THE UTILIZATION, COMPARATIVE EFFECTIVENESS, AND SAFETY OF LONG-ACTING INSULIN ANALOGUES AND NEUTRAL PROTAMINE HAGEDORN INSULIN AMONG PATIENTS WITH TYPE 2 DIABETES IN THE UNITED KINGDOM

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Abstract

Long-acting insulin analogues (glargine, detemir, and degludec) and Neutral Protamine Hagedorn (NPH) insulin are recommended for the treatment of patients with type 2 diabetes whose glycaemia is poorly controlled with other glycose-lowering drugs. Randomized controlled trials reported similar efficacy of long-acting insulin analogues and NPH for glycaemic control, but data on their real-world utilization, effectiveness, and safety are lacking. The overall goal of my thesis was to evaluate the real-world utilization, comparative effectiveness, and hypoglycaemic risk of long-acting insulin analogues and NPH insulin among patients with type 2 diabetes.

In the first manuscript, I conducted a population-based study to evaluate the utilization of long-acting insulin analogues and NPH insulin between 2003 and 2018 among patients with type 2 diabetes in the United Kingdom (UK). I constructed 3 separate cohorts of patients with type 2 diabetes using the UK Clinical Practice Research Datalink (CPRD) Aurum: 1) all individuals who used an antidiabetic drug (n=686,170, all-user cohort); 2) all initiators of antidiabetic drugs (n=382,247); and 3) all initiators of basal insulin (n=85,369). In the all-user cohort, the prescription rates of insulin analogues increased from 118.3 (95% confidence interval [CI]: 116.4, 120.2) prescriptions per 1000 person-years in 2003 to 579.4 (95% CI: 576.9, 582.0) prescriptions per 1000 person-years in 2018, while prescription rates of NPH decreased during the same study period. In addition, I found that initiators of detemir were more likely to switch insulin treatment compared to initiators of NPH (adjusted hazard ratio [HR]: 1.31, 95% CI: 1.25, 1.37) and initiators of glargine were less likely to switch than initiators of NPH (adjusted HR: 0.85, 95% CI: 0.82, 0.88).

In the second manuscript, I conducted a population-based cohort study to evaluate the comparative effectiveness of long-acting insulin analogues and NPH insulin for the prevention of

major adverse cardiovascular events (MACE, a composite endpoint of myocardial infarction [MI], ischaemic stroke, and cardiovascular death) among patients with type 2 diabetes. I used the CPRD, linked with hospital and vital statistics data to assemble a cohort of initiators of basal insulins between 2002 and 2018. I used a time-varying exposure definition, inverse probability of treatment weights and two inverse probability of censoring weights to build a marginal structural Cox model to estimate the HR and 95% CI for the risk of MACE with current use of long-acting insulin analogues versus NPH. I found that use of long-acting insulin analogues were associated with a decreased risk of MACE compared to NPH insulin (HR: 0.89, 95% CI: 0.83, 0.96). In secondary analyses, I found that long-acting insulin analogues were associated with a reduced risk of cardiovascular death (HR: 0.90, 95% CI: 0.82, 0.99), all-cause mortality (HR: 0.88, 95% CI: 0.82, 0.94), hospitalization for heart failure (HR: 0.82, 95% CI: 0.77, 0.88), and MI (HR: 0.85, 95% CI: 0.74, 0.99), but they were not associated with ischaemic stroke (HR: 0.95, 95% CI: 0.81, 1.13).

In the third manuscript, I conducted a population-based cohort study to examine the association between long-acting insulin analogues and NPH and the risk of severe hypoglycaemia using a similar approach to that of Manuscript 2. Severe hypoglycaemia was defined by hospitalization for hypoglycaemia. A marginal structural model was used to estimate the HR and 95% CI for the risk of severe hypoglycaemia with the use of long-acting insulin analogues and NPH. I found a reduced risk of hypoglycaemia for long-acting insulin analogues compared to NPH insulin (HR: 0.87, 95% CI: 0.79, 0.95). In secondary analyses, I found a modest reduction in hypoglycaemia risk with glargine (HR: 0.83, 95% CI: 0.74, 0.94) but not with detemir (HR: 0.93, 95% CI: 0.79, 1.11). The HR for degludec versus NPH was 1.22 (95% CI: 0.62, 2.37).

