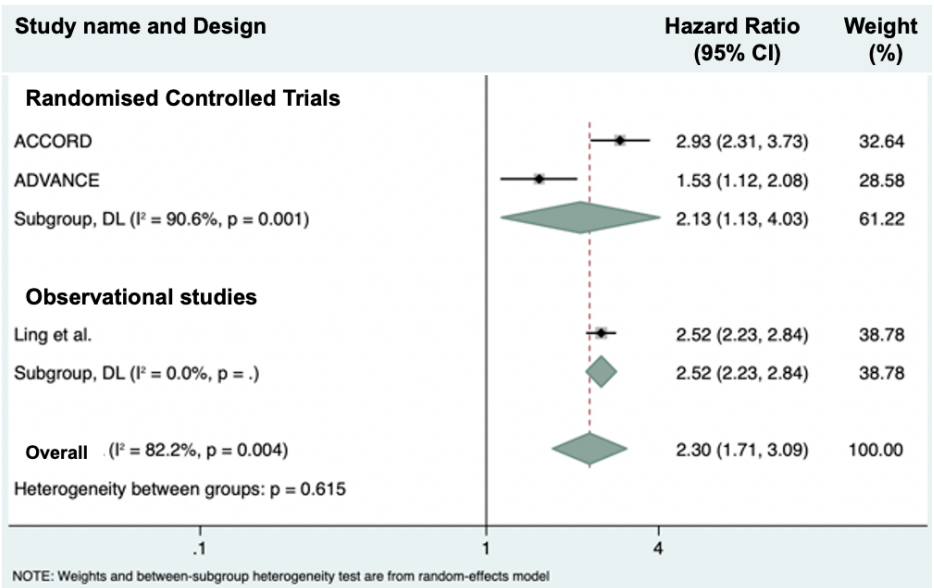
hypoglycaemia with intensive glycaemic control - strongly favouring standard over tight control (HR 2.30; 95% CI 1.71-3.09, random-effects model). Inter-study heterogeneity was high with a Q statistic of 11.24 (2 d.f.) and I^2 statistic=82.2%. Two studies were not included in meta-analysis but did contain some data of interest. The first study by Davis et al[290] investigated nursing home residents with a HbA1c≤53mmol/mol [≤7.5%]. Severe hypoglycaemia occurred at a rate of 36.8 events per 100person/months for those aged >65 years. The rate of hypoglycaemia further increased when stratified by age, with event rates per 100person/months of 46.2 and 65 in those aged >75 years and >85 years respectively. This study also showed that hypoglycaemia in those with more intensive glycaemic control increases further with advancing age. Secondly, the study by Chen et al.[291], was a controlled trial performed on a small group of people with T2DM and Alzheimer's disease. Participants were randomised to three different types of glycaemic management – with "strength" corresponding to a target HbA1c of <53mmol/L [<7.0%] and "mitigate" responding to much less stringent control. The 30 people in each of these groups were compared and an odds ratio between these groups calculated. This showed a significant and large increase in hypoglycaemia in intensive versus standard control in this cohort (odds ratio 10.55, 95% CI 1.23-90.66).

Figure 10. Forest plot showing individual study and pooled hazard ratios (subgroup and overall) for the effect of intensive treatment to a lower HbA1c target versus standard care on the risk of mortality in frail and or elderly patients with type 2 diabetes



→ Increased risk with lower HbA1c

Figure 11. Forest plot showing individual study and pooled hazard ratios (subgroup and overall) for the effect of intensive treatment to a lower HbA1c target versus standard care on risk of severe hypoglycaemia in frail and/or elderly patients with type 2 diabetes



→ Increased risk with lower HbA1c

Hospital admission

Three observational studies had outcome data available for hospitalisation rates, although none of these studies were suitable for meta-analysis and one only contained data for hospitalisation rates secondary to hyperglycaemia (or related complications). No RCTs reported hospitalisation rates as an outcome.

The 2011 Diabetes and Aging study[294] reported significantly lower rates of hospitalisation for hyperglycaemic complications in those with a HbA1c ≤53mmol/mol [≤7.0%] compared to those with levels >53mmol/mol [>7.0%] (HR 0.27, 95% CI 0.08-0.46). Rates were lowest in the <42mmol/mol [<6.0%] group and highest, as might be expected, in those with the highest HbA1c levels (>97mol/mol [>11.0%] in this study). Similarly, van Hateren et al's 2010 analysis of their Dutch cohort showed reductions in hospitalisation rates within the same HbA1c group of ≤53mmol [≤7.0%], for intensive versus standard glycaemic control (HR 0.56, 95% CI 0.33-0.95)[289]. However, this is with the caveat that this analysis only included those with a diabetes duration <5 years. In contrast to the above, Oliver et al reported higher rates of admission in their cohort amongst those described as being "over-treated" – defined as those with a HbA1c ≤53mmol/mol [≤7.0%]– and suggested a significant increase in risk for hospitalisation in those who were "over-treated" (the calculated odds ratio 1.8, 95% 1.23-2.64)[297].

The designs of these studies are heterogenous, and the evidence available gives no uniform signal on whether intensives or standard control reduces hospitalisation rates in an elderly population.

Macrovascular disease

Of the included studies, four contained outcome data for macrovascular disease, two being RCTs. All of the studies with data available for this outcome were suitable for inclusion in meta-analysis, summarised in the forest plot **figure 12a.** The overall result slightly favoured intensive glycaemic control (HR 0.88, 95% CI 0.77-1.00, random effects) versus standard glycaemic control (P=0.047). This was similar in both observational and RCT subgroups. All studies, except Anyanwagu et al[83], favoured intensive glycaemic control in reducing the rates of macrovascular disease. The calculated Q and I^2 statistic for the RCT subgroup suggested little heterogeneity (I^2 0.00%; Q 0.68, 1 d.f.) but both the Q and I^2 values for the observational were consistent with high levels of heterogeneity (I^2 79.8%; Q 4.96, 1 d.f.). The net effect of these translated into moderate levels of inter-study heterogeneity when the data was pooled, with an overall I^2 of 62.4% and Q statistic of 7.98 (3 d.f.).

Microvascular disease

Two of the identified studies reported the required a composite outcome for rates of microvascular complications but when included in meta-analysis suggested no overall benefit of intensive glycaemic control on microvascular outcomes (HR 0.78, 95% CI 0.69-1.02, random effects), as shown in **figure 12b**. In additional to this overall outcome, the more

recent analysis of those aged≥65 in the ADVANCE study by Ohkuma et al. failed to reach significance for this outcome[303]. No subgroup analysis was performed as only one study of each type was identified. The I^2 value of 88.6% and Q statistic of 8.76 (1 d.f.) represent potentially high levels of heterogeneity between the two studies.

One further study, a sub-analysis of the ACCORD study by Tang et al.[302], reported odds ratios for cardiac autonomic neuropathy only and was not included in meta-analysis. In this study, intensive versus standard glycaemic control was not associated with any increased or decreased odds of developing of cardiac autonomic neuropathy in those aged ≥65 years (odds ratio 0.98; 95% CI 0.8-1.21) and was therefore found to be of neutral risk or benefit.

Figure 12. Forest plots showing individual study and pooled hazard ratios (subgroup and overall) for the effect of intensive treatment to a lower HbA1c target versus standard care on risk of a) macrovascular complications b) microvascular complications in frail and/or elderly patients with type 2

Fig 12a.

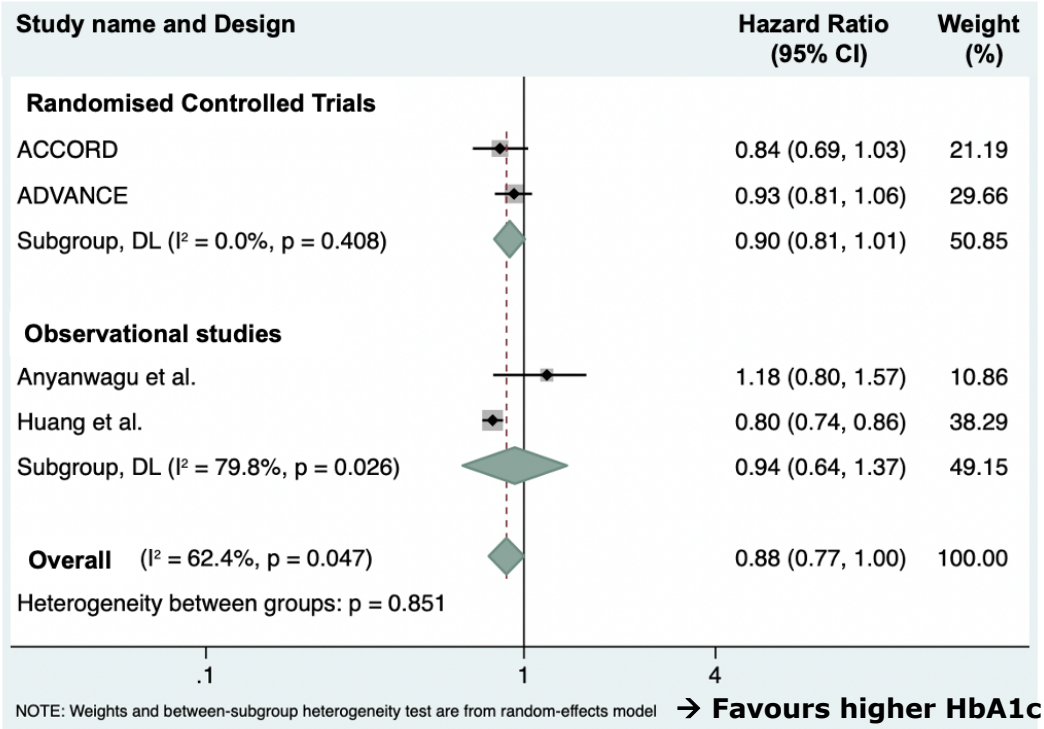
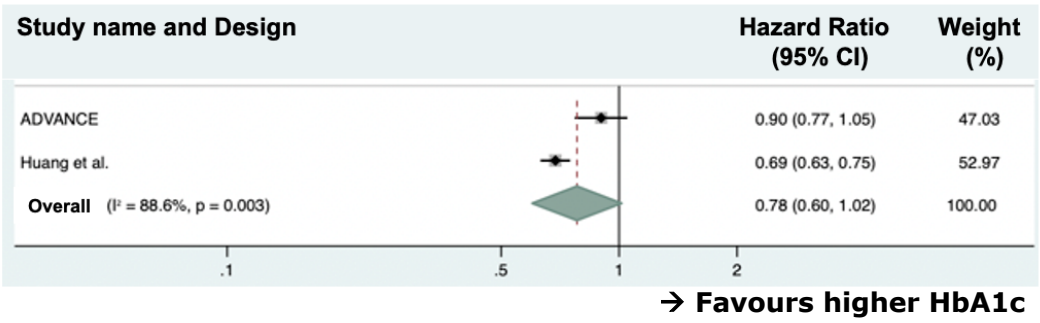


Fig 12b.



Memory and cognition

Two RCTs contained outcome data on the effect of intensive glycaemic control on memory or cognitive function. The results were not presented in a format suitable for meta-analysis. The first RCT by Chen et al. did no favour intensive glycaemic control on reducing diagnoses of dementia in their cohort (odds ratio 0.63, 95% CI 0.21-1.88)[291]. Conversely,

Ohkuma et al.'s ADVANCE analysis revealed a near neutral effect of intensive glycaemic control (HR 1.01, 95% CI 0.9-1.12)[303]. These results give no clear overall signal of effect and should be interpreted with caution due to the small numbers in the study by Chen et al. and significant differences between the two studies.

Falls and fractures.

Fall or fracture outcomes were reported by three studies but were not in a format suitable for meta-analysis. Two of these were observational studies. The one RCT, an analysis from ACCORD, showed no overall effect of intensive glycaemic control versus standard control on risk of falls (HR 1.1, 95% CI 084-1.43), however this analysis included some participants aged less than 65 years[301]. Favouring less stringent control, the observational study by Schwartz et al showed significantly increased falls in those with intensive glycaemic control in insulin users with HbA1c <42mmol/mol [<6.0%] (odds ratio 4.36, 95% CI 1.32-14.46) compared to those with a HbA1c >64mmol/mol [>8.0%][298]. A further study found that 45% of those admitted to hospital with a fracture had a low HbA1c (<48mmol/mol [<6.5%])[288].

Overall, these results are suggestive of an increased risk of falling with lower HbA1c levels, but there is such marked variation in outcomes, design, and reporting that any clear conclusion is impossible to draw. A summary of all systematic review and meta-analysis is described in **table 15.**

Table 15. Summary of the results of the systematic review for each outcome including numbers of observational or randomised controlled trials (RCT) included, pooled hazard ratios (HRs), assessments of heterogeneity and bias and overall conclusions

Outcome	Observational studies	RCTs	Pooled HR (95% CI)	I^2 heterogeneity	Assessment of bias	Conclusions
All-cause mortality	6 (1)*	2	0.96 (0.90-1.03) *Fixed effects*	00.0% - Low	Potential high risk of bias in some of the concluded studies.	No convincing evidence that favours lower HbA1c targets in reducing mortality
Severe hypoglycaemia	2 (1)*	3 (1)*	2.30 (1.71-3.09) *Random effects*	82.2% - High	Significant heterogeneity. Included studies relatively free from bias. Clear signal from pooled HR	Current evidence favours standard glycaemic targets in reducing severe hypoglycaemia
Hospital admission	3*	0	n/a	n/a	Relatively unbiased studies, significant difference in study design.	Conflicting results from small number of available studies means no conclusion can be drawn
Macrovascular	2	2	0.88 (0.77-1.02) *Random effects*	64.25 – Moderate	Included studies show little evidence of bias	Three of the studies show consistent results and meta-analysis of all four studies is in favour of lower HbA1c targets to reduce the risks of macrovascular complications
Microvascular	1	2 (1)*	0.78 (0.69-1.02) *Random effects*	88.6% - High	Included studies show little evidence of bias but heterogeneity is large.	Reduced rates of microvascular complications in all studies, as further evidence by pooled HR. Favours lower HbA1c targets. Effect seemingly greater than for macrovascular.
Cognition	0	2*	n/a	n/a	Significant potential bias in one of the studies. Significant differences in study design, one with very small numbers	Conclusions difficult to draw given paucity of evidence. Probable neutral to beneficial effect of intensive control but more high-quality studies are needed
Falls/Fractures	2*	1*	n/a	n/a	Significant heterogeneity in design and reporting	Conclusions cannot be drawn. From available data effect of lower HbA1c targets likely neutral or increased risk of falls and fractures

*number not suitable for meta-analysis in brackets or no studies identified suitable for meta-analysis

Discussion

The estimated overall effect for the impact of intensive glycaemic control on all-cause mortality was neutral. The outcomes of the included studies were heterogenous. Whilst several favoured tight glycaemic management in reducing mortality, others reported significantly increased mortality. Ultimately, the neutrality of the pooled HR along with the significant differences in study design and divergence in individual study results means it is difficult for us to conclude one way or another whether intensive glycaemic control reduce mortality rates.

Despite differences in study design and significant heterogeneity it is reasonable to conclude from this systematic review that intensive glucose control is associated with increased rates of severe hypoglycaemia in frail or elderly individuals. The identified studies were universally in favour of less intensive control with the pooled HR for intensive control amongst meta-analysed studies further supported by the results of the studies included in narrative. The impact of hypoglycaemia on quality of life is well established, and increased rates of hypoglycaemia will likely have a deleterious effect on frailty as well as potentially increased rates of cognitive decline or vascular complications[305-307]. However, it is also important to recognise that most of the selected studies included large numbers (or even exclusively) of those treated with insulin and/or sulphonylureas where the hypoglycaemia risks are highest.

The effect of HbA1c target on hospital admissions is similarly unclear, very little data was available; the data identified was not suitable for meta-

analysis and the results of the studies on an individual level were conflicting with two favouring intensive control and one significantly favouring less stringent control.

This meta-analysis favours intensive control for reducing the risk of macrovascular complications to a degree of statistical significance. Additionally, we have demonstrated a trend, although failing to meet significance, towards reductions in microvascular complication rates. These results are not unique to frail and elderly people with diabetes as similar findings in younger cohorts have been demonstrated in earlier meta-analyses[308].

Evidence to assess the role of intensive glycaemic control in reducing cognitive decline or the risk of falls and fractures is, however, lacking. The identified studies were small and contained limited quantitative data. It has been suggested that as intensive control increases the rate of cognitive decline and falls due to increased rates of hypoglycaemia, but this is not fully borne out by current data and further dedicated studies are needed beyond the current evidence derived from imaging or animal studies[309-311].

Limitations and strengths

Whilst there are numerous RCTs examining intensive glycaemic control in people with T2DM, there is less data on those who are elderly or frail. The identified studies are heterogenous in design including the range of medications used and the level of HbA1c targeted. It can be presumed that

differing levels of HbA1c less than 53mmol/mol likely confer differing levels risk although the exact effect of this is not clear, especially to the individual. Additionally, the included RCTs are from more than a decade ago, in an era where many of the currently available drugs with additional cardiovascular or mortality benefits and lower risks of hypoglycaemia, such as sodium-glucose linked transporter 2 inhibitors (SGLT2s) or glucagon-like-peptide 1 agonists (GLP1 agonists) were not available[312]. Furthermore, there are studies underway to assess whether SGLT2s may increase sarcopenia and therefore increase frailty[313] – an interaction that may need to be considered moving forwards. Given this, it is difficult to predict if the risks and benefits of intensive control would shift if newer medications were used to achieve these targets. Som of the included studies lacked data for some outcomes of interest making some conclusions difficult to draw. Finally, we did not use an Egger's test to assess publication bias – this is something to consider in future updates to this systematic review as evidence develops.

Although there are significant limitations this review highlights several important points. They key strength of this study is that it aimed to assess a wide range of important outcomes including those of particular interest to the care of frail and elderly individuals with diabetes. In doing this, we have highlighted the overall lack of robust evidence to support current practice. In addition, this study reaffirms that older patients with T2DM are at significant risk of hypoglycaemia irrespective impact of the heterogeneity in the studies used. The impact of glycaemic control on other outcomes of interest is unclear in view of the limitations of the

study and the evidence around glycaemic targets and important frailty specific outcomes such as fractures, falls or cognitive impairment is near non-existent.

Implication for further research

At present consensus and experience appear to be in agreement for how glycaemic control in frail individuals should me managed. Nevertheless, we should continue to seek to support this with robust observational or RCT evidence which, as we have demonstrated, is currently severely lacking. Further studies must be undertaken using recognised frailty scoring systems and recognise the potential differing impacts of newer glucose lowering therapies on outcomes of interest. Particular focus should be paid to important frailty specific outcomes of interest. Furthermore, there needs to be consideration in all diabetes research of the interplay of frailty on outcomes, and the possible phenotypic differences that may affect outcomes in those with and without frailty.

Conclusion

This systematic review and meta-analysis has confirmed the risks of severe hypoglycaemia resulting from intensive glycaemic control in frail and elderly people with type 2 diabetes. Whilst intensive glycaemic control has no overall effect on mortality, it may reduce the risk of macrovascular complications and, although less significant, microvascular complications too. However, the heterogeneity of studies included suggest that these results should be interpreted with caution. When it comes to glucose control in the elderly or frail individual, a balance of risk and benefits need

to be made, tailored to the individual and although a more holistic and less glucose centric approach is needed, an understanding of the role of glucose levels in this balance will continue to be key. Finally, our review highlights the significant gaps in current evidence and emphasises the need for further works using recognised markers of frailty to establish as well as important frailty specific outcome measures such as falls, fractures of cognitive impairment.

Research in context

This systematic review supports the need for the subsequent work contained in this thesis. By using the electronic frailty index (EFI) to identify frail individuals with diabetes it is hoped that targets can be adjusted appropriately to maximises the benefits of glucose lowering without introducing risks. It also emphasises the need for and novelty of this work, as current works utilising frailty specific scoring systems to model outcomes do not currently exist.

This work has already had impact and has subsequently been referenced since publication by the latest edition of the ADA/EASD hyperglycaemia management guidelines[59].

Chapter 5 – The associations between electronic frailty index, HbA1c and outcomes in older adults with type 2 diabetes

Chapter abstract

Background: The number of individuals with type 2 diabetes (T2DM) aged≥65 years is increasing, as is the recognition of frailty within this cohort. Existing guidelines are derived from limited evidence as frailty status is rarely incorporated into study designs. We aimed to establish whether the addition of the electronic frailty index (EFI) improved the performance of prediction models for HbA1c levels for all-cause mortality and hospital admission and explore the associations between HbA1c and outcomes at different frailty levels.

Methods: We included patients with T2DM aged >65 within UK primary care electronic database (the Clinical Practice Research Datalink) and Hospital Episode Statistics from 2014-19. Multivariate Cox regression models were developed to assess the relationship between HbA1c and outcomes of interest, and measures of model performance were assessed with and without the addition of EFI. Risk associated with 4 EFI frailty groups (non-frail; mild; moderate and severe) and six HbA1c groups were assessed using multivariate Cox regression analysis adjusted for demographic and clinical characteristics. The reference group was defined as "non-frail" individuals with HbA1c 48-57.9mmol/mol [6.5-7.4%].

Results: The addition of EFI categories improved Akaike's Information Criteria, Harrel's C and Rosyton-D statistics for both outcomes. For our primary outcomes, the risk of all-cause mortality increases at HbA1c levels above and below 48-57.9mmol/mol [6.5-7.4%] in every frailty category; those in higher frailty categories had increased risk of mortality at all levels of HbA1c. The risk of hospital admission is lowest at a HbA1c of 70-80.9mmol/mol [8.5-9.4%] among individuals with moderate and severe frailty with increasing risk observed at higher and lower HbA1c levels. Fall and fracture and cognitive outcomes are also reported.

Conclusions: EFI provides an easy to implement and reproducible definition of frailty which improves the performance of models for all-cause mortality and hospital admission in older individuals with T2DM. Lower HbA1c levels are associated with increased risk of mortality and hospital admissions and the optimal HbA1c levels in frail individuals appears to be higher than recommended by existing guidelines. EFI may have clinical utility in identifying frailty and individualising HbA1c targets in older individuals with T2DM.

Introduction

As previously discussed, we know many individuals with T2DM will also have significant frailty, defined as reduced physiological reserve associated with aging[314]. Studies have identified an increased proportion of frailty amongst individuals with T2DM compared to those without[315]. The relationship between frailty and T2DM has been suggested to be bi-directional: many of the frequently co-occurring conditions and vascular complications associated with T2DM may lead to significant disability and increase frailty and frailty may accelerate the accumulation of diabetes complications due to the reduction in physiological reserve[316]. There are further interactions between frailty and diabetes that may influence the selection of appropriate treatments and the collaborative setting of treatment targets.

Most of the evidence underpinning the HbA1c targets recommended by clinical guidelines is derived from the treat to target trials such as the *UK Prospective Diabetes Study* (UKPDS) or the *Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation study* (ADVANCE) which demonstrated reductions in microvascular complication rates but not impact on macrovascular complication rates or all-cause mortality[73, 76]. These trials contained a significant number of younger individuals so the generalisability of these findings to an older or more frail cohort is unclear. Additionally, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial highlighted in chapter 1, was discontinued early due to increases in all-cause mortality with lower HbA1c targets – notably the cohort in this trial were older which raises questions around the

potential risks of intensive glycaemic management in older, and potentially frail individuals[74, 75].

The review in chapter 4 highlights further the paucity of data exploring optimal HbA1c levels for key outcomes in older individuals with type 2 diabetes and no studies available using recognised definitions of frailty or frailty scores[317]. It describes an increased risk of hypoglycaemia in older populations with lower HbA1c targets which may carry a significant risk of reducing quality of life and increasing mortality[318]. No statistically significant differences were found between lower HbA1c targets compared with higher targets for other outcomes including the risk of macrovascular and microvascular complications, hospital admissions, all-cause mortality, cognitive decline or rates of falls and fractures.

The differing needs or individuals with frailty are highlighted as a key point in the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) consensus guidelines[59], National Institute for Health and Care Excellence (NICE)[68] guidelines and the consensus work produced by Strain et al[104], all of which we have discussed earlier, despite limited evidence. Of most interest, the consensus produced by European Diabetes Working Party for Older People (EDWPOP) categorised individuals into either healthy/mildly frailty, moderate or severe frailty. This broadly maps to the categorisations generated by use of the electronic Frailty Index (EFI). The HbA1c targets recommended by the consensus and the similar EFI category are displayed in **table 16.**

The electronic Frailty Index is a validated scoring system to identify individuals aged≥65 years with frailty in electronic healthcare records[98]. It uses 32 different criteria including a range of diagnoses (e.g. diabetes, thyroid disease), symptoms (e.g. dizziness) and physical limitations (e.g. visual impairment, requirement for care) to generate a score which can be used to categorise individuals into "fit", mild, moderate, and severe frailty. The EFI score has been used in observational studies in other areas previously to explore the relationship between frailty and outcomes of interest[99] and can be derived from Clinical Practice Research Datalink (CPRD) data.

Table 16. Consensus HbA1c targets mapped to electronic frailty index scores (EFI)

Consensus Category[104]	**EFI Category[98]**	**EFI Score**	**Target HbA1c level**
Healthy/Pre-Frail/Mild Frailty	Fit	0 to 0.12	<58mmol/mol (<7.5%)
	Mild Frailty	>0.12 to 0.24	
Moderate Frailty	Moderate Frailty	>0.24 to 0.36	<64mmol/mol (<8.0%)
Severe Frailty	Severe Frailty	>0.36	≤69mmol/mol (≤8.5%)

The aim of this study is to assess whether the inclusion of EFI scores within models linking HbA1c and key clinical outcomes improves their performance. In addition, we will delineate the optimum HbA1c level to minimise risk of our key outcomes within the models across each EFI category. This will provide vital evidence around HbA1c levels in individuals with frailty and type 2 diabetes where it is currently lacking.

Methods

Data

This study utilises data from the Clinical Practice Research Datalink GOLD (CPRD) database with linked data from Hospital Episode Statistics (HES) and mortality data from the Office of National Statistics (ONS). The CPRD database is widely used in research and contains data compiled from electronic medical records in primary care, with data from over 2,000 practices and coverage of 20% of the UK population[190]. It has been demonstrated to be broadly representative of the UK population in terms of key demographics (e.g. age, ethnicity, gender)[172].

Study population

An open cohort of individuals aged 65 years or older with a diagnosis of type 2 diabetes were included. Type 2 diabetes cases were defined via Read codes in CPRD data and ICD-10 codes in HES data. Individuals with a previous or concurrent diagnosis of any other type of diabetes were excluded. Data were obtained for the period 1st January 2009 to 31st December 2019 to allow for a minimum 5-year look-back period and 2 years of follow-up.

The study start date was defined as 1st January 2014. Individuals entered the study on the latest of: study start date; practice up-to-standard date; 1st January of the year of the patients 65th birthday or on diagnosis of type 2 diabetes.

Individuals were followed for 2-years or until their date of death, first occurrence of the outcome of interest or transfer out of practice. As the study aim is to assess the impact of EFI by comparing models, no comparison group or controls were required.

Outcomes and covariates

The primary outcome of interest was all-cause mortality as defined by ONS mortality data. Secondary outcomes of interest included: first incident of all-cause hospitalisation (defined by HES data) and cognitive decline (new onset dementia or documented cognitive impairment), falls and fractures (defined using Read codes in CPRD and ICD-10 codes in linked HES data) during the study period. For hospitalisation, those with an admission ending within 90 days of study entry date were excluded. For cognitive decline, falls and fractures, those with a diagnosis prior to entry were excluded.

Patient characteristics, concomitant conditions, medications, and clinical measurements at baseline were extracted from CPRD and assessed for inclusion within the model. Patient characteristics included sex, height, body mass index, ethnicity, alcohol and smoking status and clinical and laboratory measurements such as blood pressure, lipid profile, renal function (including urine albumin levels) and HbA1c group. Concomitant conditions included were as per the electronic frailty index score. Medications included all classes of diabetes drugs and injectable pharmacotherapies, insulin, antihypertensive drugs, and lipid lowering drugs. The complete list of potential co-variates for which data was

obtained is outlined in **appendix 5.** EFI scores were produced using the 36 items and methodology as outlined by the original paper[98]. This assigns one point for each item and the score is expressed as a proportion of the total possible score. This can then be used to assign individuals to different frailty categories as shown in **table 16.** For consistency, we updated Read codes used to generate in other studies including newer codes where applicable for the latest version of CPRD[99]. Polypharmacy was defined as receiving ≥4 medications within different drug classes prescribed over the 6-months period prior to study entry.

Statistical analysis

Incidence rates for each outcome were calculated by dividing the number of patients with the outcome by the number of person years. Kaplan-Meier curves have been used to present this information across the population and for the different categories of the EFI score.

Missing data were imputed using multiple chained equations and all analyses were performed using Rubin's rules to combine effect estimates and standard errors across 5 imputed sets[206]. Sensitivity analyses were performed on those with only complete data.

Multivariate Cox regression analysis was used to assess the ability of co-variates to predict our outcomes of interest, clustered by GP practice. Proportional hazard assumptions and the distribution for included factors and EFI were checked, and we included variables violating the assumption

as a stratifying factor if they were selected for the model. Continuous variables were assessed for distribution and non-linear risk association and included in the model as categorical variable (e.g. HbA1c) or fractional polynomial terms. The initial model for each outcome ("model 1") was developed using stepwise selection and Akaike's Information Criteria (AIC)[262] was used to identify when the addition of further variables stopped adding information to the model (defined as AIC change less than -2). Age and HbA1c group were included in the model as *a priori* covariates. Insulin use was used as a stratum *a priori* due to existing evidence of increased risk of outcomes including mortality in older cohorts[84].

For model 2, EFI was added to model 1 and the Likelihood-ratio test was used to assess the effect. For both models, Royston's D[222] and Harrell's C[263] statistics were derived as measures of discrimination. AIC was calculated for both model and the addition of EFI to the model was considered significant with a reduction in AIC greater than 4.

Subgroup analysis for each outcome was performed, across each EFI category and five HbA1c categories broadly representing those described within existing clinical guidelines as follows: HbA1c<48mmol/mol [6.5%], 48-57.9mmol/mol [6.5-7.4%], 58-69.9mmol/mol [7.5-8.4%], 70-80.9mmol/mol [8.5-9.4%] and ≥81mmol/mol [≥9.5%]. When comparing these groups, the "fit" EFI group and HbA1c 48-57.9mmol/mol [6.5-7.4%] were used as the reference categories. STATA 17 was used for all analyses.

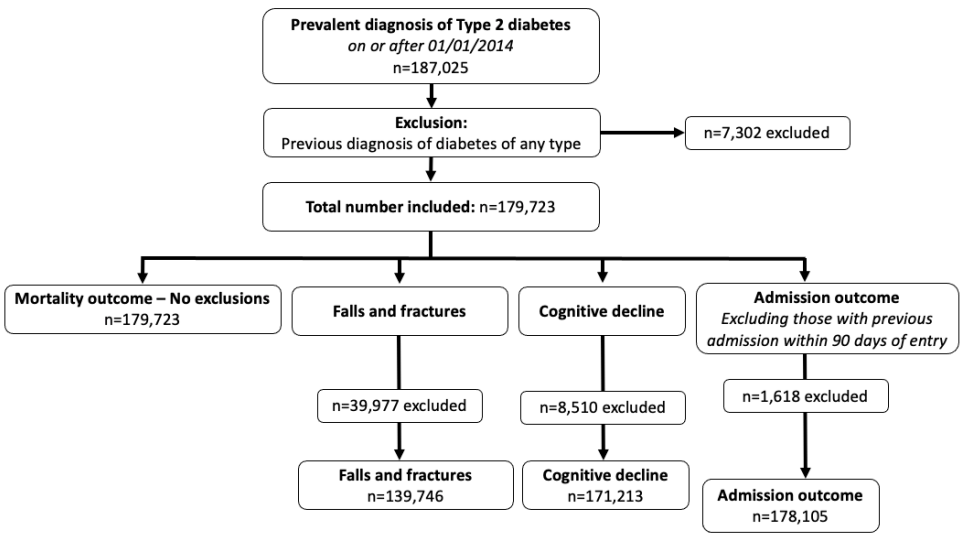
Ethics and funding

The study is approved by the Independent Scientific Advisory Committee (ISAC) of CPRD and the Medicines and Health products Regulatory Authority (Protocol 20_098) and is funded by the University of Nottingham.

Results

In total 187,025 individuals with prevalent type 2 diabetes during the study period were identified. After excluding those with a prior or concurrent diabetes diagnosis of any other type, the total number of individuals included was 179,723. The flowchart for inclusion and numbers for each outcome are demonstrated in **figure 13.** The baseline characteristics of the cohort, including the prevalence of each EFI criteria, are summarised in **table 17.**

Figure 13. Flow chart for inclusion in the study with numbers available for each outcome



During the observed time-period, 17,412 (4.1%) of individuals died; 34,302 (19.3%) first hospital admissions occurred; 5,793 (3.4%) were diagnosed with new cognitive decline and 7,586 (4.3%) experienced a fall or fracture. The event rates per 100/person-years (95% confidence interval) for each outcome was: mortality 5.26 (5.18-5.34) per 100/person-years; first hospital admission 11.6 (11.5-11.7) per 100/person-years; declining cognition 1.83 (1.79-1.88) per 100/person-years and falls or fractures 2.98 (2.91-3.05) per 100/person-years. The rates within each EFI category are summarised in **table 18.** The Kaplan-Meier graphs for each outcome are displayed in **figures 6a-d.** The median follow-up and max follow-up for all outcomes was 2.00 years.

Models and addition of EFI

The Cox models developed for each outcome by stepwise selection of covariates with and without EFI score are displayed in **appendices 6a-d,** along with the hazard ratio for each item. The final AIC value for each model is included as our primary outcome measure of the usefulness of adding EFI to our models, as well as C and D statistics as measures of model discrimination.

For every outcome AIC fell by more than 4, confirming the hypothesis that EFI was beneficial and added additional information to the developed models. The greatest AIC change was observed for the admission model (ΔAIC -1423.1) followed by mortality (ΔAIC -308.4), fall and fractures (ΔAIC -287.9) and finally cognitive decline (ΔAIC -114.0).

Table 17. Baseline characteristics of the cohort (part 1 – Core Characteristics)

Characteristic		
Age (Years)	mean (SD)	74.80 (7.61)
Diabetes duration (Years)	mean (SD)	7.33 (6.08)
Weight (kg)	mean (SD)	81.75 (18.69)
BMI (kg/m2)	mean (SD)	29.16 (5.90)
Systolic BP (mmHg)	mean (SD)	136.37 (12.38)
Diastolic BP (mmHg)	mean (SD)	74.75 (7.21)
Total Cholesterol (mmol/L)	mean (SD)	4.23 (1.05)
HDL (mmol/L)	mean (SD)	1.28 (0.42)
LDL (mmol/L)	mean (SD)	2.25 (0.92)
Triglycerides	mean (SD)	1.78 (1.03)
HbA1c (mmol/mol)	mean (SD)	55.70 (15.75)
eGFR (ml/min.1.73m2)	mean (SD)	67.74 (19.36)
Gender		
Male	n (%)	97386 (54.19)
Ethnicity		
White	n (%)	115267 (64.14)
Black	n (%)	1708 (0.95)
Asian	n (%)	5394 (3.00)
Other	n (%)	1444 (0.80)
Unknown	n (%)	55920 (31.1)
EFI Score Group		
Fit	n (%)	18568 (10.33)
Mild Frailty	n (%)	72761 (40.49)
Moderate Frailty	n (%)	59452 (33.08)
Severe Frailty	n (%)	28942 (16.10)
Alcohol Intake		
None	n (%)	65710 (36.56)
Trivial	n (%)	58334 (32.46)
Light	n (%)	20190 (11.23)
Moderate	n (%)	12638 (7.03)
Heavy	n (%)	3610 (2.01)
Very Heavy	n (%)	1898 (1.06)
Previous	n (%)	13325 (7.41)
Smoking		
Never	n (%)	86954 (48.38)
Ex-Smoker	n (%)	76072 (42.33)
Current smoker (light)	n (%)	9014 (5.02)
Current smoker (moderate)	n (%)	4341 (2.42)
Current smoker (heavy)	n (%)	3025 (1.68)
HbA1c group		
<48mmol/mol (<6.5%)	n (%)	65591 (36.5)
48-57.9mmol/mol (6.5-7.4%)	n (%)	56401 (31.4)
58-68.9mmol/mol (7.5-8.4%)	n (%)	32367 (18.0)
69-80.9mmol/mol (8.5-9.4%)	n (%)	12597 (7.0)
≥81mmol/mol (≥9.5%)	n (%)	12767 (7.1)

Table 17. Baseline characteristics of the cohort (part 2 – EFI Characteristics)

EFI Criteria		
Reduced Haematinics/Anaemia	n (%)	83851 (46.66)
Vulnerable	n (%)	5887 (3.28)
Low weight	n (%)	11323 (6.30)
Vision impaired	n (%)	45147 (25.12)
Valve disease	n (%)	7629 (4.24)
Urinary Problems	n (%)	74545 (41.48)
Thyroid disease	n (%)	24329 (13.54)
Syncope	n (%)	18428 (10.25)
Shortness of breath	n (%)	49410 (27.49)
Sleep disturbance	n (%)	25675 (14.29)
Respiratory disease	n (%)	113059 (62.91)
Peripheral vascular disease	n (%)	32916 (18.31)
Peptic ulcer disease	n (%)	13753 (7.65)
Parkinson's disease	n (%)	6682 (3.72)
Osteoporosis	n (%)	11046 (6.15)
NAFLD	n (%)	3629 (2.02)
Poor mobility	n (%)	15014 (8.35)
Memory problems	n (%)	8406 (4.68)
Incontinence	n (%)	19569 (10.89)
Ischaemic heart disease	n (%)	45972 (25.58)
Hypertension	n (%)	132617 (73.79)
Hearing impaired	n (%)	39831 (22.16)
Housebound	n (%)	58289 (32.43)
Fragility fractures	n (%)	13470 (7.49)
Foot disease	n (%)	35712 (19.87)
Dizziness	n (%)	56712 (31.56)
Previous Stoke	n (%)	23042 (12.82)
Chronic Kidney Disease	n (%)	40650 (22.6)
Congestive Cardiac Failure	n (%)	13258 (7.38)
Requires Care	n (%)	5129 (2.85)
Arthritis	n (%)	66232 (36.85)
Atrial Fibrillation	n (%)	35121 (19.54)
Limited activity	n (%)	21448 (11.93)
Polypharmacy†	n (%)	158254 (88.05)

Footnotes

*Including both oral medications and non-insulin injectables

‡Dipeptidyl peptidase-4

§Glucagon-like peptide 1

¶Sodium-glucose link transporter 2

†Defined as ≥4 different medication classes in the 6-months prior to study entry

Table 18. Event rates for each outcome by electronic frailty index category

Event rates						
Outcome	**EFI Frailty Group**	**Total n=**	**person-years at risk**	**Events n=**	**Events %**	**rate per 100/person-years (95%CI)**
Admissions	All groups	178,105	295,269	34,302	19.3	11.6 (11.5-11.7)
	Fit	18,433	33,904	1,515	8.2	4.47 (2.25-4.70)
	Mild	72,200	126,333	10,874	15.1	8.61 (8.45-8.77)
	Moderate	58,862	94,537	13,303	22.6	14.07 (13.83-14.31)
	Severe	28,610	40,495	8,610	30.1	21.26 (20.82-21.72)
Mortality	All groups	179,723	331,250	17,412	9.7	5.26 (5.18-5.34)
	Fit	18,568	35,610	572	3.1	1.61 (1.48-1.74)
	Mild	72,761	138,294	3,951	5.4	2.86 (2.77-2.95)
	Moderate	59,452	108,563	6,632	11.2	6.11 (5.96-6.26)
	Severe	28,942	48,783	6,257	21.6	12.83 (12.51-13.15)
Falls or Fractures	All groups	139,746	254,755	7,586	5.4	2.98 (2.91-3.05)
	Fit	17,513	33,334	337	1.9	1.01 (0.91-1.12)
	Mild	63,204	118,360	2,412	3.8	2.04 (1.96-2.12)
	Moderate	43,782	78,130	3,033	6.9	3.88 (3.75-40.23)
	Severe	15,247	24,932	1,804	11.8	7.24 (6.91-7.58)
Cognition	All groups	171,213	315,805	4,246	2.4	1.35 (1.30-1.39)
	Fit	18,482	35,357	165	0.8	0.47 (0.40-0.54)
	Mild	71,450	135,380	1,121	1.6	0.83 (0.78-0.88)
	Moderate	56,155	102,407	1,709	3.0	1.67 (1.59-1.75)
	Severe	25,126	42,662	1,251	5.0	2.93 (2.77-3.10)

Figure 14a-d Kaplan-Meier survival estimate graphs for each a) mortality, b) admissions, c) cognitive decline and d) falls and fractures in each EFI group.

Fig 14a.

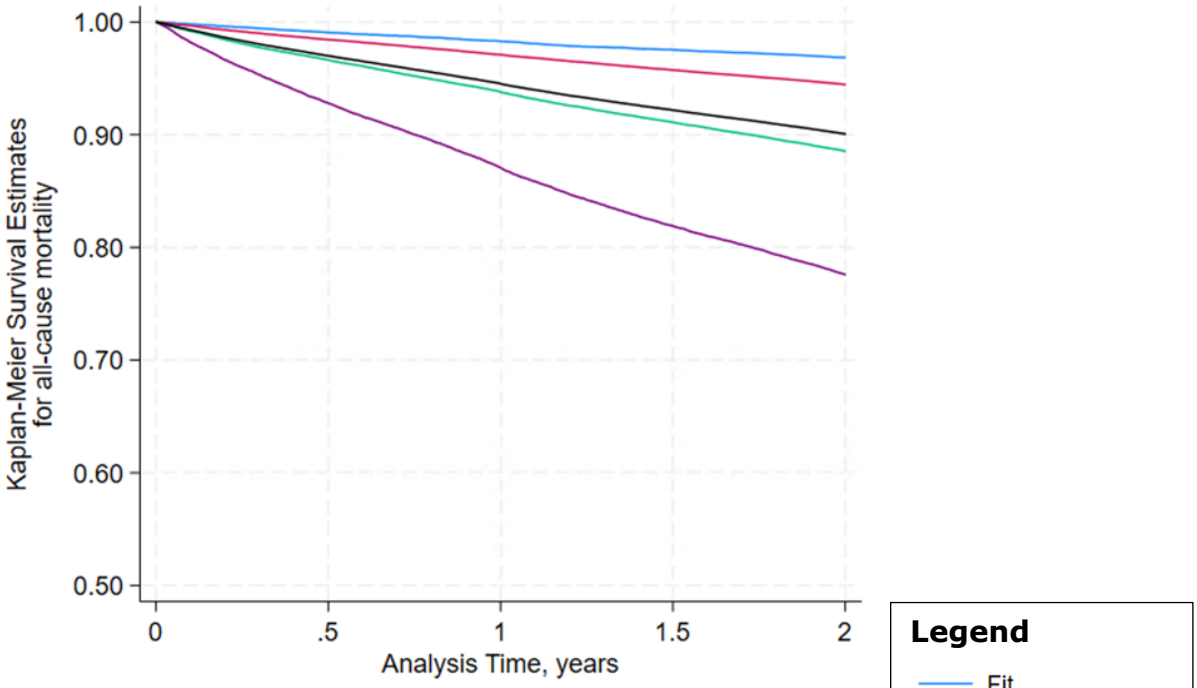


Fig 14b.

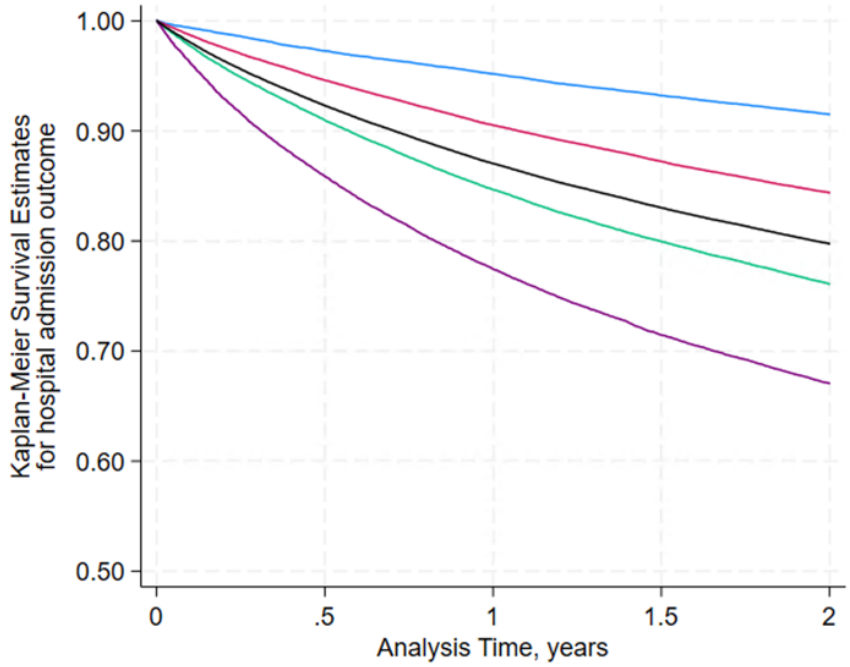


Fig 14C.

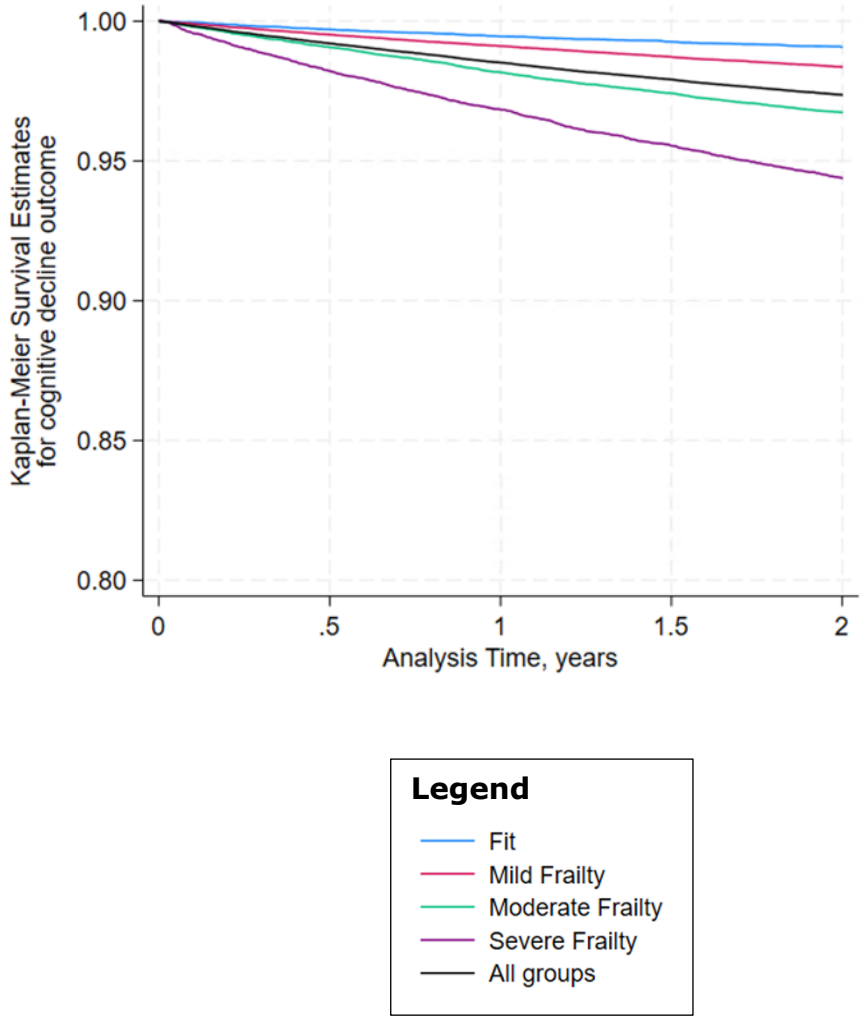
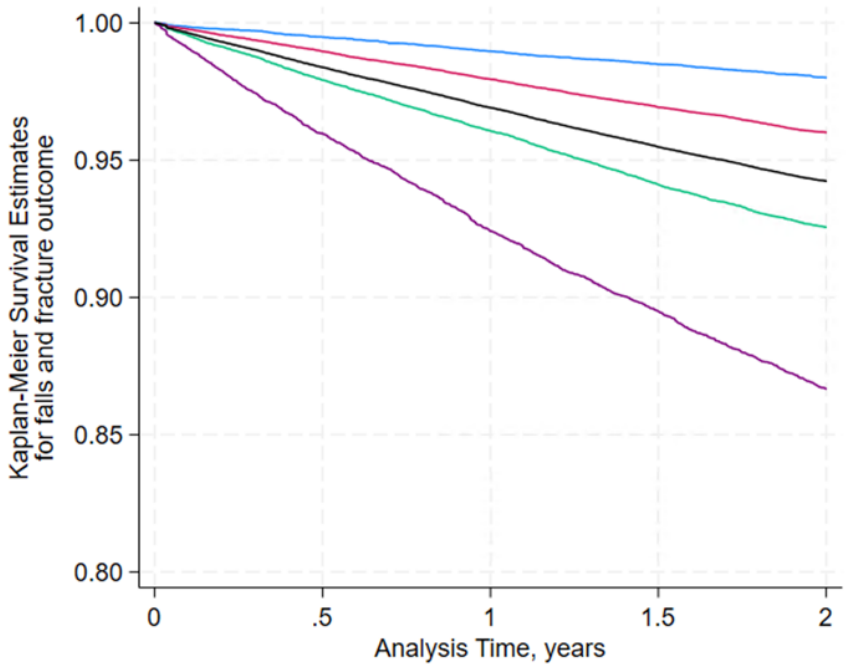


Fig 14D.



Harrell's C statistics improved with the addition of EFI for all outcomes and were (model 1 vs model 2): mortality 0.776 vs 0.778; admission 0.616 vs 0.631; cognitive decline 0.735 vs 0.737 and for falls and fractures 0.703 vs 0.712. Royston's D Statistics also improved with the addition of EFI across all outcomes and were (model 1 vs model 2): mortality 0.409 vs 0.415; admission 0.316 vs 0.331; cognitive decline 0.290 vs 0.295 and for falls and fractures 0.243 vs 0.264.