Résumé

Les analogues de l'insuline à durée prolongée (glargine, détémir et degludec) et l'insuline à action intermédiaire Neutral Protamine Hagedorn (NPH), sont recommandés pour le traitement des patients atteints de diabète de type 2 dont la glycémie est mal contrôlée par d'autres médicaments antidiabétiques. Des essais comparatifs à répartition aléatoire ont rapporté une efficacité similaire des analogues de l'insuline à durée prolongée et de l'insuline NPH pour le contrôle de la glycémie, mais les données sur leur utilisation, leur efficacité et leur innocuité dans un contexte de vie réelle font défaut. L'objectif global de ma thèse était d'évaluer l'utilisation, l'efficacité et l'innocuité comparative des analogues de l'insuline à action prolongée et de l'insuline NPH dans un contexte de vie réelle chez les patients atteints de diabète de type 2.

Dans le premier manuscrit, j'ai mené une étude de cohorte rétrospective évaluant l'utilisation des analogues de l'insuline à action prolongée et de l'insuline NPH entre 2003 et 2018 chez les patients atteints de diabète de type 2 au Royaume-Uni. Avec l'aide de la base de données cliniques du *Clinical Practice Research Datalink* (CPRD) Aurum du Royaume-Uni, j'ai construit 3 cohortes distinctes de personnes diabétiques incluant: 1) tous les individus ayant utilisé un médicament antidiabétique (n=686 170, cohorte tous utilisateurs), 2) tous les initiateurs de médicaments antidiabétiques (n=382 247), et 3) tous les initiateurs d'insuline basale (n=85 369). Dans la cohorte de tous les utilisateurs, les taux de prescription d'analogues de l'insuline à action prolongée ont augmenté de 118,3 (intervalles de confiance à 95 % [IC] : 116,4, 120,2) ordonnances pour 1 000 personnes-années (p-a) en 2003 à 579,4 (IC à 95 % : 576,9, 582,0) ordonnances pour 1 000 p-a en 2018, tandis que les taux de prescription de NPH ont diminué au cours de la même période d'étude. En outre, j'ai constaté que les initiateurs de détémir étaient plus susceptibles de modifier leur traitement par rapport aux initiateurs de NPH (rapport de risque instantané [RRI]

ajusté : 1,31, IC à 95% : 1,25, 1,37) et que les initiateurs de glargine étaient moins susceptibles de modifier leur traitement que les initiateurs de NPH (RRI ajusté : 0,85, IC à 95% : 0,82, 0,88).

Dans le second manuscrit, j'ai mené une étude de cohorte rétrospective pour évaluer l'efficacité comparative des analogues de l'insuline à action prolongée et de l'insuline NPH pour la prévention des événements cardiovasculaires majeurs (ÉCM : critère composite d'infarctus du myocarde [MI], d'accident vasculaire cérébral ou de décès d'origine cardiovasculaire) chez les patients atteints de diabète de type 2. J'ai utilisé les données du CPRD, lié aux données d'hospitalisation et aux données de statistiques vitales pour assembler une cohorte d'initiateurs d'insulines basales entre le 1er septembre 2002 et le 30 novembre 2018. J'ai utilisé une définition de l'exposition variable dans le temps, des poids de probabilité inverse de traitement (PPIT) et deux poids de probabilité inverse de censure (PPIC) pour construire un modèle structurel marginal de Cox afin d'estimer le RRI et l'IC à 95% pour le risque d'ÉCM avec l'utilisation des analogues de l'insuline à action prolongée par rapport à l'insuline NPH. J'ai constaté que l'utilisation des analogues de l'insuline à action prolongée était associée à une diminution du risque d'ÉCM par rapport à l'insuline NPH (RRI : 0,89, 95% CI : 0,83, 0,96). Dans les analyses secondaires, j'ai constaté que les analogues de l'insuline à action prolongée étaient associés à un risque réduit d'infarctus du myocarde (RRI : 0,85, IC à 95%: 0,74, 0,99), de décès d'origine cardiovasculaire (RRI : 0,90, IC à 95% : 0,83, 0,96), de mortalité toutes causes confondues (RRI : 0,88, IC à 95 % : 0,82, 0,94) et d'hospitalisation pour insuffisance cardiaque (RRI : 0,82, IC à 95 % : 0,77, 0,88), mais n'étaient pas associés au risque d'accident vasculaire cérébral (HR : 0,94, IC à 95 % : 0,79, 1,12).