All-cause mortality outcomes

The lowest risk of all-cause mortality was observed in the reference HbA1c group (48-57.9mmol/mol [6.5-7.4%]) and increased at both lower and higher HbA1c levels as demonstrated in **figure 15a.** The hazard ratio for all-cause mortality in those with a HbA1c<48mmol/mol [<6.5%] was 1.16 (95% CI 1.07-1.25). Those in higher frailty categories had an increased all-cause mortality at all levels of HbA1c.

The lowest risk of all cause-mortality in every EFI group at 48-57.9mmol/mol [6.5-7.4%]. In every EFI category, the risk of all-cause mortality increased from this nadir with both lower and higher HbA1c levels. This is demonstrated in **figure 16a.**

Admission outcomes

The risk of hospital admission was lowest in in the 70-80.9mmol/mol [8.5-9.4%] group (HR 0.90; 95% CI 0.85-0.95) and highest in the HbA1c<48mmol/mol [<6.5%] group (HR 1.14, 95% CI 1.10-1.19) as demonstrated in **figure 15b**. The risk was similar in the 58-68.9mmol/mol

and ≥81mmol/mol [≥9.5%] groups compared to the 69-80.9mmol/mol groups, not increasing significantly at higher HbA1c levels.

As with all-cause mortality, increasing the EFI category increased the risk of hospital admission. The results of the combined cohort are mirrored in every frailty category with lowest risk of admission compared to the reference group (fit, 48-57.9mmol/mol [6.5-7.4%]) occurring with HbA1c levels of 70-80.9mmol/ml [8.5-9.4%] for those with moderate (HR 2.49; 95% CI 2.15-2.89) or severe frailty (HR 3.54; 95% CI 2.93-4.28) and at ≥81mmol/mol [≥9.5%] in those with mild frailty (HR 1.81; 95% CI 1.62-2.07) with no significant difference between the three highest HbA1c groups in these categories. The lowest risk in the "fit" category occurred at a lower HbA1c, in the HbA1c 58-69.9mmol/mol [7.5-8.4%] group (HR 0.90; HR 0.75-1.07). The highest risk of admission in every category was in the HbA1c<48mmol/mol [<6.5%] group. These results are demonstrated in **figure 16b.**

Cognitive decline outcomes

In the entire cohort, the risk of cognitive decline was lowest in the reference group (HbA1c 48-57.9mmol/mol [6.5-7.4%]) and increased at both lower and higher HbA1c levels; the risk was highest in the HbA1c ≥81mmol/mol [≥9.5%] group (HR 1.25; 95% CI 1.10-1.41) as shown in **figure 15c.** Increasing frailty category tended to increase the risk of cognitive decline at lower HbA1c levels but at higher levels the impact of EFI category is less clear, with multiple overlapping confidence intervals**.** Within the mild, moderate, and severe EFI categories, the risk did not

change significantly across HbA1c groups; in the "fit" EFI group only those with HbA1c≥81mmol/mol [≥9.5%] had an increased risk of cognitive decline compared to the reference group (HR 1.54; 95% CI 1.09-2.16). These results are summarised in **figure 16c**.

Falls and fracture outcomes

There was no significant difference between the risk of falls and fractures between the reference group (HbA1c 48-57.9mmol/mol [6.5-7.4%]), 58-69.9mmol/mol [7.5-8.4%] (HR 1.3; 95% CI 0.96-1.11) and 70-80.9mmol/mol [8.5-9.4%] groups (HR 1.05; 95% CI 0.95-1.17) when assessing the entire cohort. Risk did increase in both the lowest HbA1c <48mmol/mol [<6.5%] (HR 1.17; 95% CI 1.10-1.24) and highest HbA1c ≥81mmol/mol [≥9.5%] group (HR 1.21; 95% CI 1.09-1.35). These results are displayed in **figure 15d.**

Like the risk of all-cause mortality and admission, the risk of falls and fractures increased with increasing EFI category. There was no significant difference in risk noted between the HbA1c groups within any of the EFI categories as demonstrated by **figure 16d.**

Figure 15. Graphs showing hazard ratios (HR) in each HbA1c group across the entire cohort for a) all-cause mortality, b) risk of hospital admission, c) risk of cognitive decline and d) risk of falls and fractures compared to the reference group (HbA1c 48-57.9mmol/mol [6.5-7.4%]). Vertical error bars representing 95% confidence intervals. Horizontal error bars representing interquartile range (IQR) of HbA1c within the group

Fig 15a.

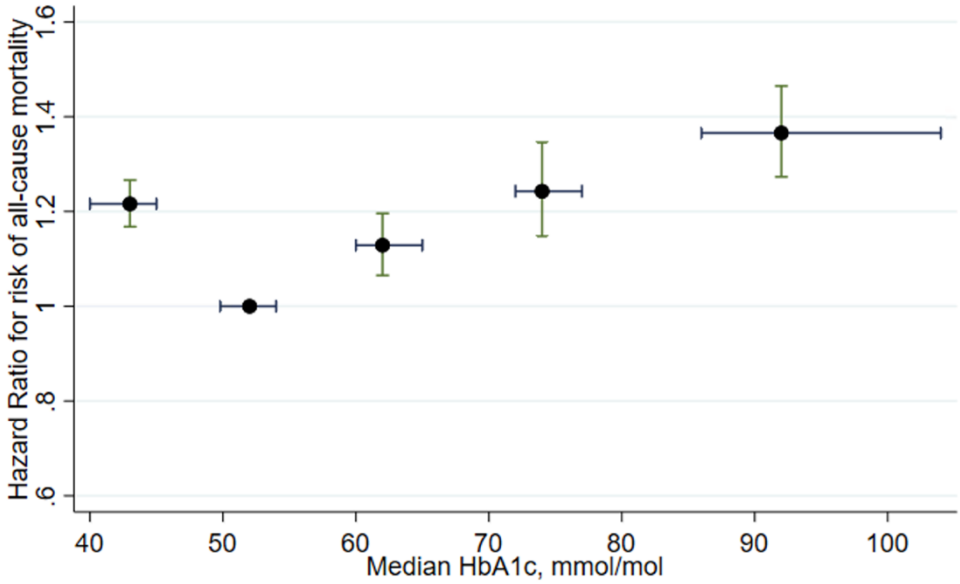


Fig 15b.

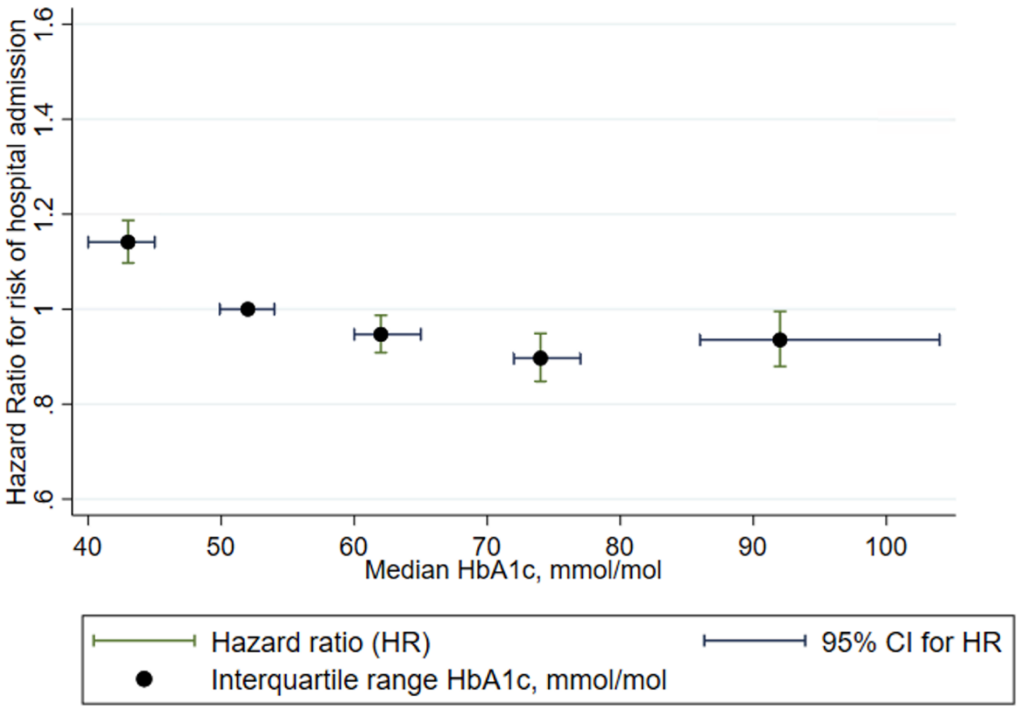


Fig 15c.

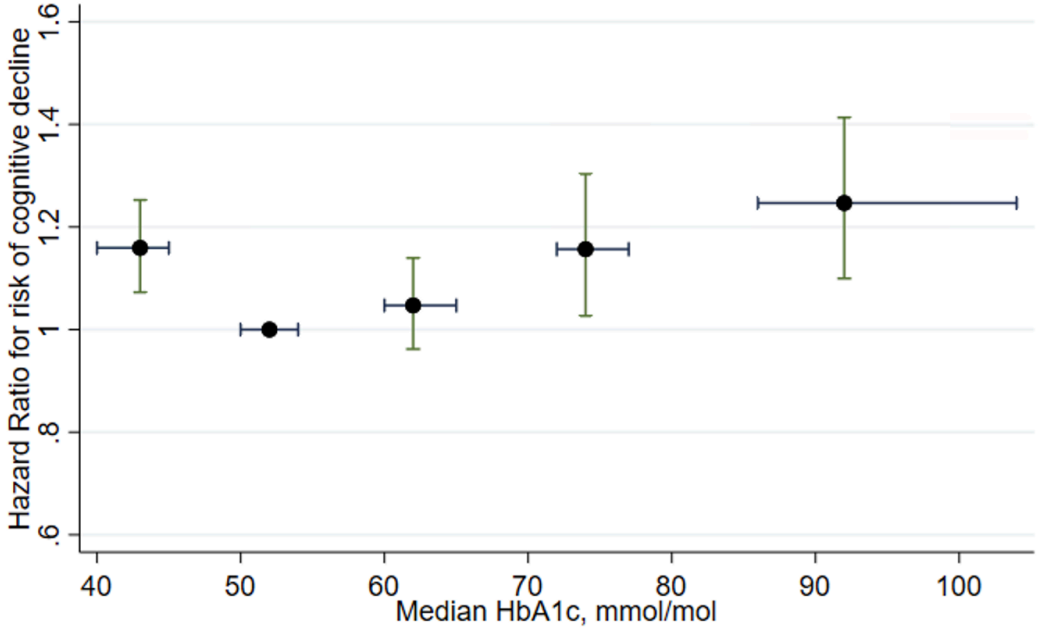


Fig 15d.

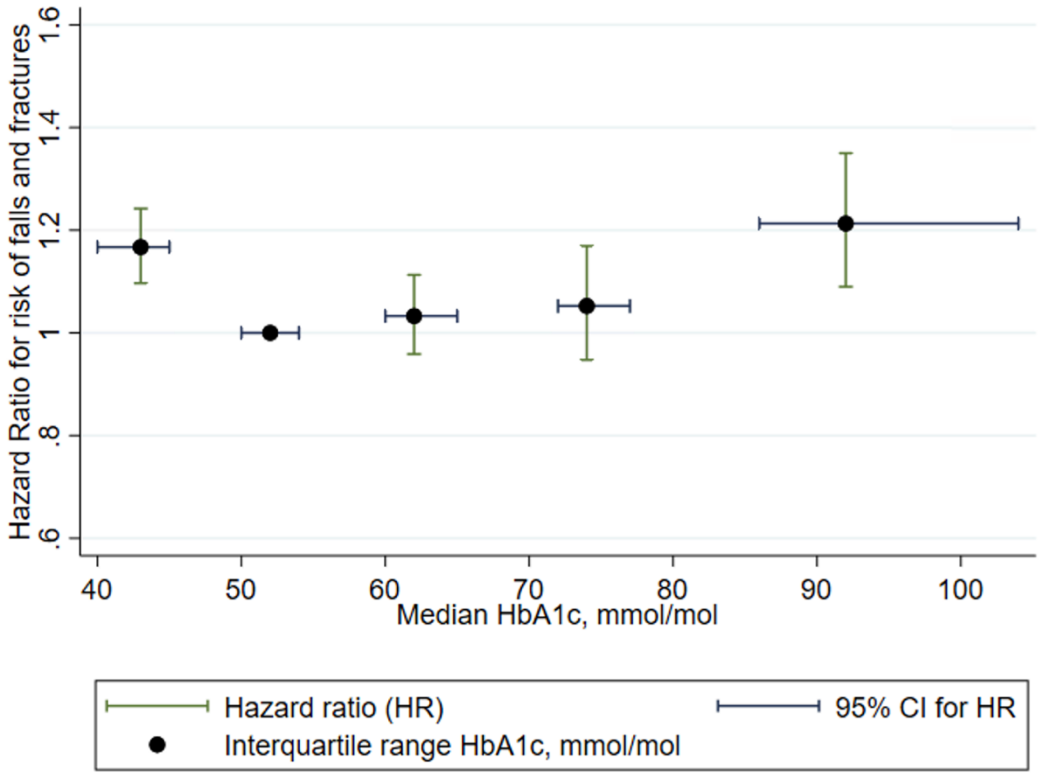


Figure 16. Graphs showing hazard ratios (HR) in each HbA1 group within each EFI category for a) all-cause mortality, b) risk of hospital admission, c) risk of cognitive decline and d) risk of falls and fractures compared to the reference group ("fit" EFI group; HbA1c 48-57.9mmol/mol [6.5-7.4%]). Shaded area representing 95% confidence intervals (CI) for relevant EFI category.

Fig 16a.

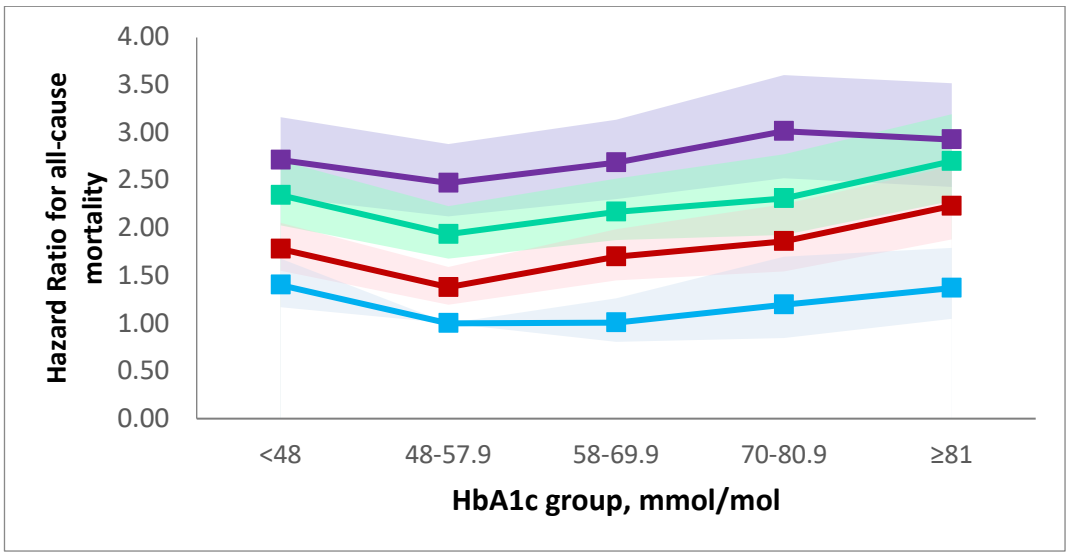
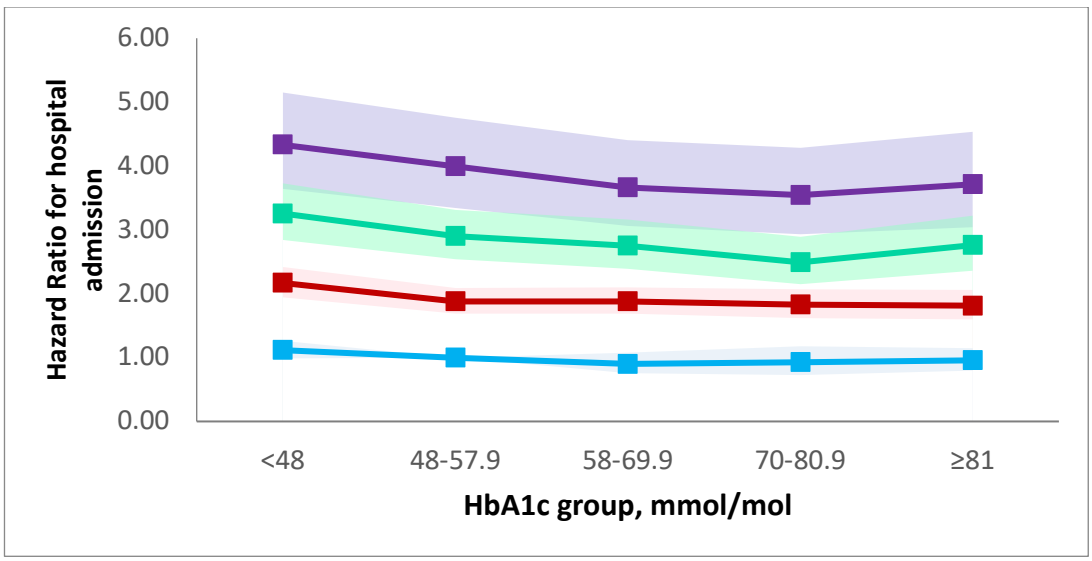


Fig 16b.



HbA1c dual report	
<48mmol/mol	<6.5%
48-57.9mmol/mol	6.5-7.4%
58-68.9mmol/mol	7.5-8.4%
69-80.9mmol/mol	8.5-9.4%
≥81mmol/mmol	≥9.5%

Fig 16c.

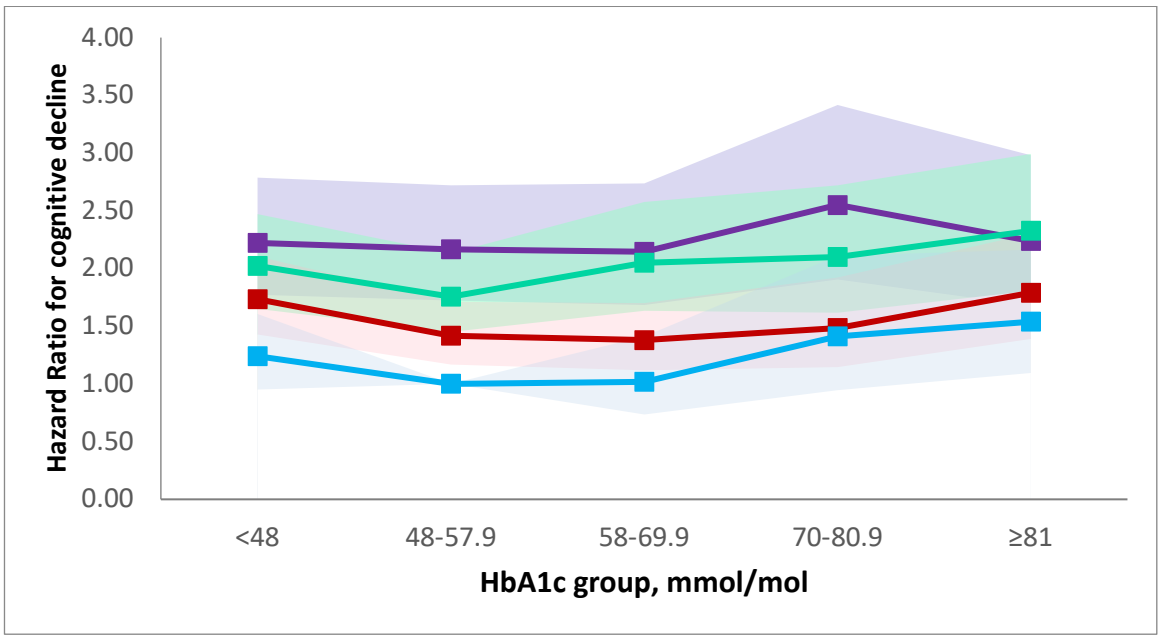
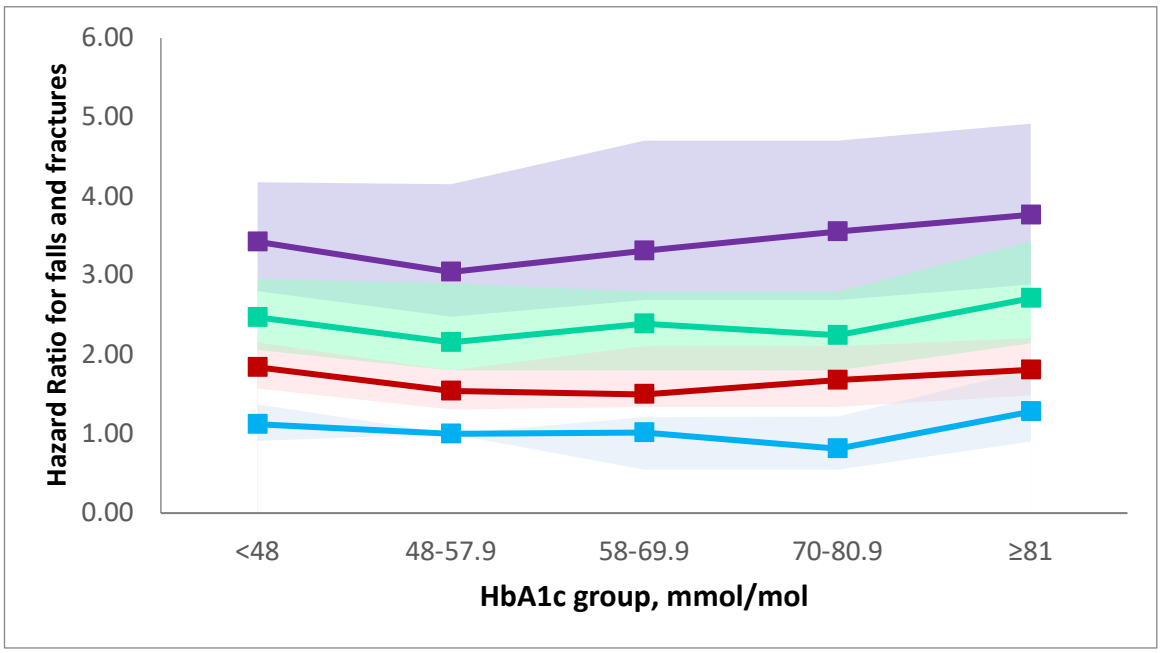
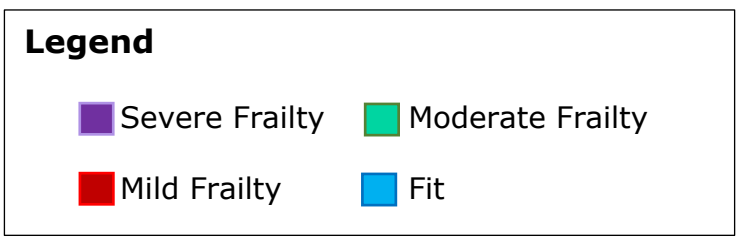


Fig 16d.





Discussion

This study has demonstrated that the addition of EFI as a covariate improves the performance of models developed for key outcomes in older adults with type 2 diabetes – this is demonstrated by improvements in AIC and increases in Harrel's C sand Royston's D statistic values – and is comparable to its utility in other conditions such as heart failure[99]. As such, EFI score is supported by post-estimation statistics as a consistent and reproducible means of including frailty within observational study designs beyond simply relying on age as a proxy. Furthermore, it should be considered for incorporation into any future observational studies of older adults with diabetes. This is particularly important as frailty in adults with diabetes is both an area of interest where evidence is currently limited and an area that has been highlighted as a priority by organisations including Diabetes UK[317, 319].

When exploring the risk of all outcomes across HbA1c groups, this increased at both high and low HbA1c levels – this "U-shaped" curve has been demonstrated in studies in the past amongst older individuals with diabetes using insulin[84]. The risk of cognitive decline and of falls and fractures was not significantly different across a broad range of HbA1c levels from 48-80mmol/mol [6.5-9.4%]. The lowest risk of all-cause mortality occurred with HbA1c 48-57.9mmol/mol [6.5-7.4%] and is similar to current guidelines[68], but the risk of hospital admission was lowest at a higher HbA1c level of 70-80.9mmol/mol [8.5-9.4%] . Notably, this is higher than is currently recommended even in the severe frailty group of the 2021 international consensus statement[104].

When further subdividing by EFI group, increasing frailty clearly increases the risk of all-cause mortality and hospital admission. Similar "U-shaped" curves were demonstrated for these outcomes in every frailty group. For all-cause mortality and falls and fractures the lowest risk HbA1c categories were similar in every frailty group, but for all cause admission lowest risk shifted towards higher HbA1c levels in individuals with increased frailty (HbA1c 58-69.9mmol/mol [7.5-8.4%] in "fit" individuals vs 70-80.9mmol/mol [8.5-9.4%] in those with moderate and severe frailty). This implies that frailty status may have a role in HbA1c target setting to reduce the risk of admission.

The risk cognitive decline and falls and fractures seem unrelated to HbA1c levels and other factors and including other long-term conditions are likely to be more important. Higher HbA1c levels (above 70mmol/mol) only increased the risk in those who were in the "fit" EFI group and may imply that early intervention to prevent high levels of glucose exposure may have a role in reducing the risk. Multiple studies have linked high HbA1c levels to increased risk of dementia and cognitive decline[320], but also implied that maintenance of HbA1c levels within target for a prolonged period is beneficial with additional risks associated with HbA1c levels that vary significantly over many years[321].

HbA1c levels below 48mmol/mol were associated with an increased the risk of all outcomes within all frailty groups. This finding may have implications for the de-escalation of therapy in older individuals with below target HbA1c levels irrespective of frailty status, although the increase in

risk at this level is often larger in those in the moderate and severe frailty groups as assessed by EFI. This mirrors closely that of the ACCORD trial, which randomised individuals to HbA1c<42mmol/mol [<6.0%] versus standard care and was discontinued early due to significant increases in all-cause mortality, with no reduced risk of all-cause mortality or macrovascular disease in those in the intervention arm[75].

Strengths

This study is novel in its approach and, to our knowledge, is the first study in type 2 diabetes utilising EFI scores and frailty definitions when exploring outcomes. It fills a clear evidence gap as identified by our systematic review and meta-analysis for HbA1c targets in older adults with diabetes and frailty, especially around all-cause mortality and risk of hospital admission[317]. It includes large numbers of individuals from a representative UK cohort and has findings that are likely to be generalisable with this setting.

Additionally, it further emphasises that overtreatment to a HbA1c<48mmol/mol [<6.5%] may have deleterious effects in almost all adults older than 65, which may be more significant in more frail individuals.

Limitations

This study was conducted over a relatively short observation period and during a period when many of the newer drugs, with known additional benefits beyond glucose levels and lower risk of hypoglycaemia, were less

frequently used[69, 271]. It may be that with increasing uptake of these medications the risk versus benefit of a given HbA1c level may be different.

The EFI score itself has its own limitations and does not give insight into the functional status of an individual – rather reflecting the presence of multiple long-term conditions. Future work may want to explore the use of other frailty scales, such as the Rockwood clinical frailty scale[95], although these may be more subjective or less reliably coded within digital databases.

Future work

Repeating this study in future to explore the association between HbA1c and outcomes in frailty, across different databases and once more data has accrued in an era of prevalent sodium glucose link transporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP1 agonists) use will be important. Work to examine the positive cardiovascular and renal outcomes of these drugs, and safety, in frail individuals by using EFI should also be considered.

Conclusions

The EFI score should be considered for incorporation into future models due to its ease of derivation, objective nature, and benefits in improving model performance. Additionally, it broadly maps to existing guidelines and can therefore be easily utilised in clinic. Optimal HbA1c levels for various outcomes often differ so the individualisation of targets will require discussion of relative risks versus, taking into account the priorities of the

person with diabetes. There is increased risk of all adverse outcomes studied at HbA1c levels below 48mmol/mol irrespective of frailty status which may need consideration in practice and have implications for de-escalation of diabetes therapies.

Research in context

This study provides a basis for the use of EFI in future observational studies in diabetes. It will hopefully encourage others to use this to do dedicated work on various aspects of type 2 diabetes care and improve the management of individuals with type 2 diabetes and frailty. Additionally, it provides much need evidence of associations between HbA1c and outcomes in individuals with frailty that will assist clinicians in practice.

Chapter 6 – Predicting response to semaglutide: Evidence from the real-world

Chapter abstract

Background: Previous randomised control trials have observed individual differences in response to Glucagon-Like Peptide-1 Receptor Agonists (GLP1) according to baseline characteristics such as HbA1c and weight. The Association of British Clinical Diabetologists (ABCD) launched a UK nationwide audit in January 2019 to assess the clinical utility, efficacy, and safety of injectable semaglutide in routine practice. The aim of this analysis was to investigate associations between baseline characteristics and HbA1c and weight reductions with semaglutide in real-world use.

Methods: Data were extracted from the secure online tool and individuals with baseline and follow-up data available within a defined 6 (3-9) month window were included. Variables were assessed as both continuous variables and categorical variables in a multivariate regression model. Missing data were multiply imputed.

Results: In total, 620 individuals were included. Baseline characteristics: (mean±SD) age was 58.7±10.7years, HbA1c 81.6±18.5mmol/mol (9.5±1.7%), weight 108.2±24.2kg and BMI 37.6±7.6kg/m^2. Median diabetes duration was 11.2 years (IQR 6.6-16) and 50.5% (313/620) were male. The median follow-up time was 0.5 years. HbA1c reduced by 14.9mmol/mol (95% CI 13.5, 16.1) [-1.4% (95%CI -1.2, -1.5)]; P<0.001, and weight reduced by 4.2kg (95% CI 3.6, 4.8; P<0.001). Higher HbA1c,

younger age and GLP1 agonist naivety associated with larger HbA1c reduction. Higher baseline weight/BMI and GP1RA naivety associated with larger weight reduction.

Conclusion: In this real-world study, baseline HbA1c and weight are important predictors of HbA1c and weight reduction outcomes following initiation of semaglutide in routine clinical practice. This data mirrors existing randomised control trial data, but further evidence over a longer follow-up period is being collected.

Please note: a version of this work was published in the British Journal of Diabetes[322]

Crabtree, T., et al., The factors predicting glucose and weight response to injectable semaglutide (Ozempic): real-world data from the Association of British Clinical Diabetologists' audit programme. British Journal of Diabetes, 2023. 23(2): p. 94-100.

Introduction

Type 2 diabetes is estimated to affect 3.4 million people in England and 537 million worldwide[323, 324] and is increasingly recognised as a heterogenous condition[4, 144, 325]. Individuals with different clinical phenotypes may have varying responses to the range of therapies currently available and there is increasing interest in utilising precision medicine approaches to stratify individuals towards the best treatment option for individual patients[326, 327]. Whilst work is ongoing to identify potential biomarkers and genetic factors, the cost of these may prohibit their use widely in public-funded healthcare systems[328]. Using routinely measured clinical data may be useful to stratify individuals, identifying those who are most likely to benefit from a given treatment, though evidence in this area is remains limited[325].

Glucagon-like peptide 1 receptor agonists (GLP1 agonists) are increasingly used in the management of type 2 diabetes, with increased emphasis on their use in recent national and international guidelines[59, 68, 72]. Semaglutide is a once-weekly injectable GLP1 receptor agonist licensed for the treatment of type 2 diabetes, for which it is also available as a once daily oral preparation[329].

The SUSTAIN series of randomised controlled trials has consistently demonstrated efficacy of semaglutide with mean weight loss of 4.11kg and HbA1c reductions of 15mmol/mol [approx. 1.4%] at the maximally titrated 1mg dose when pooled by meta-analysis[330]. Reductions in major adverse cardiovascular events have also been reported across the

trials[331, 332]. Although SUSTAIN6 reported increased rates of retinopathy, these were not observed across the trials by meta-analysis[333, 334] . However, the trials included in this meta-analysis were of a relatively short duration – work is ongoing to understand retinopathy risk with more prolonged follow-up[180].

Whilst several trials have reported no difference in HbA1c and weight response to semaglutide across individuals with different baseline clinical characteristics[335] two of note reported differential responses across baseline characteristics. Firstly, SUSTAIN8 demonstrated larger HbA1c reductions in individuals with higher baseline BMI and HbA1c levels[336]. Secondly, real-world evidence from an Italian clinic found HbA1c reductions were greatest at 6-months in individuals with higher baseline HbA1c, greater weight loss and longer diabetes duration[337]. This study also identified higher baseline BMI predicting greater weight loss and GLP1 agonist naïve individuals were found to reach similar endpoints to those switching from alternative GLP1 receptor agonists. Previous Association of British Clinical Diabetologists (ABCD) audit programme has also reported the additional benefits of switching to semaglutide from alternative GLP1 agonist preparations[338]. Only minor differences have been observed in terms of race or ethnicity across the SUSTAIN trails[339].

The nationwide ABCD injectable semaglutide audit was launched in January 2019 with the aim to collect routine clinical data on individuals in the UK using semaglutide and assess outcomes in the real-world clinical practice. The aim of this analysis was to assess the clinical characteristics

which may predict HbA1c, and weight responses associated with semaglutide in the real-world, using data from the ABCD audit.

Methods

Participating centres were invited to collect anonymised routinely collected clinical data on individuals commenced on injectable semaglutide (0.25-1mg, Ozempic) to a secure online tool. De-identified data were then extracted for analysis in this cohort study. All individuals with baseline data and at least one follow-up entry for HbA1c and/or weight were included. Individuals with high levels of missing data in key covariates of imputation (e.g. age, gender) were excluded (n=14). The follow-up period was defined as 6-months – with a window of 3-9 months. Key co-variates were identified as follows: baseline HbA1c, baseline weight, age, gender, duration of diabetes and previous GLP1 agonist use. Ethnicity could not be assessed due to missing data. For all other variables, missing data were multiply imputed with 10 imputations and Rubin's rules were applied for the analysis[340].

HbA1c, absolute and relative weight change from baseline were assessed using a multivariate linear regression analysis incorporating the above characteristics into the model as continuous covariates.

The overall model co-efficient and significance levels were also calculated and reported. Subgroup analyses were then performed by classifying these characteristics into groups as follows:

- Age - <60 years; ≥60years
- Gender
- Duration of diabetes - <10years; ≥10 years
- HbA1c – 48-64mmol/mol [6.5-8%]; 64.1-80mmol/mol [8-9.4%]; >80mmol/mol [≥9.4%]
- BMI - <30kg/m^2; 30-40 kg/m^2; >40 kg/m^2
- Previous GLP1 receptor agonist use

Statistical significance was defined as $P<0.05$. When including multiple groups (e.g. BMI) pairwise comparisons were adjusted for multiple comparisons using a Bonferroni correction. All analyses were performed in Stata 16.

The ABCD audit programme is approved by the Confidentiality Advisory Group and a Caldicott Guardian[184].

Results

In total 620 individuals from 22 centres were included in this analysis. The baseline characteristics are summarised in **table 19.** Fourteen individuals were excluded due to having data unsuitable for imputation (due to missing core characteristics such as age or gender).

Over a median follow-up time of 0.5 years (0.4-0.7), across the entire population HbA1c reduced by 14.9mmol/mol (95% CI 13.5, 16.1; P<0.001) [-1.4% (95%CI -1.2, -1.5)]. Absolute weight reductions of 4.2kg (95% CI 3.6-4.8; P<0.001) and relative weight reductions of 3.9% (95% CI 3.4-4.5%; P<0.001) were observed.

Table 19. Baseline characteristics of the included individuals; reported as mean±SD or median (IQR)

Characteristic	n=620
Age, years ± SD	58.7 ± 10.7
Male, % (N)	50.5% (313)
Median diabetes duration, year (IQR)	11.2 (6.6-16)
Mean HbA1c, % ± SD	9.2 ± 1.3
mmol/mol ± SD	81.6 ± 18.5
Mean BMI, kg/m2 ± SD	37.6 ± 7.6
Mean weight, kg ± SD	108.2 ± 24.2
Mean serum creatinine, umol/L ± SD	79.8 ± 27.6
Mean systolic BP, mmHg ± SD	133.4 ± 14.6
Mean diastolic BP, mmHg ± SD	78.2 ± 9.8
Total cholesterol, mmol/L ±SD	4.3 ± 1.1
ALT, u/L ±SD	31.1 ± 17.5
Previous GLP1 use, %	23.5%

BMI, body mass index; eGFR, estimated glomerular filtration rate; BP, blood pressure; IQR, interquartile range; ALT, Alanine aminotransferase; SD, standard deviation

The models and coefficients calculated for baseline characteristics when used in continuous data format are displayed in **table 20.** The coefficients represent the difference in HbA1c reduction per-one unit change in the covariate assessed (for continuous values) or compared to reference (for categorical i.e. GLP1 naïve vs previous GLP1 use). Baseline HbA1c, baseline weight and previous GLP1 use were significant predictors of HbA1c response to injectable semaglutide. Those with high baseline HbA1c

levels had greater HbA1c reductions, and those switching from an alternative GLP1 agonist to semaglutide had attenuated HbA1c reductions.

Table 20. Multivariate linear regression models and coefficients for both change in HbA1c (mmol/mol) and weight (kg).

Outcome	Covariate	β (95% CI)†	P-Value
-ΔHbA1c, mmol/mol	Age, Years	-0.01 (-0.14, 0.13)	0.874
	Gender, Male	-0.39 (-3.13, 2.37)	0.783
	Baseline HbA1c, mmol/mol	6.8 (6.05, 7.64)	<0.001
	Baseline weight, kg	-0.08 (-0.15, -0.02)	0.007
	Diabetes duration, Years	-0.17 (-0.37, 0.03)	0.096
	Previous GLP1 agonist use*	-4.05 (-7.42, -0.69)	0.018
-ΔWeight, Kg	Age, Years	0.02 (-0.04, 0.09)	0.482
	Gender, Male	-0.71 (-1.97, 0.55)	0.270
	Baseline HbA1c, mmol/mol	-0.01 (-0.01, 0.01)	0.792
	Baseline weight, kg	0.04 (0.01, 0.07)	0.004
	Diabetes duration, Years	-0.06 (-0.16, 0.04)	0.245
	Previous GLP1 agonist use*	-1.39 (-2.98, 0.19)	0.084
-ΔWeight, % baseline	Age, Years	0.01 (-0.54, 0.06)	0.861
	Gender, Male	-0.67 (-1.81, 0.47)	0.249
	Baseline HbA1c, mmol/mol	-0.02 (-0.08, 0.04)	0.594
	Baseline weight, kg	-0.01 (-0.31, 0.02)	0.584
	Diabetes duration, Years	-0.06 (-0.15, 0.03)	0.208
	Previous GLP1 agonist use*	-1.14 (-2.57, 0.29)	0.119

**GLP1 - Glucagon-like peptide-1*

†Negative values represent smaller changes from baseline per one-unit change in covariate, positive values represent larger changes from baseline

Only baseline weight significantly predicted weight loss response to semaglutide, although previous GLP1 agonist use was trending towards statistical significance. Those with higher weight at baseline lost more weight in association with injectable semaglutide use. For relative weight change, no factors predicted weight loss in response to semaglutide.

The change in HbA1c from baseline in the subgroup analysis is demonstrated in **figure 17.** Those with HbA1c≥80mmol/mol [≥9.4%] had larger HbA1c reductions than those in the lower HbA1c groups and those switched from alternative GLP1 agonist drugs had a smaller magnitude HbA1c reduction than GLP1 agonist naïve individuals. This persisted for relative HbA1c changes, although we have not reported these as we considered it would not be clinically meaningful. In addition, individuals aged <60years also had greater HbA1c reductions than those aged ≥60years.

The change in absolute weight from baseline in the subgroup analysis is demonstrated in **figure 18.** Those with BMI>40kg/m^2 at baseline had larger weight reductions associated with semaglutide than those with BMI 30-40kg/m^2 at baseline but not those <30kg/m^2. Those who switched to semaglutide from an alternative GLP1 agonist were observed to experience less weight loss than GLP1-naïve individuals. The relative change in weight from baseline is demonstrated in **figure 19.** – no statistically significant differences were noted between subgroups.

*Figure 17. Forest plot showing change in HbA1c amongst different subgroups. Results non-significant unless other stated. *P<0.05*

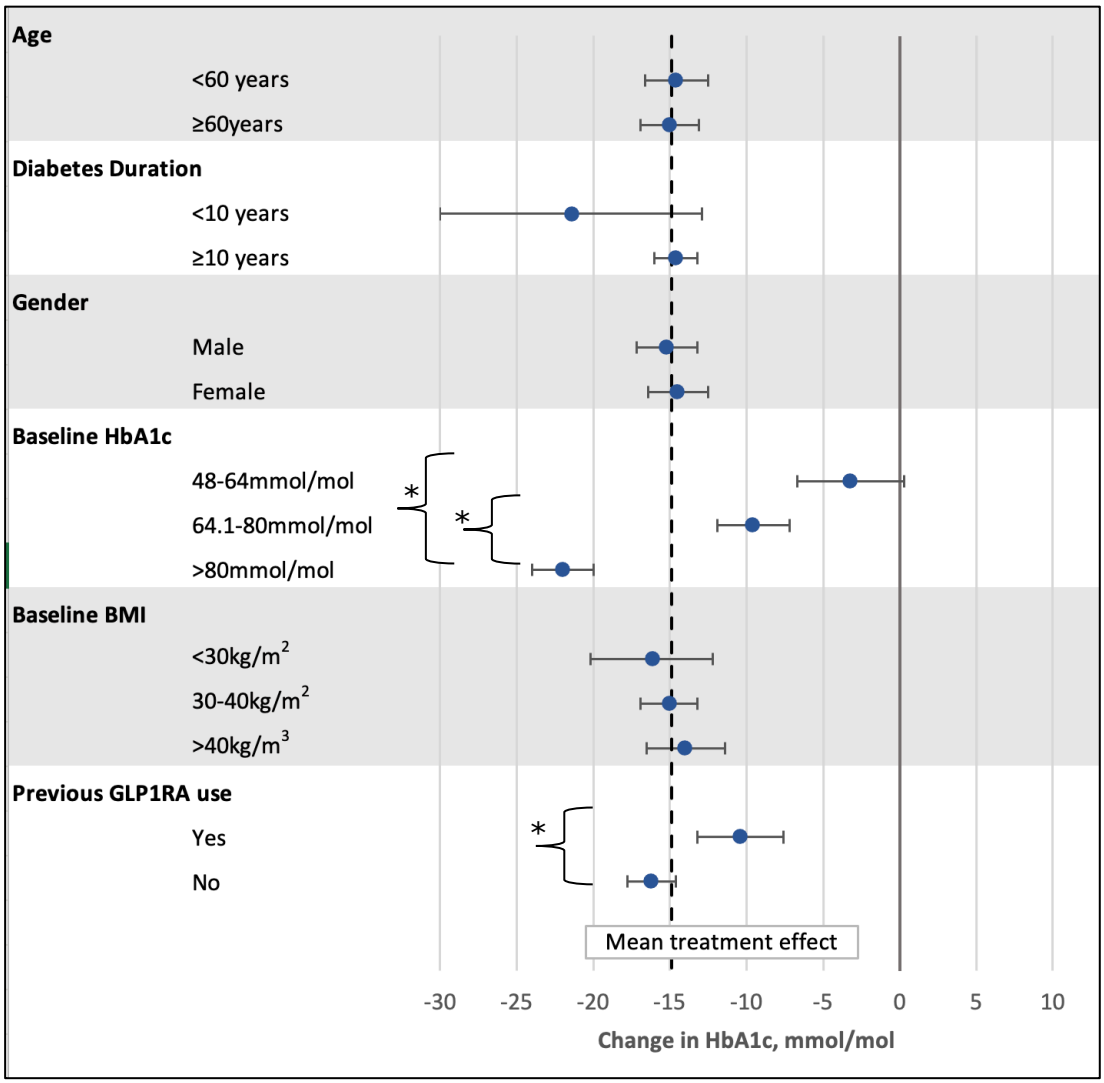


*Figure 18. Forest plot showing change in absolute weight amongst different subgroups. Results non-significant unless other stated. *P<0.05*

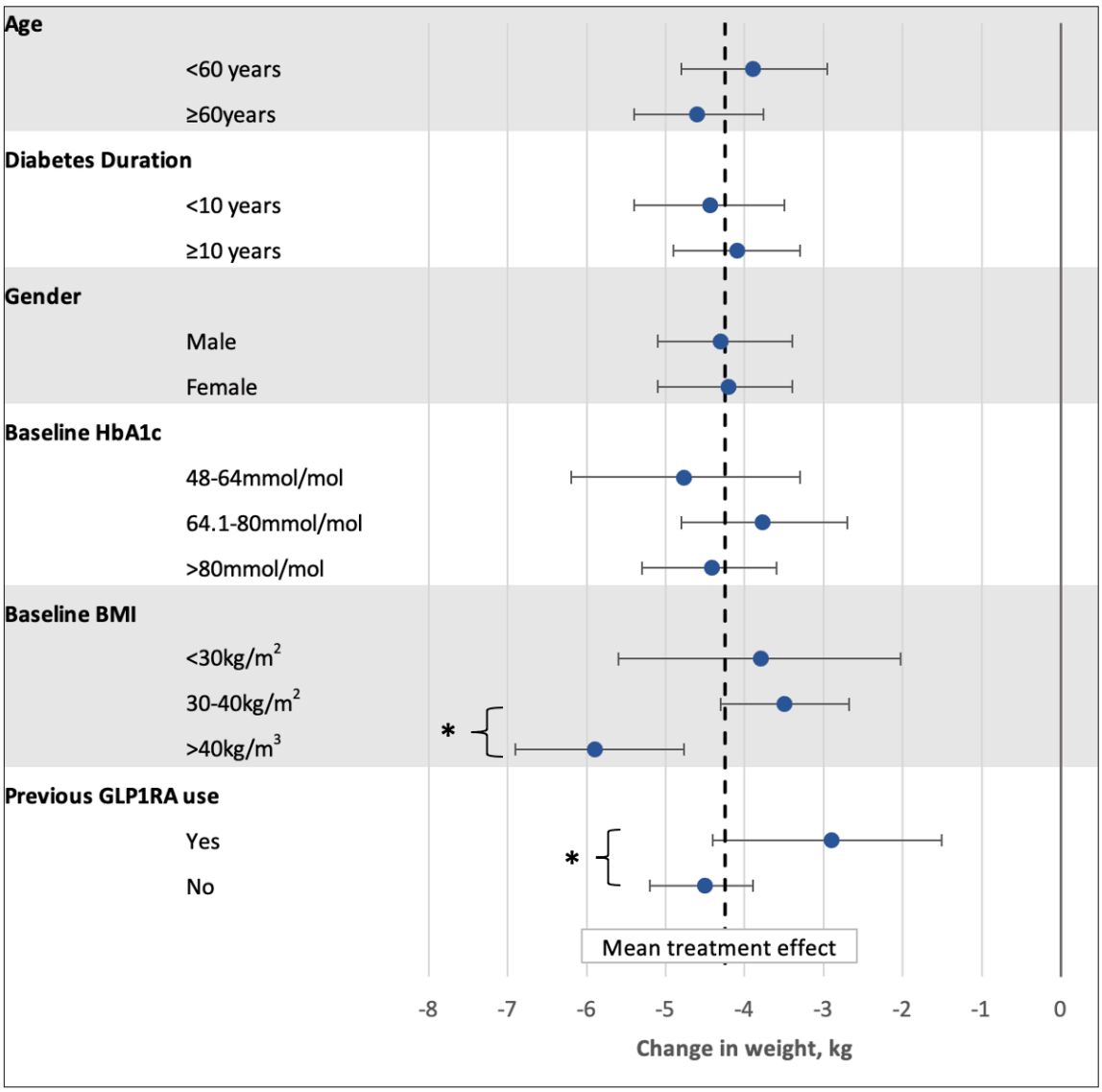
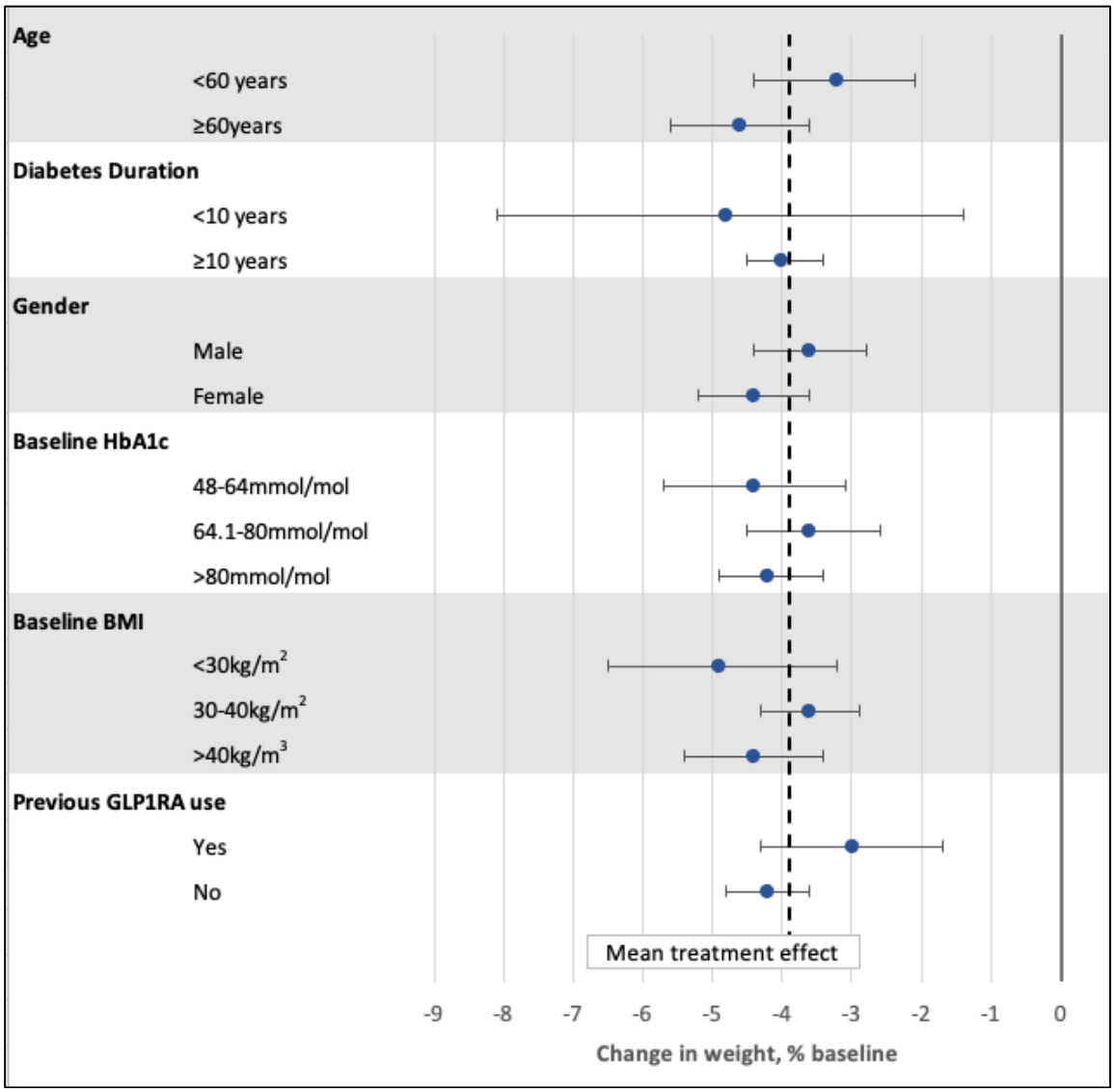


*Figure 19. Forest plot showing change in relative weight (percentage of baseline weight) amongst different subgroups. Results non-significant unless other stated. *P<0.05*



Discussion

Our results from the ABCD audit programme demonstrate that HbA1c and both absolute and relative weight reductions with injectable semaglutide translate evidence from randomised control trial into real-world clinical practice. The HbA1c and weight reductions observed are comparable to those in the SUSTAIN trials[330, 336]. Additionally, our results mirror the findings from SUSTAIN8 in that those with higher HbA1c and weight baseline achieve larger reductions by follow-up[336]. There was no significant difference noted between individuals with BMI<30kg/m^2 and those with BMI>40kg/m^2 – this is likely due to relatively small numbers in the lowest BMI group (n=74).

We did not observe any difference in response across different diabetes durations as reported in SUSTAIN8 and the real-world Italian study highlighted in the introduction[336, 337]. We report similar observations to SUSTAIN8 with a statistically significant impact of baseline weight on HbA1c change, with heavier individuals achieving statistically larger reductions[336]. It should be noted however that the coefficient for this is small, and therefore unlikely to be clinically meaningful. The difference across weight did not persist within the subgroup analysis.

GLP1 agonist-naïve individuals had larger HbA1c and weight reductions than those switching from other GLP1 agonist medications – although reductions were observed in both groups. This is a finding we have reported previously and that was reported in SUSTAIN8[336, 338]. It suggests individuals who have already been exposed to GLP1 agonists

have had a partial treatment effect but that further benefits can be gained from switching to Semaglutide.

Strengths and limitations

The pragmatic real-world study design allows us to observe the use of injectable semaglutide in clinical practice and compare findings in this population to existing RCT data. Our findings confirm that trial results can be generalised to UK clinical practice, despite such practice including individuals who are less closely monitored or perhaps have more extreme baseline characteristics and would therefore have been excluded from trials. In our analysis, baseline HbA1c (81.6 vs 67.2mmol/mol in SUSTAIN-8) and weight (108kg vs 90.6kg in SUSTAIN-8) were higher, and diabetes duration (11.2years vs 7.5 years in SUSTAIN-8) was longer than in clinical trials. Additionally, if shortages persist these data may help in guiding who may benefit the most from semaglutide[341].

Real-world data has its limitations. Although the use of multiple imputations may mitigate problems caused by missing data, it does not resolve this completely. Nonetheless, we excluded individuals with high levels of missing data in key covariates. Notably, dose data was not available. Although it is assumed individuals were maximally titrated, assessment or adjustment for doses was not possible. Additionally, unobserved confounders may impact the results, but we are reassured that our findings complement well and mirror the existing extensive data on semaglutide. Regression to the mean may also have impacted the results and account for some of the reductions in HbA1c and weight observed,

however the extent and degree of statistical significance makes this less likely. Ethnicity and deprivation data were not available and further work should focus on uptake and outcomes in these key groups to assess real-world equitability.

Conclusion

In this real-world analysis from the ABCD audit programme, injectable semaglutide was associated with greater HbA1c reduction in those who were younger, vs. older, and in those who had higher, versus lower, baseline HbA1c. Weight reductions were largest in those who weighed most at baseline. Whilst reductions in weight and HbA1c were observed in individuals switching to semaglutide from other members of the GLP1 agonist class, these were of lesser magnitude than in GLP1 agonist-naïve individuals. Data collection for the ABCD audit is ongoing, and further follow-up will allow us to assess the impact of semaglutide on key outcomes in the long-term.

Research in context

This study is an example of insights than can be gained from real-world studies. Although the numbers are relatively small and there are issues with missing data, as discussed in chapter 2, real-world data can show us how treatments are performing outside of well-resourced research environments and, can even help us learn how individuals in the clinical practice respond to new therapies allowing us to better target their use. This might be of particular relevance with GLP1 agonists where supply

issues are ongoing and so careful and those who may gain the biggest benefit need to be identified.

Chapter 7 - Hybrid closed-loop therapy in adults with type 1 diabetes and above target HbA1c

Chapter abstract

Introduction: This study explores longitudinal changes associated with switching to hybrid closed loop (HCL) insulin delivery systems in adults with type 1 diabetes and elevated HbA1c levels despite the use of intermittently scanned continuous glucose monitoring (isCGM) and insulin pump therapy.

Methods: This study undertook a pragmatic, pre-planned observational study of participants included in the NHS England closed-loop pilot. Adults using isCGM and insulin pump across 31 diabetes centres in England with a HbA1c 69mmol/mol [≥8.5%], who were willing to commence HCL therapy were included. Outcomes included change in HbA1c; sensor glucometrics; Diabetes Distress Score; Gold Score (hypoglycaemia awareness); acute event rates and user opinion of HCL.

Results: In total, 570 HCL users were included; median age 40 (IQR 29-50) years, 67% female, and 85% White. Baseline HbA1c was 9.4±0.9% [78.9±9.1mmol/mol] with a median follow-up of 5.1 (IQR 3.9-6.6) months. Of 520 users continuing HCL at follow-up, mean adjusted HbA1c reduced by 1.7% (95% CI 1.5, 1.8, P<0.0001) [18.1mmol/mol; 95%CI 16.6, 19.6; P<0.0001]. Time in range (70-180mg/dL) increased from 34.2% to 61.9% (P<0.001). Individuals with HbA1c of ≤58mmol/mol

rose from 0% to 39.4% (P<0.0001) and those achieving ≥70% glucose time in range and <4% time below range increased from 0.8% to 28.2% (P<0.0001). Almost all participants rated HCL therapy as having a positive impact on quality of life (94.7%, 540/570).

Conclusions: Use of HCL is associated with improvements in HbA1c, time in range, hypoglycaemia and diabetes-related distress and quality of life in people with type 1 diabetes in the real-world.

A version of this chapter has been peer-reviewed and published in Diabetes Care[342]

Crabtree, T.S.J., et al., Hybrid Closed-Loop Therapy in Adults with Type 1 Diabetes and Above-Target HbA1c: A Real-world Observational Study. Diabetes Care, 2023. 46(10): p. 1831-1838.

Introduction

Whilst the focus of this thesis so far has been on type 2 diabetes, it is important to recognise that there are currently over 400,000 people living with type 1 diabetes in England and Wales and the incidence is increasing[4, 343]. Many of the same problems exist within type 1 diabetes research as type 2 diabetes, and there is concern that evidence from randomised control trials may not represent outcomes in the real-world.

Type 1 diabetes is one of the most challenging long-term conditions to self-manage. It requires multiple daily glucose measurements, counting carbohydrates, and calculating and injecting insulin doses multiple times daily in the unrelenting endeavour to achieve normoglycaemia. Unsurprisingly, glucose levels in many people living with type 1 diabetes remain above target and according to the 2021/22 UK National Diabetes Audit, in England only 12.7% achieved the recommended HbA1c target of ≤48 mmol/mol [≤6.5%] and only 36.3% achieved HbA1c level ≤58 mmol/mol [≤7.5%] [4].

Whilst insulin pump therapy and structured education may increase the chance of achieving this target, evidence from the National Diabetes Pump Audit demonstrated similar numbers achieving HbA1c≤58mmol/mol [≤7.5%] among people who were using and not using insulin pumps with an average HbA1c amongst pump users of around 64mmol/mol [8.0%][344]. Furthermore, the risks of hypoglycaemia remain a major barrier while the constant vigilance over

glucose levels and need for multiple self-care tasks can lead to diabetes burnout and distress[345].

Hybrid closed-loop (HCL) insulin delivery systems combine insulin pump therapies with continuous glucose monitoring (CGM) sensors to automate insulin delivery between meals and overnight to maintain glucose near a pre-specified target level using algorithmic software contained within the insulin pump or a separate device (e.g. smart phone)[346]. Currently available systems require a user-initiated meal bolus (a "hybrid" approach). In the UK, the use of these systems has been limited by access to real-time CGM nationally and the need to meet criteria for insulin pump therapy as per the National Institute for Health and Care Excellence (NICE) TA151 *"Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus"*[347]. Whilst updates to NICE Type 1 diabetes (NG17) guidelines may facilitate increased uptake of HCL through improved access to HCL compatible real-time CGM, specific guidelines for HCL use in the UK not currently available[348].

In the available randomized controlled trials looking at single devices, HCL systems improve glycaemic outcomes when compared to insulin pump alone, multiple daily injections with CGM and sensor augmented pump therapy[349-353]. However, the benefits demonstrated in these clinical trials reflect the outcomes in a group of people motivated to take part in research and often with HbA1c levels close to target at baseline with intensive protocolized follow-up. This limits the generalizability of these findings to the wider population with type 1 diabetes who will

undergo standard follow-up, especially in a UK context where almost 66% of individuals have HbA1c levels above target (≥58mmol/mol [≥7.5%])[4].

Real-world evidence exists but is limited to single-system studies and, similar to the randomized controlled trial data, frequently included individuals who were at or near target HbA1c at baseline. Additionally, these studies often lack data on HbA1c (instead reporting sensor derived glucose data) and hospital admissions[354-357]. In recognition of the disconnect between the evidence and observed clinical experience with HCL systems, NHS England (NHSE) funded a real-world pilot scheme for the use of HCL systems in individuals with a high HbA1c level who were already using an insulin pump. The Association of British Clinical Diabetologists (ABCD) Closed-Loop audit was designed to capture routine anonymized outcome data from adults who participated in this scheme. The aim was to assess the real-world effectiveness and safety of HCL systems commercially available in the UK in an NHS outpatient setting.

Methods

The methodology for this observational study was published and peer reviewed prior to undertaking[358]. The population included in the NHSE adult HCL pilot were those attending adult diabetes services with a diagnosis of type 1 diabetes managed with an insulin pump and intermittently scanned continuous glucose monitoring (isCGM) with an HbA1c ≥69mmol/mol. Thirty-one adult diabetes centres across England

were selected by NHSE to participate based on geography and pump experience. Patients were started on HCL between August and December 2021. Anonymized clinical outcome data were collected prospectively during routine clinical care, review of clinical systems and electronic health records and submitted via a secure online tool. This analysis reflects the data captured between 3 and 9 months of follow-up. The primary outcome was change in laboratory derived HbA1c. Secondary outcomes include CGM metrics time in range (TIR, 3.9-10mmol/L), time below range (TBR, <3.9mmol/L), Glucose Management Indicator (GMI, "estimated HbA1c"), Diabetes Distress 2 score (DDS2)[150], Gold score[149], event rates, weight, body mass index (BMI) and user opinion of HCL (using a 7 point Likert; 1=strongly negative/would not recommend, 7=strongly positive/would recommend). The proportion of individuals experiencing diabetes distress (DDS2≥3) or impaired hypoglycaemia awareness (Gold score≥4) before and after treatment were assessed to make changes in these parameters more clinically meaningful, as small score changes are unlikely to be relevant in clinical practice. Sensor glucometrics were reported over 14-days as per the international consensus guidelines and in keeping with routine clinical practice[61]. Events of interest included hospital admission, paramedic callouts and severe hypoglycaemia (requiring third-party assistance to treat) and were reported by the clinical teams via the online tool. Sensor glucometrics were extracted from the relevant HCL system for the 14-days preceding follow-up. Follow-up frequency was determined by the responsible clinical teams purely on clinical need. The most recent available data for each patient, within the 3–9-month follow-up window,

was used in this analysis. Only available paired data were included for each outcome of interest.

Sensitivity analysis was performed comparing the baseline characteristics of those with follow-up data compared to those who discontinued the system or in whom follow-up data was not available (i.e., not entered, failed to attend, lost to follow-up). Data were assessed for accuracy and completeness and analysed using Stata SE 16. The analysis was conducted by two individuals independently (TSJC and TPG). Data were expressed as mean and standard deviation (SD) for continuous outcomes with a parametric distribution, and median and interquartile range (IQR) for non-parametric distributed continuous outcomes (determined by tests of skew). Paired t-tests were used for the analysis of continuous variables with a parametric distribution. Mann Whitney U (Wilcoxon Rank Sum) tests were used to assess outcome variables with a non-parametric distribution. A P-value <0.01 was considered statistically significant to account for multiplicity. Change in HbA1c from baseline was adjusted for baseline characteristics and change in other covariates using a multivariate linear regression model with clustering by centre to correct for key covariates determined *a priori* as follows: baseline HbA1c and weight, gender, age, duration of diabetes and pump use, deprivation level, HCL system, time in closed loop, ethnicity and change in weight. Mann Whitney U tests were used to assess changes in patterns of hospital admissions and paramedic callouts.

Role of the funding sources

NHS England funded the provision of HCL systems as part of a real-world pilot scheme launched in 2021[359]. The independent collection of outcome data including the secure anonymized online tool was funded by the Association of British Clinical Diabetologists.

Patient and public engagement

The importance of closed-loop to people with diabetes has been emphasized repeatedly by groups on social media and in meetings with both UK based charities (e.g., Diabetes UK) and NHS England. Many campaigns (e.g. #WeAreNotWaiting) exist with the aim to improve access to diabetes technology[360]. Research into closed loop systems has been established as a priority research area in diabetes by the James Lind Alliance[361]. Acknowledging the importance of the lived experience of people with diabetes, simple questions were asked on the impact of these systems on quality of life and whether users would recommend these systems to others. Qualitative outcomes were explored in more depth in a dedicated study which will report at a later date.

Ethics

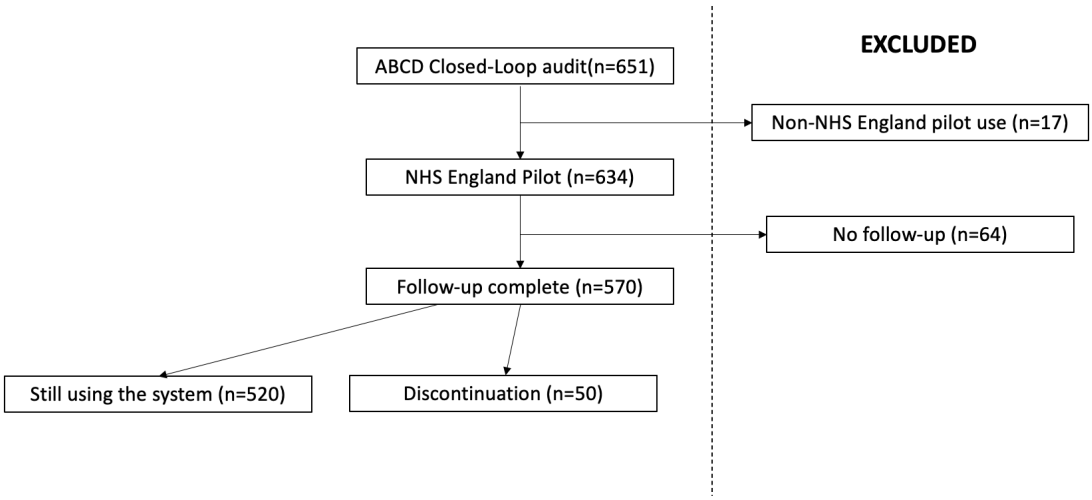
As a service evaluation and audit, this program only collects anonymized routinely available clinical data. Tests not performed routinely were not required to be performed. As such there was no requirement for approval by a research ethics committee. The ABCD nationwide audit program,

which includes this audit, has Caldicott Guardian Approval and has also been approved by Confidentiality Advisory Group[184].

Results

Baseline data were available for 634 adults across the 31 centres, with follow up data reported for 570 people (89.9%), of whom 91.2% (520/570) continued to use HCL**. Figure 20.** Contains the flow-diagram for this analysis.

Figure 20. Flow diagram for individuals included in analysis of the hybrid closed-loop study



Baseline characteristics

For the 520 individuals with baseline and follow up data the median age was 40 years (IQR 29-50), 67% (n=348) were female with a median diabetes duration of 21 years (IQR 15-30), 83% (n=433) were white British, 10% (50/500) were from the 2 most deprived quintiles with median index of multiple deprivation decile of 6 (IQR 3-8). The baseline

characteristics of the cohort are summarized in **table 21.** The HCL systems initiated in the NHS England pilot included Medtronic 780G (46%, n=241), Tandem Control IQ (37%, n=193), CAM APS (5%, n=27), Medtrum closed loop system (4%, n=19) and the Medtronic 670G (2%, n=8); the system was not reported in 32 (6%) individuals.

HbA1c and sensor-based outcomes

Across the population HbA1c reduced from 78.9±9.1mmol/mol at baseline to 62.1±9.1mmol/mol over a median follow-up of 5.1 months (IQR 3.9-6.6). The mean unadjusted decrease in HbA1c was 16.7mmol/mol (95%CI 15.8, 17.6; P<0.001). Using a multivariable linear regression model to correct for key covariates, mean adjusted HbA1c reduced by 18.1mmol/mol (95%CI 16.6, 19.6; P<0.0001). These results are demonstrated in the violin plot and scatter plot **Figures 21 and 22.** There is no evidence for difference in HbA1c changes associated with HCL across baseline deprivation status or ethnicity (P=0.999 for both) when assessed by pairwise comparisons within the regression model.

Table 21. Baseline characteristics and sensitivity analysis (for those included vs discontinuation/lost to follow-up) in the hybrid-closed loop study

Baseline Characteristics	**All** n=634	**Follow-up Complete** n=520	**Discontinued/ Missing** n=114	**P-Value**
Age, Years†	40 (29-50)	40 (29-51)	38 (26-47)	0.27
Diabetes Duration, Years†	21 (14-30)	21 (15-30)	21 (14-32)	0.95
Pump Duration, Year†	8 (5-11)	8 (5-11)	7 (4-10)	0.49
Weight, kg*	81±18	82±18	79±15	0.21
Body Mass Index, kg/m²*	29±6	29±6	28±5	0.26
Median index of multiple deprivation decile†	6(3-8)	6 (3-8)	5 (3-8)	0.10
Most deprived quintile of deprivation‡	65 (10)	50 (10)	15 (13)	0.26
Ethnicity‡				0.70
White - British	537 (85)	433 (83)	104 (91)	
White - Other	14 (2)	11 (2)	3 (3)	
Mixed	10 (2)	10 (2)	0 (0)	
Asian	16 (3)	14 (3)	2 (2)	
Black	7 (1)	6 (1)	1 (1)	
Other	5 (1)	4 (1)	1 (1)	
Unknown	45 (7)	42 (8)	3 (3)	
Gender‡				0.90
Female	425 (67)	348 (67)	77 (68)	

Baseline Characteristics	All n=634	Follow-up Complete n=520	Discontinued/ Missing n=114	P-Value
HbA1c/CGM Metrics*				
Mean HbA1c, %	9.4±0.9	9.4±0.9	9.3±0.9	0.25
Mean HbA1c, mmol/mol	79±10	79±10	78±10	0.25
Total Daily Insulin Dose, units	50±30	51±31	46±18	0.14
Glucose Management Indicator, mmol/mol	72±11	72±11	74±13	0.13
Time above 14mmol/L, %	39±20	38±19	43±23	0.03
Time above range (10.1-13.9mmol/L), %	26±11	27±11	23±12	0.01
Time in range (3.9-10mmol/L, %	34±15	34±15	33±17	0.41
Time below range, Level 1 (3-3.8mmol/L), %	2±2	2±2	2±2	0.85
Time below range, Level 2 (<3mmol/L), %	0±1	0±1	0±1	0.74
Number of scans per day at baseline	7±6	7±6	8±7	0.28
Coefficient of variation	38±7	38±7	38±6	0.66
Insulin Pump/Closed-Loop System‡				
Medtronic 780G	303 (48)	241 (46)	62 (54)	
Tandem Control IQ	217 (34)	193 (37)	24 (21)	
CAMAPS FX	31 (5)	27 (5)	4 (4)	<0.001
Medtrum	31 (5)	19 (4)	12 (11)	
Medtronic 670G	8 (1)	8 (2)	0 (0)	
Not recorded	44 (7)	32 (6)	12 (11)	

*Data reported as mean±standard deviation; P-Value comparing those with and without follow-up derived from unpaired T-Test †Data report as median (Interquartile range); P-Value comparing those with and without follow-up derived from Mann Whitney U (Wilcoxon Rank Sum) tests. ‡Data reported as number (percentage); P-Value comparing those with and without follow-up derived from Chi-2 testing

The median % time spent in closed-loop mode was 96% (IQR 92-99%). The glucose management indicator decreased from 71.6mmol/mol to 57.3mmol/mol at follow-up (-15.4mmol/mol; 95% CI -13.7, -17.0; P<0.0001). Time in range (3.9-10mmol/L) increased from 34.2% to 61.9%, a mean increase of 27.8% (95% CI 26.2, 29.4, P<0.001). Time below range (<3.9mmol/L) reduced from 2.1% to 1.6% (P=0.01), with level 1 hypoglycaemia (3.0-3.8mmol/L) reducing from 1.8% to 1.3% (P<0.001). There was no significant change in level 2 hypoglycaemia (<3.0mmol/L).

Coefficient of variation fell from 38.0% to 35.2% (-2.8; 95% CI -1.9, -3.6; P<0.0001). The changes in CGM derived glucose metrics are displayed in **figure 23 and table 22.** The paired HbA1c and CGM derived glucose metric outcomes are summarized in **table 23.**

Figure 21. Violin plot demonstrating HbA1c at baseline and follow-up (P<0.0001)

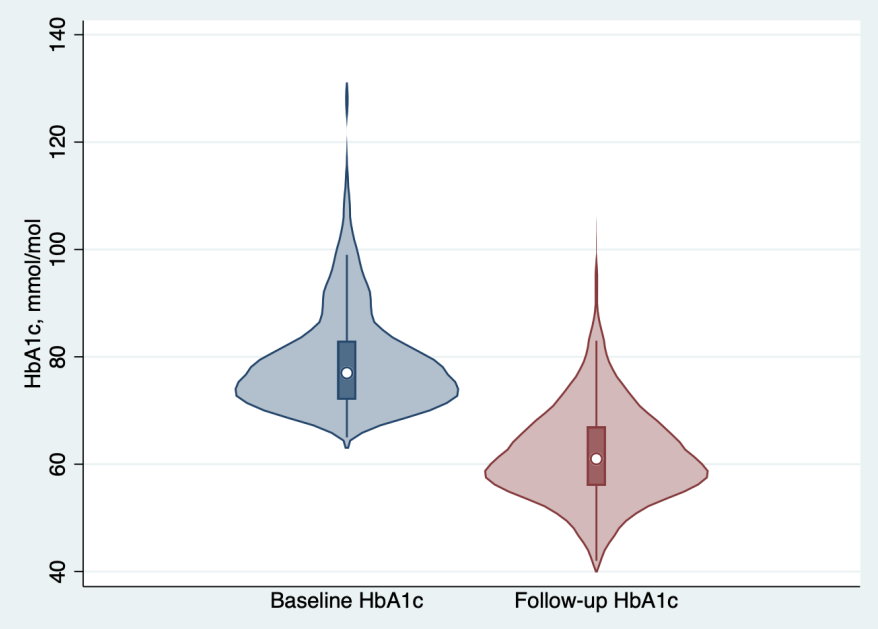


Figure 22. Scatter plot showing individual patient data for HbA1c at baseline and HbA1c at follow-up with line of best fit + 95% confidence intervals (adjusted with regression model)

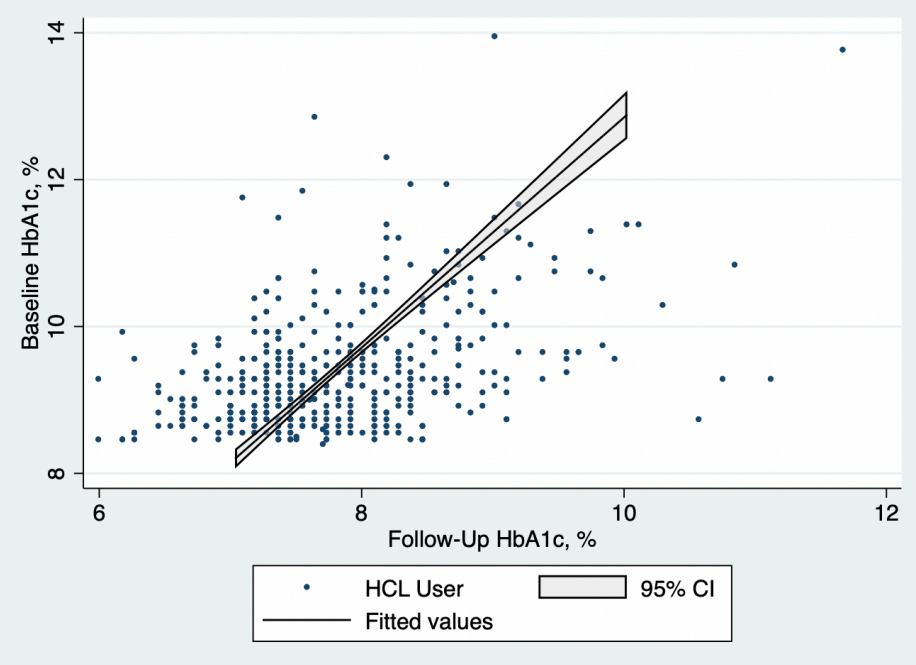


Figure 23. Stacked bar chart demonstrating time-in-glucose ranges at baseline and follow-up. Note: Data for individuals with complete sensor data only (n=380)

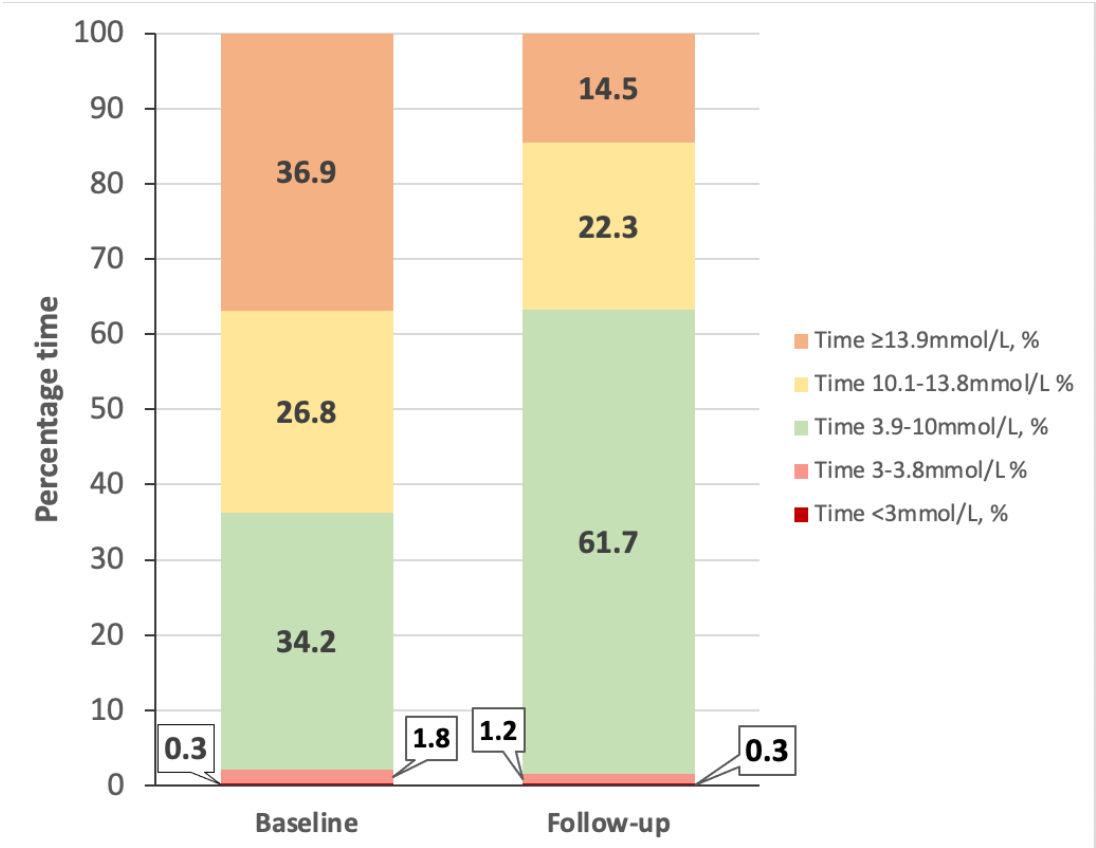


Table 22. Table showing baseline & follow-up time spent in glucose ranges where complete sensor data was available

	Baseline	**Follow-up**
Time <3mmol/L, %	0.3	0.3
Time 3-3.8mmol/L %	1.8	1.2
Time 3.9-10mmol/L, %	34.2	61.7
Time 10.1-13.8mmol/L %	26.8	22.3
Time ≥13.9mmol/L, %	36.9	14.5

As per entry criteria, no individuals were achieving a HbA1c of ≤58mmol/mol at baseline; 39.4% (176/447) of users met this HbA1c target at follow-up; 14.1% (63/447) achieved HbA1c 53mmol/mol. At baseline, 0.8% met the internationally recommended targets of ≥70% time in range and <4% time below range: this increased to 28.2% (135/478) at follow-up (P<0.0001)[61]. **Figure 24** demonstrates the proportion of the cohort achieving recognized glycaemic targets before and after closed-loop therapy. In total, 91.0% (n=473) had a HbA1c drop ≥0.5% with 79.6% (n=414) achieving reductions ≥1.0%. Only 11 (2.1%) individuals using HCL experienced an increase in HbA1c.

Weight, BMI, and total daily dose of insulin

Weight increased from a mean±SD of 80.8±18.1kg at baseline to 82.7±20.0kg at follow-up, a mean increase of 1.9kg (95% CI 0.9, 2.9; P<0.001; n=282). Amongst those with available data, the increase in BMI from 28.9±6.9kg/m^2 at baseline to 29.2±6.8kg/m^2 at follow-up was non-significant (P=0.07). Total daily insulin doses increased from 49.4±23.2units to 55.8±1.7units, an increase of 6.4 units (95% CI 4.6, 8.3; P<0.001; n=250).

Table 23. Baseline and follow-up HbA1c, CGM derived glucose metrics (uncorrected changes) and patient reported outcome measure scores (Diabetes Distress Scores and Gold Scores)

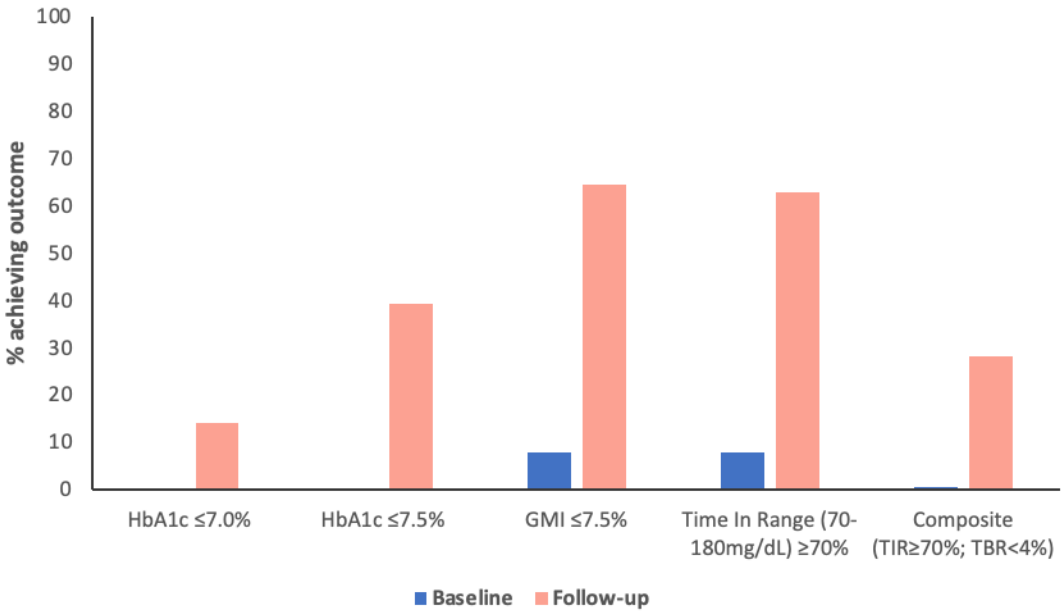
	N §	Baseline	Follow-up	Change (95% CI)	P-Value*
HbA1c and glucose data					
HbA1c, mmol/mol	436	78.9±9.1	62.1±9.1	-16.7 (-15.8, -17.6)	<0.001
HbA1c, %	436	9.4±0.8	7.8±0.8	-1.5 (-1.4, -1.6)	<0.001
Time >250mg/dL, %	407	37.2±19.1	14.9±11.8	-22.4 (-20.5, -24.2)	<0.001
Time 180-250mg/dL, %	381	26.8±10.3	22.3±11.7	-4.5 (-3.0, -6.1)	<0.001
Time 70-180mg/dL, %	417	34.2±14.5	61.9±13.1	27.8 (26.2, 29.4)	<0.001
Time 54-69mg/dL %	411	1.8±2.4	1.3±1.6	-0.5 (0.2, 0.8)	<0.001
Time <54mg/dL, %	397	0.37±1.00	0.35±0.57	-0.03 (-0.13, 0.18)	0.729
Coefficient of variation	325	38.0±6.9	35.2±6.7	-2.8 (-1.9, -3.6)	<0.001
Patient reported outcome measures					
Gold Score	415	2.3±1.4	1.9±1.2	-0.4 (-0.2, -0.5)	<0.001
Diabetes Distress	412	3.3±1.3	2.2±1.0	-1.1 (-1.0, -1.3)	<0.001
Diabetes Distress (Average Score ≥3) †, % (n)	412	69.2% (285)	22.8% (94)	-46.4% (-191)	<0.001
Impaired Awareness of hypoglycaemia (Gold ≥4), % (n)	415	16.9% (70)	9.4% (39)	-7.5% (-31)	<0.001

**Statistical significance calculated using unpaired T-Tests for all covariates included in this table, following assessment for skew*

†Statistical significance calculated using Chi-squared tests

§ N=number with available data therefore included in analysis for this outcome; total cohort=520

Figure 24. Proportion of individuals achieving targets for HbA1c, glucose management indicator (GMI), time-in-target range (TIR) and a composite outcome of TIR and time-below-range (TBR) at baseline and follow-up



Diabetes distress, Gold score and user satisfaction

Improvements in patient reported outcome measures were observed with reduction in Diabetes Distress from 3.3 to 2.2, a mean reduction of -1.1 (95% CI -1.0, -1.3; P<0.001). The proportion of individuals with high diabetes distress (DDS2≥3) reduced from 69.0% baseline to 22.8% (P=0.001). Gold score reduced from 2.3 to 1.9 (P<0.001). These results are summarized in **table 23.** Within the NHS England pilot (including those who discontinued the system), 96.3% (549/570) would recommend HCL therapy to others with diabetes and 94.7% (540/570) rated HCL therapy as having had a positive impact on their quality of life.

Acute and adverse events

A total of 37 adverse events were reported. The majority (24/37) of these adverse events were related to either pump or cannula issues (11/37, 29.7%) or sensor failures, inaccuracies, and skin reactions (13/37, 35.1%). A total of 50 users (8.8%) discontinued closed-loop therapy. Reasons given included: lack of trust in the system/anxiety (4/50, 8%), erratic glucose levels (5/50, 10%), issues with cannulas/skin site reactions (6, 12%), early problems in adjusting to closed-loop (6/50, 12%), and failing to attend follow up appointments so discontinued by the clinical team (5/50, 10%). Five individuals (10%) were moved off one closed-loop system due to technical issues and did not restart. No reasons were provided for discontinuation in the remaining cases (19/50, 38%).

Sensitivity analysis

Sensitivity analysis comparing individuals with complete follow up versus those who discontinued the system or had missing follow-up data is shown in **table 21.** Those with absent follow-up had higher time ≥ 14.0mmol/L at baseline, were more likely to be using ultra-fast acting insulin ($P<0.05$ between groups for all). Baseline HbA1c between those with and without follow-up was not significantly different ($P=0.25$). All other baseline characteristics were similar between the groups.

Discussion

This real-world evaluation of the NHS England pilot of HCL system use in people living with type 1 diabetes demonstrates substantial improvements in glycaemic and patient reported outcomes over 5 months of follow up.

The observed -18.1mmol/mol HbA1c change is greater than that reported in both randomized control trials and existing real-world studies, which report HbA1c reductions between 5-10mmol/ between baseline and follow-up, although the average HbA1c of participants included in these studies was lower at baseline[349-351, 356]. Closer comparisons can be made to the ADAPT study, which randomized those with similar HbA1c levels (>64mmol/mol), mean baseline HbA1c 75mmol/mol, to either HCL or standard care (multiple daily injections with isCGM)[353]. In the ADAPT study a 16mmol/mol HbA1c reduction was observed in the HCL arm at follow-up with a relative difference of 14mmol/mol between intervention and control arm. Our results are similar but in a larger cohort already using insulin pump therapy at baseline and with a higher HbA1c. The reductions in HbA1c we report and the follow-up HbA1c levels achieved are likely to translate into significant reductions in complications in the long-term. The proportion of people achieving HbA1c targets ≤58mmol/mol in this real-world study increased from 0% to 39.4%. This exceeds the proportion of individuals already achieving this target within the National Diabetes Audit (36.3%) and National Diabetes Pump Audit (34.4% in 2017-18)[4, 344]. Although follow-up glucose time in range (61.2% in 3.9-10mmol/L) was lower than

in many existing HCL studies, our observed population had much lower time-in-range at baseline (34.2%) and the change in time-in-range, an increase of 27.8%, was much greater[349-351, 356, 362, 363]. Of note, any change in glucose management indicator should be interpreted with caution, as sensors are limited in their ability to calculate this due to inability to account for extremely high glucose values.

There was a 28% reduction in sensor detected level 1 hypoglycaemia and user-reported improvements in hypoglycaemia awareness and diabetes distress. This may however, be related to the switch from isCGM to rtCGM and the provision of more advanced alarms as has been previously demonstrated in trials[364]. The majority of users reported a positive impact on quality of life and would recommend the use of HCL systems to other people living with diabetes. Some of this may be explained by the significant reductions in hyperglycaemia which have previously been linked to multiple quality of life factors including mood, cognition and even driving skills [365-368]. This is consistent with existing qualitative evidence supporting the use of closed-loop insulin systems[369, 370].

Although significant reductions in HbA1c and glucose levels were associated with HCL in this real-world study, over 50% still had HbA1c levels above target. This may further be improved in future by improving the education, support and training provided to users of HCL, alongside further developments in HCL systems. This is echoed by other studies including the ADAPT study[371].

A small amount of weight gain (1.9kg) was observed which may be due to improved glucose levels and reductions in glycosuria and subsequent urinary calorie loss. This is comparable to findings from randomized control trials (e.g., 2.1kg in Tauschmann et al, 2018)[349, 372].

These data also demonstrate that, despite the advances in technology and general positive response to HCL, the current generation of closed loop systems are not for everyone. It should be noted that a small but significant proportion of people (8.8%) discontinued use despite all users already being familiar with and established on stand-alone insulin pump therapy. The reasons for this are multifaceted, are not limited purely to technology or equipment issues and should be explored further in future studies.

The main strength of our analysis is the real-world nature of the data captured, encompassing a large number of diverse HCL users across multiple different systems and across multiple centres. We know that in the longer-term, despite the benefits of structured education, insulin pump therapy and intermittently scanned continuous glucose monitoring, a large proportion of people living with type 1 diabetes are unable to achieve target glucose levels and remain at high risk of complications[373]. Within a UK context, we know that only a third of insulin pump users achieve a target HbA1c ≤58mmol/mol[4]. The HbA1c reductions observed in this study are likely to significantly reduce these future risks with important health-economic implications. By including

data from multiple HCL systems, our observations are generalizable to a broad population of individuals with type 1 diabetes and HbA1c levels above target, irrespective of the system used. The findings observed are less generalizable to individuals with lower baseline HbA1c levels, though HCL use is supported in these individuals by existing RCT evidence[349, 350, 352].

There are limitations to this real-world study including the lack of a control group; the possibility of unmeasured confounders contributing to the changes observed, under-reporting of adverse events and missing data. Despite this, there is novelty in assessing the use of these technologies outside of an RCT environment. Our findings mirror what has been reported in previous trials, particularly the ADAPT study, over a similar 5.1-month median follow-up period[4, 371]. Our data provide additional supportive evidence that benefits associated with HCL accrue in the real-world, not just in a research setting. Only 7% of individuals were from a non-white ethnic background limiting the generalizability of the findings.

There are few other specific limitations. The time in range data compared the data from isCGM (FreeStyle Libre) at baseline to real-time CGM (varied depending on the system used) at follow-up, and accuracy and data capture may differ between these devices. The short 6-month follow-up period is comparable to other studies in the field of HCL, and longer-term follow-up for outcomes of interest are awaited.

It should be noted that whilst the sites selected for inclusion were those with the greatest numbers of pump users and therefore experience in diabetes technology, many participants were initiated on HCL systems rapidly and during a period when face-to-face visits were less routine as services recovered from the COVID-19 pandemic. Other than initial support in commencing the technology, centres managed this cohort of HCL via usual pathways. The expertise of the teams may have contributed to the results in part, and it will be vital to ensure healthcare professionals from smaller services are supported in promoting, on-boarding, and managing HCL systems in the future. A comprehensive best-practice and service delivery guide has already been developed from our experiences in the pilot to support teams in the further roll-out of HCL[346].

This work has informed the National Institute of Health and Care Excellence (NICE) technology appraisal of hybrid-closed loop technology. Ongoing surveillance to understand longer-term glycaemic outcomes in this cohort remains of interest.

Conclusion

Among adults with type 1 diabetes treated with insulin pump therapy and intermittently scanned continuous glucose monitoring with a high HbA1c, commencement of HCL was associated with reductions in HbA1c levels, improved CGM derived glucose outcomes, reduced diabetes related distress and improved quality of life. These findings mirror those reported in existing randomized control trial data, provide evidence that

those findings translate into a less resourced real-world setting and support wider access to HCL therapy in people living with type 1 diabetes.

Research in context

Although the remainder of my thesis focuses on HbA1c targets and selecting therapies for individuals with type 2 diabetes, this study is an example of the impact that real-world observational studies can have. The work here is a product of experience from the other studies in terms of data processing, handling and analysis from the larger observational studies in this thesis. The data generated by this study have already led to changes in national policy and widened provision of HCL in the UK, with the recent publication of NICE technology appraisal 943[374]. They are also an excellent example of how results in the real-world may differ significantly from randomised control trial data due to populations being different but can complement the results and inform policy decisions and clinicians.

Chapter 8 – Discussion and conclusions

The introduction gives a broad overview of type 2 diabetes, it's prevalence and the costs of managing this condition and its complications both to the NHS and more globally. It also highlights that the burden of diabetes is predicted to increase according to the World Health organisation[3] – this is not a problem that is going to go away anytime soon. Treatment targets in diabetes are derived from randomised control trial evidence, but often from trials performed well over a decade ago and with mixed conclusions as shown in **table 3.**

Current guidelines recommend HbA1c targets, generally, of ≤48mmol/L or ≤53mmol/L where the hypoglycaemia risks from treatment are significant[59, 68]. As repeatedly noted, these guidelines also suggest the adjustment of treatment targets taking a broad view of patient characteristics, overall health and the presence of other medical conditions, to advise collaborative goal setting. In clinical practice, it is clear that agreeing goals with individuals with diabetes is key to both effective consultations and improving clinical outcomes. Chapter 1 also highlights the heterogeneity of presentations within type 2 diabetes, which is ultimately a spectrum of disease, as highlighted by the likes of Ahlqvist et al. and McCarthy et al.[21, 139], ranging from mild age-related hyperglycaemia to young onset severe insulin resistance. The development of type 2 diabetes depends on both genetic risk factors and environmental factors which may be modifiable, delineating subgroups of individuals with different diabetes phenotypes may be key in future to

selecting the most appropriate treatments and targets, but genetic and biochemical testing to do this may be prohibited by cost. In the meantime, clinicians must rely on clinical acumen and the evidence and guidelines available to support the selection of the more appropriate targets and the treatments which are likely to be most effective. That being said, there are areas where the evidence is less clear or where evidence is lacking altogether – the optimisation of HbA1c levels to reduce the risk of all-cause mortality, reduce the risk macrovascular complications and optimise management in individuals with frailty.

This overview raises the question – what is the optimal HbA1c target for a given individuals and what factors should clinicians be aware of that may mediate this? The initial idea was to create a near patient risk calculator that could inform discussions between healthcare professional and the person with diabetes. In the past, large-randomised control trials were perhaps the most effective means to collect data to support optimal HbA1c targets. In the current era however, access to large electronic healthcare databases provides a means to perform large observational studies and generate further evidence at a lower cost. This is especially pragmatic in the context of diabetes where new treatments are constantly emerging – SGLT2i and GLP1 agonist drugs being good examples. There are established robust methodologies to undertake these studies which have been followed to establish the association between HbA1c and outcomes in two studies. Observational research isn't without its complexity. It relies on accurate coding by patient-facing clinicians, careful identification of the correct codes by researchers, and

implementation of methods to address some of the concerns often raised from the use of observational data – such as the impact of missing data. Whilst the initial aim of the work was to produce a predictive model, issues arose that were not foreseen when writing the protocol that limited how realistic it would be to undertake this – research after all is a journey and as much can be learnt in failure as in success. The methods chapter additionally suggests ways in which this could be changed in future, perhaps with newer methodologies such as machine learning although whether this would be desired by clinicians remains unanswered. Equally, the exploratory approach undertaken still provides some key insights which may support clinicians in their decision making.

The HbA1c individualisation study demonstrates that optimum HbA1c levels to prevent macrovascular complications and reduce all-cause mortality may not be ≤48mmol/mol [≤6.5%] as suggested by current guidelines. Moreover, there may in fact be an increase in risk of adverse outcomes from over-treatment and there is an argument to increase the emphasis placed on de-escalation of treatment. This "U-shaped" association has been observed repeatedly in the past, particularly amongst insulin users and within other observational studies and there are also signals from randomised control trials, such as ACCORD, that this may be the case[74, 83, 84]. Furthermore, the HbA1c individualisation study suggests that insulin and sulphonylurea use may increase the risk of outcomes at all levels and, in users of these medications, the associations between HbA1c and key outcomes becomes less clear. In the modern era of newer drugs, such as

Semaglutide explored in chapter 6, a move away from a glucocentric approach towards selection of appropriate medications to reduce overall risk may be most appropriate. Stopping insulin and sulphonylurea medications and switching to newer drugs may therefore be doubly beneficial.

Additionally, appropriate de-escalation of treatment may in turn reduce the cost of complications as well as the cost of therapies and have a positive health economic benefit. We should also be mindful that, for individuals treated with medications with significant risk of hypoglycaemia, the risks often increase irrespective of the glucose levels achieved. These risks may be further modified by the presence or absence of cardiovascular disease at baseline or patient age at diagnosis – all things that could be considered by a clinician when agreeing a treatment target in clinic.

Frailty is a particular concern, and one where evidence is currently lacking. Current guidelines suggest that treatment targets should be modified, and even suggest an algorithmic approach to the stepwise de-escalation of therapies[102, 104]. However, these are derived from consensus and a limited evidence base. I assessed the existing evidence in the systematic review and meta-analysis in chapter 4 searched across a wide range of study designs in individuals in older age groups due to the anticipated paucity of studies and meta-analysis was only possible for some of the outcomes. This suggested significant risks of intensive glycaemic control in increasing the risk of hypoglycaemia. There is a lack

of research attention at present directed towards HbA1c and outcomes that are more relevant in individuals with frailty such as falls, fractures and cognitive decline. None of the studies identified included recognised definitions of frailty which is especially important because frailty whilst associated with age is independent of it, and in individuals with diabetes frailty may occur earlier in life[98, 274, 316]. This work has been published and has already had significant impact being cited by the 2022 update to the ADA/EASD consensus guidelines on the management of hyperglycaemia[59, 272].

Having identified a gap in evidence in chapter 4, the electronic frailty index study in chapter 5 has significant novelty is the first of its kind to assess the associations between HbA1c and outcomes using a recognised and validated definition of frailty, rather than using age as a proxy[98]. The aims were two-fold, firstly to validate he use of EFI within diabetes models for observation research. It demonstrates improvements in AIC and calibration statistics by adding EFI to selected models. This has significant implications for observational research in diabetes moving forwards and will allow researchers to increase their ability to appropriately identify and study frailty. Secondly, the associations between HbA1c and key outcomes across the spectrum of frailty were explored. "U-shaped" associations were noted in this older population, with increased risks of mortality, admission to hospital, falls and fractures and cognitive decline at HbA1c levels below a certain threshold. For most outcomes this was 48-57.9mmol/mol [6.5-7.4%], but for the risk of hospital admission the optimal HbA1c was notably much higher –

in the 70-80.9mmol/mol [8.5-9.4%] age group. Following the application of EFI scores it was clear that individuals with higher frailty scores were at higher risk of adverse outcomes across all HbA1c levels. In some circumstances, such as for risk of hospital admission, the optimum HbA1c level increased from 58-69.9mmol/mol [7.5-8.4%] in "fit" individuals to 70-80.9mmol/mol [8.5-9.4%] in those with moderate or severe frailty. Additionally, the increase in risk from lower HbA1c levels was often more marked. This work has clear clinical implications and may help inform future guidelines around HbA1c targets in individuals with diabetes and frailty. This work has been submitted and is currently awaiting peer review.

The studies above demonstrate the impact that observational studies and real-world data can have when derived from large datasets. There are also benefits to smaller studies and within NHS governance clinical audit is a recognised means of data capture which can accrue data for analysis. This data can be used to establish whether outcomes within often narrow clinical trial populations can be generalised to a broader, often more poorly resourced, clinical environment. Whilst observational studies should never be used to draw conclusions on efficacy, they can often complement the findings of randomised control trials and allow us to see how research moves into the real-world. The studies shared in chapter 6 and 7 are examples of the studies conducted in my role as an Association of British Clinical Diabetologists' research fellow.

The study in chapter 6 fits well with theme of this thesis due to its focus on exploring which individuals may benefit the most from semaglutide, a GLP1 agonist drug. This is even more relevant in the context of supply issues and can provide valuable information for clinicians who may have to prioritise access to these medications as supply returns[341]. Whilst selecting appropriate targets is important, targeting and therapies and using them where the benefit is likely to be greatest is another example of precision medicine approaches in action. This small study contained a population more representative of a UK clinic population, notably with higher baseline HbA1c and higher weight at baseline compared to randomised control trials[333], and identified individuals with higher baseline HbA1c and BMI at baseline as standing to benefit the most from treatment. It also identified additional benefits from switching from alternative GLP1 agonist drugs which are perhaps less potent to semaglutide in a real-world setting. This work has been peer reviewed and published in the British Journal of Diabetes[322].

Finally, the work shared in chapter 7 on hybrid closed-loop therapy in individuals with type 1 diabetes is shared and is a good example of the high impact observational studies can have (even with small numbers) and how they can complement randomised control trial data to inform diabetes management guidelines and national policy. This demonstrated significant reductions in HbA1c, improvements in time in range and improvements in quality of life with HCL. This work has fed directly into the recent NICE technology appraisal which has broadened criteria for access to this new technology and will revolutionise management of

diabetes for a generation of individuals living with type 1 diabetes[374]. There remain unanswered questions about the longevity of these changes and further follow-up is planned in due course.

Future research

Observational studies are a powerful source of relevant information for clinicians and my studies open the possibilities of further work.

Firstly, having identified that optimal HbA1c targets may differ in different populations, it would be relevant to expand this further to look at the impact on microvascular complications or in other subgroups of interest such as those with pre-existing CKD or on dialysis.

Using more recently established methodologies, such as machine learning, it may be possible to develop a near patient risk calculator that will be able to inform clinicians in their discussion with people with diabetes when setting targets.

The work around the EFI score opens the possibility of multiple future studies on frailty. The impact of newer drugs in this cohort is relevant, as concerns do exist around the risk of adverse events or unintended side-effects such as ketoacidosis in the case of SGLT2i or weight loss in the case of GLP1. Both of which may have significant implications in a cohort with frailty. Additionally, type 1 diabetes and frailty remain poorly explored and unresearched and work needs to be done in this area where management with insulin is necessary and often complex.

Finally, the work of the ABCD audit programmes will continue to provide new real-world insights on the use of new technologies and therapeutics and are always of interest to clinicians. Work on dual-agonists (Tirzepatide) is anticipated and the HCL audit continues to capture long-term data from the NHSE pilot scheme cohort and will broaden its scope to include individuals commencing HCL as part of the wider national roll-out.

Hybrid closed-loop therapy continues to improve the treatment possibilities for people with type 1 diabetes and exploring this novel technology in subgroups of interest including those on dialysis, with gastroparesis or other established complications to see if the outcomes differ from those included in current work. Real research effort is needed is also needed to understand the impact of this technology in older age groups and establish if and when appropriate de-escalation of technology may be needed with advancing age or towards the end of life.

To conclude, there are many types of diabetes, but this oversimplifies the condition. Even within these types, there is significant heterogeneity and type 2 diabetes is perhaps best considered a cluster or conditions with an underlying pathophysiology of insulin resistance. At all times, it is important that we tailor our treatments and the targets to the individuals in front of us living with the condition. It is up to clinicians to draw from all available evidence and, where evidence is lacking, for researchers to find ways of filling these gaps. There is utility in observational studies to achieve this, or to complement randomised control evidence in the

context of new therapies. Ultimately, everything we do, either as a clinician or as a researcher in diabetes must be with the same goal – to improve the lives of people with diabetes.

Appendices

Appendix 1. Baseline characteristics in individuals with <1yr vs ≥1 year follow-up in the HbA1c individualisation study (see next page)

Baseline Characteristics

		>1yr data	<1yr data	All
Years of data	Mean (SD)	5.4 (2.9)	0.5 (0.3)	4.7 (3.2)
Age (Years)	Mean (SD)	62.7 (14.0)	67.1 (15.8)	63.3 (14.3)
Charlson Comorbidity Score	Mean (SD)	2.1 (1.5)	2.6 (1.9)	2.2 (1.6)
Weight (kg)	Mean (SD)	92.3 (21.3)	87.5 (22.2)	91.7 (21.5)
Height (m)	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
BMI (kg/m^2)	Mean (SD)	32.5 (6.7)	30.9 (7.0)	32.3 (6.8)
Systolic BP (mm/Hg)	Mean (SD)	137.0 (16.5)	135.1 (17.5)	136.8 (16.7)
Diastolic BP (mm/Hg)	Mean (SD)	79.5 (10.4)	77.5 (11.0)	79.2 (10.5)
Total Cholesterol (mmol/L)	Mean (SD)	5.0 (1.2)	4.8 (1.3)	4.9 (1.2)
HDL Cholesterol (mmol/L)	Mean (SD)	1.2 (0.5)	1.3 (0.4)	1.2 (0.5)
LDL Cholesterol (mmol/L)	Mean (SD)	2.9 (1.1)	2.8 (1.1)	2.8 (1.1)
HBA1c (mmol/mol)	Mean (SD)	61.1 (20.1)	58.9 (19.8)	60.8 (20.1)
eGFR (mL/min/1.73m^2)	Mean (SD)	78554 (45.4)	11465 (46.8)	90019 (45.6)
Gender				
Female	n (%)	94315 (54.6)	13039 (53.2)	107354 (54.4)
Male	n (%)	54356 (31.4)	5020 (20.5)	59376 (30.1)
Ethnicity				
Unknown	n (%)	54356 (31.4)	5020 (20.5)	59376 (30.1)
Bangladeshi	n (%)	446 (0.3)	73 (0.3)	519 (0.3)
Black African	n (%)	731 (0.4)	160 (0.7)	891 (0.5)
Black Caribbean	n (%)	949 (0.5)	157 (0.6)	1106 (0.6)
Chinese	n (%)	321 (0.2)	56 (0.2)	377 (0.2)
Indian	n (%)	2327 (1.3)	430 (1.8)	2757 (1.4)
Other	n (%)	1604 (0.9)	289 (1.2)	1893 (1.0)
Asia Other	n (%)	1143 (0.7)	204 (0.8)	1347 (0.7)
Pakistani	n (%)	1364 (0.8)	227 (0.9)	1591 (0.8)
White European	n (%)	109628 (63.4)	17888 (73.0)	127516 (64.6)
Age Group				
18-35	n (%)	6709 (3.9)	982 (4.0)	7691 (3.9)
36-50	n (%)	25761 (14.9)	2775 (11.3)	28536 (14.5)
51-65	n (%)	62909 (36.4)	6527 (26.6)	69436 (35.2)
66-80	n (%)	61405 (35.5)	8794 (35.9)	70199 (35.6)
81-99	n (%)	16062 (9.3)	5384 (22.0)	21446 (10.9)
100-114	n (%)	23 (0.0)	42 (0.2)	65 (0.0)
Alcohol Intake				
None	n (%)	33881 (19.6)	5258 (21.5)	39139 (19.8)
Trivial	n (%)	36891 (21.3)	5055 (20.6)	41946 (21.3)
Light	n (%)	16260 (9.4)	2165 (8.8)	18425 (9.3)
Moderate	n (%)	13032 (7.5)	1144 (4.7)	14176 (7.2)
Heavy	n (%)	4345 (2.5)	522 (2.1)	4867 (2.5)
Very Heavy	n (%)	2691 (1.6)	344 (1.4)	3035 (1.5)
Previous	n (%)	5443 (3.1)	1091 (4.5)	6534 (3.3)
Smoking History				
Never	n (%)	75209 (43.5)	10116 (41.3)	85325 (43.2)
Ex-Smoker	n (%)	59608 (34.5)	8681 (35.4)	68289 (34.6)
Current smoker (light)	n (%)	12761 (7.4)	1872 (7.6)	14633 (7.4)
Current smoker (moderate)	n (%)	7459 (4.3)	1065 (4.3)	8524 (4.3)
Current smoker (heavy)	n (%)	6519 (3.8)	841 (3.4)	7360 (3.7)
Co-morbidities and family history				
Atrial Fibrillation	n (%)	10765 (6.2)	2432 (9.9)	13197 (6.7)
Congestive Cardiac Failure	n (%)	5713 (3.3)	1457 (5.9)	7170 (3.6)
Cardiovascular Disease	n (%)	33747 (19.5)	5841 (23.8)	39588 (20.1)
Family History: Heart Disease	n (%)	14278 (8.3)	1696 (6.9)	15974 (8.1)
Hypertension	n (%)	90297 (52.2)	12917 (52.7)	103214 (52.3)
Rheumatoid Arthritis	n (%)	2664 (1.5)	508 (2.1)	3172 (1.6)
Systemic Lupus Erythematosus	n (%)	156 (0.1)	25 (0.1)	181 (0.1)
Serious Mental Health	n (%)	1568 (0.9)	234 (1.0)	1802 (0.9)
Erectile dysfunction	n (%)	15358 (8.9)	2280 (9.3)	17638 (8.9)
Chronic Kidney Disease				
No CKD	n (%)	1237 (0.7)	516 (2.1)	1753 (0.9)
Stage 3	n (%)	242 (0.1)	83 (0.3)	325 (0.2)
Stage 4	n (%)	163963 (94.8)	22844 (93.2)	186807 (94.6)
Stage 5	n (%)	7944 (4.6)	1416 (5.8)	9360 (4.7)
Allbuminuria				
Normoalbuminuria	n (%)	163963 (94.8)	22844 (93.2)	186807 (94.6)
Microalbuminuria	n (%)	7944 (4.6)	1416 (5.8)	9360 (4.7)
Macroalbuminuria	n (%)	962 (0.6)	244 (1.0)	1206 (0.6)
Non-diabetes medication in last year				
Antipsychotics	n (%)	3248 (1.9)	545 (2.2)	3793 (1.9)
Lipid lowering drugs	n (%)	89854 (52.0)	12365 (50.5)	102219 (51.8)
Steroids	n (%)	69031 (39.9)	10302 (42.0)	79333 (40.2)
Antihypertensives	n (%)	111414 (64.4)	16531 (67.5)	127945 (64.8)

Appendix 2. List of covariates assessed for inclusion within the model for each outcome

Category	**Covariate**	
Clinical diagnoses	Rheumatoid arthritis Atrial fibrillation Cerebrovascular disease/Stroke Chronic kidney disease (stage) Heart failure Hypertension	Ischaemic heart disease Peripheral arterial disease Parkinsonism, Tremor Severe mental health problems Systemic lupus erythematous Family history of heart disease HIV/AIDS
Patient characteristics (categorical)	Ethnicity Gender HbA1c group	Alcohol consumption Smoking status
Patient characteristics (continuous)	Age at diagnosis, years Body mass index, kg/m^2 Albumin creatinine ratio, mcg/mg Blood pressure, mmHg eGFR*, ml/min/1.73 m2	High density lipoprotein, mmol/L Low density lipoprotein, mmol/L Total cholesterol, mmol/L Triglycerides, mmol/L
Medications	Insulin Metformin Dipeptidyl peptidase-4 inhibitor (DPP4i) Suphonylurea Thiazolinediones	Lipid lowering drugs Antihypertensives GLP1** receptor agonists SGLT2# inhibitors

**Estimated glomerular filtration rate; derived from serum creatinine and weight using Cockcroft-Gault equation*

***Glucagon like peptide-1 receptor agonist*

#Sodium-glucose link transporter

Appendix 3a-e. Cox models developed for the HbA1c individualisation study: a) mortality, b) cardiovascular composite outcomes, c) myocardial infarction, d) heart failure and e) stroke

Appendix 3a.

Predictor		Mortality model	
		HR	P-Value
Age (years)	FP1	0.00 (0.00 to 0.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001
High density lipopotein (mmol/L)	FP1	1.29 (1.22 to 1.36)	<0.001
	FP2	1.11 (1.08 to 1.14)	<0.001
Low density lipoprotein (mmol/L)	FP1	1.06 (0.93 to 1.21)	0.4
	FP2	1.00 (0.95 to 1.05)	0.9
Total cholesterol (mmol/L)	FP1	0.03 (0.01 to 0.06)	<0.001
	FP2	1.95 (1.56 to 2.44)	<0.001
Systolic blood pressure (mmHg)	FP1	0.64 (0.61 to 0.67)	<0.001
	FP2	1.08 (1.07 to 1.09)	<0.001
Gender	Female	Reference	
	Male	1.00 (0.96 to 1.04)	0.9
Alcohol	No alcohol	Reference	
	Ex-user	1.07 (1.00 to 1.15)	0.05
	Trivial use	0.97 (0.92 to 1.03)	0.4
	Light use	0.97 (0.90 to 1.06)	0.5
	Moderate use	1.00 (0.91 to 1.10)	1
	Heavy use	1.11 (0.98 to 1.27)	0.1
	Very heavy use	1.04 (0.84 to 1.29)	0.7
Smoking	Never smoked	Reference	
	Ex-smoker	1.33 (1.27 to 1.40)	<0.001
	Light smoker	1.73 (1.63 to 1.85)	<0.001
	Moderate smoker	1.78 (1.64 to 1.93)	<0.001
	Heavy smoker	1.98 (1.80 to 2.17)	<0.001
Urinary Albumin (stage)	Normoalbuminuria	Reference	
	Microalbuminuria	1.39 (1.34 to 1.44)	<0.001
	Macroalbuminuria	2.01 (1.86 to 2.17)	<0.001
Chronic kidney disease (stage)	Stage 1-2	Reference	
	Stage 3a	0.46 (0.39 to 0.53)	<0.001
	Stage 3b	0.69 (0.59 to 0.80)	<0.001
	Stage 4+	2.74 (2.36 to 3.19)	<0.001
Metformin		0.83 (0.81 to 0.86)	<0.001
Sulphonylureas		1.14 (1.09 to 1.19)	<0.001
Thiazolinediones		1.05 (0.94 to 1.18)	0.3
Lipid lowering therapy		0.50 (0.48 to 0.53)	<0.001
Antihyprtensives		1.10 (1.04 to 1.16)	0.001
Antipsychotics		2.27 (2.08 to 2.48)	<0.001
Steroids		1.49 (1.44 to 1.54)	<0.001
Erectile dysfunction		0.85 (0.82 to 0.89)	<0.001
Hypertension		1.06 (1.02 to 1.10)	0.002
Migraine		0.88 (0.83 to 0.94)	<0.001
Atrial Fibrillation		1.26 (1.21 to 1.31)	<0.001
Heart Failure		1.46 (1.40 to 1.53)	<0.001
Rheumatoid Artritis/Lupus		1.30 (1.20 to 1.41)	<0.001
HbA1c group (mmol/mol)	<48	1.14 (1.08 to 1.20)	<0.001
	48-57.9	Reference	
	58-69.9	1.17 (1.11 to 1.23)	<0.001
	70-80.9	1.29 (1.19 to 1.40)	<0.001
	>81	1.39 (1.28 to 1.51)	<0.001
Model Statistics			
Akaike's Information Criteria		398,114.4	
Harrell's C Statistic		0.824	
Royston's D Statistic		0.495	

Predictor		Macrovascular model	
		HR	P-Value
Age (years)	FP1	0.00 (0.00 to 0.00)	<0.001
	FP2	1.02 (1.02 to 1.03)	<0.001
Body mass index (kg/m2)	Untransformed	1.00 (1.00 to 1.00)	0.7
High density lipopotein (mmol/L)	FP1	0.81 (0.74 to 0.89)	<0.001
	FP2	1.11 (1.00 to 1.23)	0.06
Low density lipoprotein (mmol/L)	FP1	1.32 (1.03 to 1.70)	0.03
	FP2	1.00 (0.99 to 1.00)	0.2
Total cholesterol (mmol/L)	FP1	0.37 (0.14 to 0.97)	0.04
	FP2	1.32 (1.07 to 1.63)	0.009
Systolic blood pressure (mmHg)	FP1	0.00 (0.00 to 0.00)	<0.001
	FP2	4.93 (3.43 to 7.08)	<0.001
Diastolic blood pressure (mmHg)	FP1	0.81 (0.75 to 0.86)	<0.001
	FP2	1.04 (1.03 to 1.06)	<0.001
Gender	Female	Reference	
	Male	1.21 (1.17 to 1.25)	<0.001
Smoking	Never smoked	Reference	
	Ex-smoker	1.11 (1.07 to 1.16)	<0.001
	Light smoker	1.28 (1.20 to 1.36)	<0.001
	Moderate smoker	1.31 (1.22 to 1.41)	<0.001
	Heavy smoker	1.44 (1.35 to 1.55)	<0.001
Urinary Albumin (stage)	Normoalbuminuria	Reference	
	Microalbuminuria	1.15 (1.11 to 1.19)	<0.001
	Macroalbuminuria	1.54 (1.44 to 1.65)	<0.001
Chronic kidney disease (stage)	Stage 1-2	Reference	
	Stage 3a	1.12 (1.09 to 1.16)	<0.001
	Stage 3b	1.27 (1.16 to 1.40)	<0.001
	Stage 4+	1.51 (1.22 to 1.86)	<0.001
Diabetes therapy	Diet only	Reference	
	Medications	0.99 (0.96 to 1.03)	0.7
	Insulin	1.32 (1.19 to 1.45)	<0.001
SGLT2 inhibitors		0.83 (0.75 to 0.92)	<0.001
Sulphonylureas		1.11 (1.06 to 1.15)	<0.001
Steroids		1.22 (1.19 to 1.26)	<0.001
Antihyprtensives		1.35 (1.29 to 1.40)	<0.001
Erectile dysfunction		1.09 (1.05 to 1.13)	<0.001
Atrial Fibrillation		1.51 (1.46 to 1.57)	<0.001
Heart Failure		1.78 (1.67 to 1.89)	<0.001
Family history of heart disease		1.10 (1.05 to 1.16)	<0.001
HbA1c group (mmol/mol)	<48	1.01 (0.97 to 1.06)	0.5
	48-57.9	Reference	
	58-69.9	1.07 (1.01 to 1.13)	0.01
	70-80.9	1.12 (1.04 to 1.22)	0.004
	>81	1.13 (1.03 to 1.25)	0.009

Appendix 3b.

Model Statistics	
Akaike's Information Criteria	501,366.2
Harrell's C Statistic	0.739
Royston's D Statistic	0.200

Appendix 3c.

Predictor		Myocardial infarction model	
		HR	P-Value
Age (years)	FP1	0.00 (0.00 to 0.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001
Body mass index (kg/m2)	Untransformed	0.99 (0.99 to 1.00)	0.2
Total cholesterol (mmol/L)	FP1	0.15 (0.02 to 1.26)	0.08
	FP2	7.49 (1.01 to 55.43)	0.05
Low density lipoprotein (mmol/L)	FP1	1.21 (0.39 to 3.79)	0.7
	FP2	1.03 (0.70 to 1.51)	0.9
Gender	Female	Reference	
	Male	1.68 (1.58 to 1.79)	<0.001
Insulin		1.16 (0.96 to 1.39)	0.1
Lipid lowering drugs		0.43 (0.39 to 0.47)	<0.001
HbA1c group (mmol/mol)	<48	0.84 (0.78 to 0.91)	<0.001
	48-57.9	Reference	
	58-69.9	1.19 (1.09 to 1.30)	<0.001
	70-80.9	1.26 (1.09 to 1.44)	0.001
	>81	1.59 (1.40 to 1.81)	<0.001
Model Statistics			
Akaike's Information Criteria		92,676.3	
Harrell's C Statistic		0.702	
Royston's D Statistic		0.232	

Appendix 3d.

Predictor		Heart failure model	
		HR	P-Value
Age (years)	FP1	1.00 (1.00 to 1.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001
Body mass index (kg/m2)	Untransformed	1.03 (1.03 to 1.04)	<0.001
Low density lipoprotein (mmol/L)	FP1	0.84 (0.76 to 0.93)	0.001
	FP2	0.93 (0.89 to 0.98)	0.003
Systolic blood pressure (mmHg)	FP1	0.10 (0.06 to 0.19)	<0.001
	FP2	1.10 (1.07 to 1.13)	<0.001
Gender	Female	Reference	
	Male	2.08 (1.88 to 2.30)	<0.001
GLP1 receptor agonist		1.22 (0.88 to 1.70)	0.2
Insulin		1.32 (1.07 to 1.63)	0.01
Atrial Fibrillation		1.29 (1.17 to 1.42)	<0.001
HbA1c group (mmol/mol)	<48	1.08 (1.02 to 1.14)	0.01
	48-57.9	Reference	
	58-69.9	1.03 (0.96 to 1.10)	0.4
	70-80.9	1.07 (0.98 to 1.17)	0.1
	>81	1.28 (1.13 to 1.44)	<0.001

Model Statistics	
Akaike's Information Criteria	1,031,917.6
Harrell's C Statistic	0.820
Royston's D Statistic	0.486

Appendix 3e.

Predictor		Cerebrovascular event model	
		HR	P-Value
Age (years)	FP1	1.00 (1.00 to 1.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001
Body mass index (kg/m2)	Untransformed	0.99 (0.99 to 1.00)	0.07
Low density lipoprotein (mmol/L)	FP1	1.18 (1.08 to 1.28)	<0.001
	FP2	0.99 (0.99 to 1.00)	0.3
Gender	Female	Reference	
	Male	1.05 (0.99 to 1.11)	0.09
Smoking	Never smoked	Reference	
	Ex-smoker	1.09 (1.01 to 1.18)	0.02
	Light smoker	1.36 (1.18 to 1.56)	<0.001
	Moderate smoker	1.39 (1.18 to 1.64)	<0.001
	Heavy smoker	1.61 (1.37 to 1.89)	<0.001
Insulin		1.21 (1.03 to 1.41)	0.02
Sulphonylureas		1.07 (0.99 to 1.15)	0.1
Atrial Fibrillation		1.47 (1.36 to 1.58)	<0.001
HbA1c group (mmol/mol)	<48	0.97 (0.90 to 1.05)	0.4
	48-57.9	Reference	
	58-69.9	1.19 (1.09 to 1.31)	<0.001
	70-80.9	1.46 (1.30 to 1.63)	<0.001
	>81	1.45 (1.27 to 1.65)	<0.001
Model Statistics			
Akaike's Information Criteria		119,903.6	
Harrell's C Statistic		0.736	
Royston's D Statistic		0.261	

Appendix 4. Adapted Cochrane data extraction form used for systematic review and meta-analysis (next two pages)

Data Extraction Form		
Review Title/ID		
Study ID		
Report ID		
Report ID (inc errata)		
Notes		
General information		
Date form completed		
Person ID/name		
Citation		
Study author contact		
Publication Type		
Study Eligibility		
RCT?		
Intervention?		(treatment to A1c<7% or FPG)
Comparator?		(standard with(out) target, >7%)
Outcomes?		(one or more of interest as per protocol)
INCLUDE		
Methods		
Aim of study		
Design		
Unit of allocation		
Start date		
End date		
Duration of participation		
Eththics?		
Participants		
Population		
Setting		
Inclusion criteria		
Exclusion criteria		
Method of recruitment		
Consent?		
Number randomised		
Clusters		
Baseline imbalances		
Withdraws and exclusion		
Age		
Sex		
Race		
Co-mobiridty		
Sociodemo		
Subgroups measured?		
Subgroups reported?		
Group (intervention)		
Intervention randomised		
HbA1c target		
Treatments		
HbA1c achieved/compliance		
Co-interventions		
Group (comparator)		
Comparator randomised		
HbA1c target		
Treatments		
HbA1c achieved/compliance		
Co-interventions		

Outcomes	Intervention	Comparator
Non-fatal MI		
Non-fatal stroke		
CV Death		
LL Amp		
Charcot		
Painful neuro		
Photocoag		
Vis progress		
Vis loss		
2 x Cr		
ESRF		
Proteinuria		
Renal death		
Mortality		
Hospital		
Hypo		
QoL?		

Bias	Hi	Unclear
Random seq?		
Allocation concealment?		
Blinding part and pers		
Blinding of outcome assessment		
Incomplete outcome data?		
Selective outcome reporting?		
Other Biase		

Appendix 5. Covariates assessed for inclusion within models for the electronic frailty index study

Category	Covariate	
Electronic Frailty Score Criteria	Activity limitation Arthritis Atrial fibrillation Cerebrovascular disease Chronic kidney disease Diabetes Dizziness Dyspnoea Falls Foot problems Fragility fracture Haematinics & Anaemia Hearing impairment Heart failure Heart valve disease Housebound Hypertension Hypotension/Syncope	Ischaemic heart disease Memory and cognitive Mobility and transfer Osteoporosis Peripheral arterial disease Parkinsonism, Tremor Peptic ulcer Polypharmacy* Requirement for care Respiratory disease Sleep disturbance Social vulnerability Thyroid disease Urinary Incontinence Urinary system disease Visual impairment Weight loss, anorexia
Patient characteristics (categorical)	Ethnicity Gender eFI score/category	Alcohol consumption Smoking status HbA1c group
Patient characteristics (continuous)	Age, years Body mass index, kg/m^2 Diabetes duration, years Albumin, mcg/L Albumin creatinine ration, mcg/mg Blood pressure, mmHg eGFR**, ml/min/1.73 m2	High density lipoprotein, mmol/L Low density lipoprotein, mmol/L Total cholesterol, mmol/L Triglycerides, mmol/L
Other medical conditions (categorical)	Ischaemic heart disease Non-alcoholic fatty liver disease	Peripheral Arterial Disease Severe mental health problems
Medications	Insulin Metformin Dipeptidyl peptidase-4 inhibitor (DPP4i) Suphonylurea Thiazolinediones	Lipid lowering drugs Antihypertensives GLP1** receptor agonists SGLT2# inhibitors

**Defined as ≥4 different medication classes in the 6-months prior to study entry*

***estimated glomerular filtration rate; derived from serum creatinine and weight using Cockcroft-Gault equation*

Appendices 6a-d. Hazard ratios within each HbA1c group in each eFI category compared to reference ("fit" eFI category; HbA1c 48-57.9mmol/mol [6.5-7.5%]) for a) all-cause mortality, b) risk of hospital admission, c) cognitive decline and d) falls and fractures

Appendix 6a.

Predictor		Mortality Model			
		Without eFI		With eFI added	
		HR	P-Value	HR	P-Value
Age	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Gender	Female	Reference		Reference	
	Male	1.12 (1.08 to 1.16)	<0.001	1.18 (1.13 to 1.22)	<0.001
HbA1c levels (mmol/mol)	<48	1.22 (1.17 to 1.27)	<0.001	1.20 (1.16 to 1.25)	<0.001
	48-57.9	Reference		Reference	
	58.69.9	1.13 (1.07 to 1.20)	<0.001	1.14 (1.07 to 1.20)	<0.001
	70-80.9	1.24 (1.15 to 1.35)	<0.001	1.25 (1.16 to 1.35)	<0.001
	≥81	1.37 (1.27 to 1.46)	<0.001	1.38 (1.28 to 1.48)	<0.001
Ethnicity	White	Reference		Reference	
	Asian	0.78 (0.69 to 0.88)	<0.001	0.76 (0.67 to 0.86)	<0.001
	Black	0.56 (0.45 to 0.70)	<0.001	0.55 (0.45 to 0.69)	<0.001
	Other	0.67 (0.54 to 0.84)	<0.001	0.67 (0.54 to 0.84)	<0.001
Alcohol use	No alcohol	Reference		Reference	
	Ex-user	0.98 (0.91 to 1.04)	0.5	0.96 (0.90 to 1.02)	0.2
	Light user	0.96 (0.90 to 1.01)	0.1	0.97 (0.92 to 1.03)	0.4
	Moderate user	1.18 (1.09 to 1.28)	<0.001	1.23 (1.13 to 1.33)	<0.001
	Trivial alcohol user	0.87 (0.83 to 0.91)	<0.001	0.88 (0.84 to 0.92)	<0.001
	Heavy user	1.32 (1.19 to 1.48)	<0.001	1.35 (1.21 to 1.51)	<0.001
	Very heavy user	1.40 (1.20 to 1.63)	<0.001	1.39 (1.19 to 1.63)	<0.001
Smoking	Never smoked	Reference		Reference	
	Ex-smoker	1.24 (1.19 to 1.29)	<0.001	1.22 (1.18 to 1.27)	<0.001
	Light smoker	1.99 (1.86 to 2.12)	<0.001	1.97 (1.85 to 2.11)	<0.001
	Moderate smoker	2.04 (1.86 to 2.24)	<0.001	2.01 (1.84 to 2.21)	<0.001
	Heavy smoker	2.14 (1.92 to 2.39)	<0.001	2.09 (1.87 to 2.33)	<0.001
Urinary Albumin (stage)	Normoalbuminuria	Reference		Reference	
	Microalbuminuria	0.87 (0.80 to 0.95)	0.001	0.87 (0.81 to 0.95)	<0.001
	Macroalbuminuria	0.78 (0.64 to 0.95)	0.01	0.79 (0.65 to 0.96)	0.02
Chronic Kidney Disease (Stage)	No CKD/CKD1-2	Reference		Reference	
	CKD3a	0.91 (0.86 to 0.97)	0.002	0.90 (0.85 to 0.95)	<0.001
	CKD3b	0.96 (0.88 to 1.04)	0.3	0.95 (0.87 to 1.03)	0.2
	CKD4	1.01 (0.89 to 1.15)	0.9	1.01 (0.89 to 1.14)	0.9
	CKD5	1.56 (1.27 to 1.91)	<0.001	1.54 (1.26 to 1.88)	<0.001
Diabetes duration (years)	FP1	0.95 (0.90 to 1.00)	0.04	0.95 (0.91 to 1.00)	0.05
	FP2	1.03 (1.02 to 1.05)	<0.001	1.03 (1.01 to 1.04)	0.003
Diabetes management (General)	Diet Only	Reference		Reference	
	Any non-insulin medication	1.16 (1.09 to 1.22)	<0.001	1.16 (1.09 to 1.22)	<0.001
DPP4i use		0.85 (0.80 to 0.91)	<0.001	0.85 (0.80 to 0.90)	<0.001
Metformin use		0.77 (0.74 to 0.81)	<0.001	0.78 (0.74 to 0.81)	<0.001
SGLT2 use		0.55 (0.39 to 0.77)	<0.001	0.55 (0.40 to 0.78)	<0.001
Antihypertensive use		0.76 (0.73 to 0.80)	<0.001	0.75 (0.72 to 0.78)	<0.001
Antipsychotic use		1.53 (1.37 to 1.71)	<0.001	1.49 (1.34 to 1.66)	<0.001
Lipid drug use		0.63 (0.60 to 0.65)	<0.001	0.63 (0.61 to 0.66)	<0.001
Steroid use		1.26 (1.22 to 1.30)	<0.001	1.19 (1.16 to 1.23)	<0.001
Polypharmacy		1.70 (1.59 to 1.83)	<0.001	1.42 (1.31 to 1.53)	<0.001
Parkinson's Disease		1.11 (1.04 to 1.20)	0.003	1.02 (0.95 to 1.09)	0.6
Congestive Cardiac Failure		1.60 (1.53 to 1.68)	<0.001	1.48 (1.42 to 1.55)	<0.001
Memory problems		1.85 (1.76 to 1.94)	<0.001	1.72 (1.63 to 1.80)	<0.001
Previous stroke		1.34 (1.29 to 1.39)	<0.001	1.24 (1.20 to 1.29)	<0.001
Erectile dysfunction		0.57 (0.51 to 0.64)	<0.001	0.58 (0.51 to 0.65)	<0.001
Ischaemic Heart Disease		1.17 (1.13 to 1.22)	<0.001	1.08 (1.04 to 1.12)	<0.001
Atrial Fibrillation		1.32 (1.26 to 1.37)	<0.001	1.23 (1.18 to 1.28)	<0.001
Non-alcoholic fatty liver disease		0.85 (0.74 to 0.98)	0.02	0.78 (0.68 to 0.89)	<0.001
Osteoporosis		1.20 (1.14 to 1.27)	<0.001	1.11 (1.05 to 1.17)	<0.001
eGFR (mL/min/1.73m^2)	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Urine albumin creatinine ratio (mcg/mg)	FP1	1.18 (1.13 to 1.23)	<0.001	1.16 (1.12 to 1.21)	<0.001
	FP2	1.01 (0.98 to 1.03)	0.7	1.01 (0.98 to 1.03)	0.6
Triglycerides (mmol/L)	FP1	0.68 (0.58 to 0.81)	<0.001	0.68 (0.58 to 0.80)	<0.001
	FP2	1.34 (1.03 to 1.73)	0.03	1.35 (1.05 to 1.73)	0.02
HDL (mmol/L)	FP1	0.03 (0.01 to 0.07)	<0.001	0.03 (0.01 to 0.07)	<0.001
	FP2	4.16 (2.77 to 6.23)	<0.001	4.12 (2.75 to 6.17)	<0.001
Total Cholesterol (mmol/L)	FP1	0.00 (0.00 to 0.01)	<0.001	0.00 (0.00 to 0.01)	<0.001
	FP2	5.46 (4.01 to 7.44)	<0.001	5.25 (3.86 to 7.14)	<0.001
eFI Category	Fit			Reference	
	Mild frailty			1.36 (1.23 to 1.49)	<0.001
	Moderate frailty			1.87 (1.69 to 2.07)	<0.001
	Severe frailty			2.27 (2.04 to 2.53)	<0.001
Model Statistics					
Akaike's Information Criteria		255,599.1		255,290.7	
Harrell's C Statistic		0.776		0.778	
Royston's D Statistic		0.409		0.415	

Appendix 6b.

Predictor		Admission Model			
		Without eFI		With eFI added	
		HR	P-Value	HR	P-Value
Age	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Gender	Female	Reference		Reference	
	Male	1.06 (1.02 to 1.10)	0.003	1.16 (1.11 to 1.20)	<0.001
HbA1c (mmol/mol)	<48	1.14 (1.10 to 1.19)	<0.001	1.12 (1.08 to 1.17)	<0.001
	48-57.9	Reference		Reference	
	58.69.9	0.95 (0.91 to 0.99)	0.01	0.96 (0.92 to 1.00)	0.03
	70-80.9	0.90 (0.85 to 0.95)	<0.001	0.91 (0.86 to 0.96)	<0.001
	≥81	0.94 (0.88 to 1.00)	0.03	0.95 (0.90 to 1.01)	0.1
Ethnicity	White	Reference		Reference	
	Asian	1.23 (1.06 to 1.43)	0.007	1.18 (1.02 to 1.38)	0.03
	Black	1.18 (0.95 to 1.46)	0.1	1.15 (0.94 to 1.42)	0.2
	Other	1.06 (0.90 to 1.24)	0.5	1.05 (0.90 to 1.23)	0.5
Alcohol use	No alcohol	Reference		Reference	
	Ex-user	1.13 (1.02 to 1.25)	0.02	1.10 (1.00 to 1.22)	0.05
	Light user	1.02 (0.96 to 1.08)	0.5	1.04 (0.98 to 1.11)	0.2
	Moderate user	1.09 (1.02 to 1.17)	0.02	1.13 (1.05 to 1.21)	<0.001
	Trivial alcohol user	0.68 (0.59 to 0.77)	<0.001	0.72 (0.63 to 0.82)	<0.001
	Heavy user	1.08 (0.97 to 1.20)	0.1	1.12 (1.01 to 1.24)	0.03
	Very heavy user	1.37 (1.21 to 1.56)	<0.001	1.39 (1.23 to 1.57)	<0.001
Smoking	Never smoked	Reference		Reference	
	Ex-smoker	1.07 (1.02 to 1.12)	0.009	1.04 (0.99 to 1.10)	0.1
	Light smoker	1.05 (0.98 to 1.12)	0.2	1.04 (0.97 to 1.11)	0.3
	Moderate smoker	1.06 (0.97 to 1.16)	0.2	1.04 (0.95 to 1.14)	0.4
	Heavy smoker	1.05 (0.94 to 1.18)	0.4	1.01 (0.90 to 1.13)	0.9
Diabetes duration (years)	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Urinary Albumin (stage)	Normoalbuminuria	Reference		Reference	
	Microalbuminuria	0.72 (0.63 to 0.83)	<0.001	0.72 (0.63 to 0.83)	<0.001
	Macroalbuminuria	0.60 (0.48 to 0.77)	<0.001	0.62 (0.49 to 0.78)	<0.001
Diabetes management (General)	Diet Only	Reference		Reference	
	Any non-insulin medication	1.01 (0.96 to 1.07)	0.7	1.01 (0.96 to 1.07)	0.7
DPP4i use		0.91 (0.84 to 0.99)	0.02	0.90 (0.83 to 0.98)	0.01
SGLT2 use		0.77 (0.64 to 0.92)	0.005	0.76 (0.64 to 0.91)	0.003
Suphonylurea use		0.95 (0.90 to 1.00)	0.06	0.96 (0.91 to 1.01)	0.1
Polypharmacy		1.32 (1.26 to 1.39)	<0.001	0.98 (0.93 to 1.03)	0.4
Lipid drug use		0.90 (0.86 to 0.94)	<0.001	0.92 (0.88 to 0.96)	<0.001
Steroid use		1.15 (1.12 to 1.18)	<0.001	1.06 (1.03 to 1.09)	<0.001
Antihypertensive use		0.90 (0.87 to 0.94)	<0.001	0.87 (0.84 to 0.90)	<0.001
Atrial fibrillation		1.15 (1.11 to 1.19)	<0.001	1.03 (0.99 to 1.07)	0.1
Congestive Cardiac Failure		1.18 (1.13 to 1.25)	<0.001	1.05 (1.00 to 1.11)	0.04
Memory problems		1.14 (1.05 to 1.23)	0.002	1.00 (0.92 to 1.08)	0.9
Previous stroke		1.11 (1.07 to 1.15)	<0.001	0.98 (0.94 to 1.02)	0.3
Ischaemic heart disease		1.07 (1.04 to 1.11)	<0.001	0.94 (0.90 to 0.97)	<0.001
Non-alcoholic fatty liver diease		1.22 (1.07 to 1.38)	0.002	1.06 (0.93 to 1.20)	0.4
Osteoporosis		1.09 (1.01 to 1.17)	0.03	0.95 (0.88 to 1.02)	0.2
Parkinson's disease		1.23 (1.16 to 1.30)	<0.001	1.05 (1.00 to 1.11)	0.06
eGFR (mL/min/1.73m^2)	FP1	0.98 (0.97 to 0.98)	<0.001	0.98 (0.97 to 0.98)	<0.001
	FP2	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Urine albumin creatinine ratio (mcg/mg)	FP1	0.99 (0.97 to 1.01)	0.5	0.99 (0.97 to 1.01)	0.5
	FP2	1.10 (1.04 to 1.15)	<0.001	1.08 (1.03 to 1.14)	0.001
Triglycerides (mmol/L)	FP1	0.99 (0.94 to 1.04)	0.6	0.98 (0.93 to 1.03)	0.4
	FP2	1.13 (0.98 to 1.31)	0.09	1.17 (1.02 to 1.36)	0.03
Total Cholesterol (mmol/L)	FP1	0.42 (0.25 to 0.69)	<0.001	0.48 (0.29 to 0.78)	0.003
	FP2	1.20 (1.00 to 1.43)	0.05	1.16 (0.97 to 1.38)	0.1
HDL (mmol/L)	FP1	1.00 (1.00 to 1.00)	0.1	1.00 (1.00 to 1.00)	0.2
	FP2	1.21 (1.10 to 1.32)	<0.001	1.20 (1.10 to 1.31)	<0.001
LDL (mmol/L)	FP1	2.00 (1.33 to 3.02)	<0.001	1.85 (1.22 to 2.78)	0.003
	FP2	0.93 (0.83 to 1.05)	0.3	0.95 (0.85 to 1.08)	0.5
eFI Category	Fit			Reference	
	Mild frailty			1.94 (1.81 to 2.08)	<0.001
	Moderate frailty			2.92 (2.62 to 3.25)	<0.001
	Severe frailty			3.94 (3.38 to 4.60)	<0.001
Model Statistics					
Akaike's Information Criteria		753,475.3		752,052.2	
Harrell's C Statistic		0.616		0.631	
Royston's D Statistic		0.316		0.331	

Appendix 6c.

Predictor		Cognitive Decline Model			
		Without eFI		With eFI added	
		HR	P-Value	HR	P-Value
Age	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Gender	Female	Reference		Reference	
	Male	0.96 (0.90 to 1.02)	0.2	1.00 (0.94 to 1.06)	1
HbA1c levels (mmol/mol)	<48	1.16 (1.07 to 1.25)	<0.001	1.15 (1.07 to 1.24)	<0.001
	48-57.9	Reference		Reference	
	58.69.9	1.05 (0.96 to 1.14)	0.3	1.05 (0.97 to 1.15)	0.2
	70-80.9	1.16 (1.03 to 1.30)	0.02	1.16 (1.03 to 1.31)	0.01
	≥81	1.25 (1.10 to 1.41)	<0.001	1.25 (1.11 to 1.42)	<0.001
Ethnicity	White	Reference		Reference	
	Asian	0.74 (0.61 to 0.91)	0.003	0.73 (0.59 to 0.89)	0.002
	Black	1.00 (0.76 to 1.32)	1	0.99 (0.75 to 1.31)	1
	Other	1.20 (0.83 to 1.72)	0.3	1.19 (0.83 to 1.71)	0.3
Alcohol use	No alcohol	Reference		Reference	
	Ex-user	1.16 (1.05 to 1.29)	0.005	1.14 (1.03 to 1.27)	0.01
	Light user	0.76 (0.71 to 0.81)	<0.001	0.77 (0.71 to 0.82)	<0.001
	Moderate user	0.64 (0.57 to 0.71)	<0.001	0.65 (0.58 to 0.73)	<0.001
	Trivial alcohol user	0.74 (0.65 to 0.84)	<0.001	0.76 (0.67 to 0.87)	<0.001
	Heavy user	0.73 (0.58 to 0.91)	0.005	0.74 (0.59 to 0.93)	0.009
	Very heavy user	0.53 (0.36 to 0.78)	0.001	0.53 (0.36 to 0.78)	0.001
Diabetes duration (years)	FP1	1.08 (0.99 to 1.17)	0.09	1.08 (0.99 to 1.18)	0.07
	FP2	1.00 (0.98 to 1.03)	0.8	1.00 (0.97 to 1.02)	0.8
DPP4i use		0.82 (0.74 to 0.91)	<0.001	0.81 (0.73 to 0.90)	<0.001
Metformin use		1.11 (1.04 to 1.18)	0.001	1.12 (1.05 to 1.19)	<0.001
Polypharmacy		1.22 (1.10 to 1.35)	<0.001	1.03 (0.93 to 1.15)	0.5
Steroid use		0.93 (0.87 to 0.99)	0.02	0.89 (0.83 to 0.94)	<0.001
Antihypertensive use		0.76 (0.70 to 0.81)	<0.001	0.74 (0.68 to 0.80)	<0.001
Antipsychotic use		1.96 (1.60 to 2.39)	<0.001	1.89 (1.55 to 2.31)	<0.001
Atrial fibrillation		1.16 (1.08 to 1.25)	<0.001	1.08 (1.00 to 1.17)	0.04
Previous Stroke		1.36 (1.27 to 1.46)	<0.001	1.27 (1.19 to 1.36)	<0.001
Ischaemic heart disease		1.16 (1.09 to 1.23)	<0.001	1.07 (1.00 to 1.14)	0.04
Osteoporosis		1.24 (1.12 to 1.38)	<0.001	1.16 (1.04 to 1.29)	0.006
Parkinson's disease		1.54 (1.38 to 1.73)	<0.001	1.43 (1.27 to 1.61)	<0.001
LDL (mmol/L)	FP1	0.53 (0.25 to 1.12)	0.1	0.51 (0.24 to 1.07)	0.08
	FP2	1.19 (0.93 to 1.52)	0.2	1.20 (0.94 to 1.54)	0.2
Total Cholesterol (mmol/L)	FP1	1.06 (0.08 to 14.00)	1	1.26 (0.10 to 16.52)	0.9
	FP2	1.03 (0.49 to 2.20)	0.9	0.98 (0.46 to 2.09)	1
Urine albumin creatinine ratio (mcg/mg)	FP1	1.08 (1.01 to 1.16)	0.03	1.07 (1.00 to 1.15)	0.06
	FP2	1.00 (0.96 to 1.04)	1	1.00 (0.96 to 1.04)	0.9
eFI Category	Fit			Reference	
	Mild frailty			1.36 (1.18 to 1.57)	<0.001
	Moderate frailty			1.77 (1.52 to 2.07)	<0.001
	Severe frailty			1.99 (1.66 to 2.37)	<0.001

Model Statistics		
Akaike's Information Criteria	131,048.7	130,934.7
Harrell's C Statistic	0.735	0.737
Royston's D Statistic	0.290	0.295

Appendix 6d.

Predictor		Falls/Fractures Model			
		Without eFI		With eFI added	
		HR	P-Value	HR	P-Value
Age	FP1	1.00 (1.00 to 1.00)	<0.001	1.00 (1.00 to 1.00)	<0.001
Gender	Female	Reference		Reference	
	Male	0.76 (0.71 to 0.80)	<0.001	0.80 (0.76 to 0.85)	<0.001
HbA1c (mmol/mol)	<48	1.17 (1.10 to 1.24)	<0.001	1.16 (1.09 to 1.23)	<0.001
	48-57.9	Reference		Reference	
	58.69.9	1.03 (0.96 to 1.11)	0.4	1.05 (0.97 to 1.13)	0.2
	70-80.9	1.05 (0.95 to 1.17)	0.3	1.07 (0.96 to 1.19)	0.2
	≥81	1.21 (1.09 to 1.35)	<0.001	1.23 (1.11 to 1.37)	<0.001
Diabetes duration (years)	FP1	0.93 (0.86 to 1.00)	0.05	0.93 (0.87 to 1.00)	0.07
	FP2	1.15 (1.08 to 1.23)	<0.001	1.11 (1.04 to 1.19)	0.001
Ethnicity	White	Reference		Reference	
	Asian	0.82 (0.68 to 0.99)	0.04	0.79 (0.66 to 0.95)	0.01
	Black	0.83 (0.46 to 1.52)	0.6	0.82 (0.45 to 1.50)	0.5
	Other	0.78 (0.57 to 1.09)	0.1	0.78 (0.56 to 1.08)	0.1
Alcohol	No alcohol	Reference		Reference	
	Ex-user	1.25 (1.13 to 1.38)	<0.001	1.22 (1.10 to 1.35)	<0.001
	Trivial use	0.93 (0.87 to 0.99)	0.02	0.94 (0.88 to 1.00)	0.06
	Light use	0.84 (0.77 to 0.92)	<0.001	0.86 (0.79 to 0.94)	0.001
	Moderate use	0.84 (0.75 to 0.93)	0.001	0.88 (0.79 to 0.98)	0.02
	Heavy use	0.97 (0.80 to 1.18)	0.8	1.00 (0.82 to 1.22)	1
	Very heavy use	0.82 (0.63 to 1.08)	0.2	0.83 (0.64 to 1.09)	0.2
Smoking	Never smoked	Reference		Reference	
	Ex-smoker	1.10 (1.04 to 1.17)	0.001	1.07 (1.01 to 1.13)	0.03
	Light smoker	1.11 (0.98 to 1.25)	0.09	1.10 (0.97 to 1.24)	0.1
	Moderate smoker	1.28 (1.10 to 1.48)	0.001	1.25 (1.08 to 1.45)	0.003
	Heavy smoker	1.07 (0.87 to 1.31)	0.5	1.02 (0.83 to 1.25)	0.9
Urinary Albumin (stage)	Normoalbuminuria	Reference		Reference	
	Microalbuminuria	1.09 (0.99 to 1.20)	0.08	1.06 (0.96 to 1.16)	0.2
	Macroalbuminuria	1.31 (1.11 to 1.54)	0.002	1.28 (1.08 to 1.51)	0.004
Diabetes management (General)	Diet Only	Reference		Reference	
	Any non-insulin medication	1.07 (0.99 to 1.15)	0.08	1.08 (1.00 to 1.16)	0.05
Atrial fibrillation		1.29 (1.21 to 1.37)	<0.001	1.14 (1.06 to 1.21)	<0.001
Congestive Cardiac Failure		1.11 (1.02 to 1.21)	0.02	0.94 (0.86 to 1.02)	0.1
Memory problems		1.43 (1.29 to 1.59)	<0.001	1.27 (1.14 to 1.41)	<0.001
Previous stroke		1.24 (1.17 to 1.32)	<0.001	1.09 (1.02 to 1.16)	0.009
Osteoporosis		1.41 (1.25 to 1.59)	<0.001	1.24 (1.09 to 1.40)	<0.001
Parkinson's Disease		1.44 (1.29 to 1.60)	<0.001	1.23 (1.10 to 1.37)	<0.001
Polypharmacy		1.37 (1.25 to 1.50)	<0.001	1.05 (0.94 to 1.16)	0.4
Steroid use		1.20 (1.14 to 1.26)	<0.001	1.10 (1.04 to 1.16)	<0.001
Triglycerides (mmol/L)	FP1	1.10 (1.01 to 1.20)	0.02	1.11 (1.02 to 1.21)	0.01
	FP2	1.09 (0.99 to 1.20)	0.09	1.10 (0.99 to 1.22)	0.07
HDL (mmol/L)	FP1	1.30 (1.04 to 1.62)	0.02	1.38 (1.10 to 1.73)	0.006
	FP2	0.95 (0.89 to 1.01)	0.08	0.94 (0.88 to 1.00)	0.04
LDL (mmol/L)	FP1	1.21 (1.01 to 1.45)	0.04	1.19 (0.99 to 1.43)	0.07
	FP2	1.00 (1.00 to 1.00)	1	1.00 (1.00 to 1.00)	1
eGFR (mL/min/1.73m^2)	FP1	0.68 (0.54 to 0.86)	0.001	0.69 (0.55 to 0.87)	0.002
	FP2	1.01 (1.00 to 1.01)	0.02	1.01 (1.00 to 1.01)	0.003
eFI Category	Fit			Reference	
	Mild frailty			1.59 (1.40 to 1.80)	<0.001
	Moderate frailty			2.29 (1.99 to 2.64)	<0.001
	Severe frailty			3.26 (2.78 to 3.82)	<0.001

Model Statistics		
Akaike's Information Criteria	113,144.8	112,856.9
Harrell's C Statistic	0.703	0.712
Royston's D Statistic	0.243	0.264

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