Dans le troisième manuscrit, j'ai mené une étude de cohorte rétrospective pour évaluer l'innocuité comparative des analogues de l'insuline à action prolongée et de l'insuline NPH sur le

risque d'hospitalisation pour hypoglycémie en utilisant une approche similaire à celle du deuxième manuscrit. Un modèle de Cox structurel marginal a été utilisé pour estimer le RRI et l'IC à 95% pour le risque d'hospitalisation pour hypoglycémie avec l'utilisation d'analogues d'insuline à action prolongée et l'utilisation d'insuline NPH. J'ai trouvé un risque réduit d'hospitalisation pour hypoglycémie pour les analogues de l'insuline à action prolongée par rapport à l'insuline NPH (RRI : 0,87, IC à 95% : 0,79, 0,95). Dans les analyses secondaires, j'ai trouvé une réduction modeste du risque d'hospitalisation pour hypoglycémie avec l'insuline glargine (RRI: 0,83, IC à 95% : 0,74, 0.94) mais pas avec l'insuline détémir (RRI : 0,93, IC à 95%: 0,79, 1,11). L'RRI pour l'insuline degludec par rapport à l'insuline NPH était de 1,22 (IC à 95 % : 0,62, 2,96).

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Contribution of authors

Manuscript 1: Initiation of Four Basal Insulins and Subsequent Treatment Modification in People Treated for Type 2 Diabetes in the United Kingdom: Changes over the Period 2003-2018. *Diabet Med*. 2021;38(8): e14603.

I developed the research question with guidance from my supervisor Dr. Filion. I drafted the protocol for data custodian approval and research ethics board approval from UK Clinical Practice Research Datalink Independent Scientific Advisory Board and Jewish General Hospital, respectively. I was responsible for the creation of the variable definitions, data management, data analysis, and drafting of the manuscript. Dr. Yu provided clinical guidance, and Dr. Platt provided statistical guidance. All authors contributed to the study design and methodology, interpretation of the results, and revisions of the manuscript.

Manuscript 2: Comparative Effectiveness of Long-Acting Insulin Analogues versus Neutral Protamine Hagedorn Insulin for the Prevention of Major Adverse Cardiovascular Events among Individuals with Type 2 Diabetes: A Population-based Cohort Study – *Submitted to Diabetes, Obesity and Metabolism*

I conceptualized the research question of this manuscript with Dr. Filion. I drafted the protocol for data custodian approval and research ethics board approval from UK Clinical Practice Research Datalink Independent Scientific Advisory Board and Jewish General Hospital, respectively. I was responsible for data management, data analysis, and drafting the manuscript. Dr. Yu provided clinical guidance, and Dr. Platt provided statistical guidance. All authors contributed to the study design and methodology, interpretation of the results, and revisions of the manuscript.

Manuscript 3: Long-Acting Insulin Analogs versus Neutral Protamine Hagedorn Insulin and the Risk of Severe Hypoglycemia among Patients in Type 2 Diabetes in the United Kingdom – *Submitted to Diabetes Care*

I conceptualized the research question of this manuscript with Dr. Filion. I drafted the protocol for data custodian approval and research ethics board approval from UK Clinical Practice Research Datalink Independent Scientific Advisory Board and Jewish General Hospital, respectively. I was responsible for the data management, data analysis and drafting of the manuscript. Dr. Yu provided clinical guidance, Dr. Platt provided statistical guidance, and Ms Reynier provided programming support. All authors contributed to the study design and methodology, interpretation of the results, and revisions of the manuscript.

Statement of contribution of original knowledge

The research presented in this thesis consists of original contributions that add to the body of knowledge on the real-world utilization and the comparative effectiveness and safety of long-acting insulin analogues and NPH insulin.

While previous studies have assessed the utilization of basal insulins in patients with type 2 diabetes, sparse information was available on the changing use of long-acting insulin analogues and NPH insulin separately over time or prescribing patterns of different long-acting insulin analogues. In addition, limited information was available on the rates of switching and discontinuation among patients with type 2 diabetes using these medications. In the first manuscript, we found that the rate of basal insulin use has increased over time, while the rate of NPH decreased. In addition, we also found that patients who initiated basal insulin treatment with detemir were more likely to switch insulin treatments than patients initiating glargine, degludec, or NPH insulin.

The aim of the second manuscript was to evaluate the comparative effectiveness of long-acting insulin analogues and NPH for the prevention of cardiovascular events. While previous studies assessing the cardiovascular effects of basal insulins have been conducted, they were affected by important biases that may have altered their conclusions. In our second manuscript, we were able to address these methodological issues. We found that long-acting insulin analogues were associated with a reduced risk of MACE as compared to NPH insulin. We also found that long-acting insulin analogues were associated with a reduced risk of cardiovascular death, all-cause mortality, hospitalization for heart failure, and MI, but not ischaemic stroke.

The aim of the third manuscript was to evaluate the risk of hospitalization for hypoglycaemia in patients with type 2 diabetes using long-acting insulin analogues or NPH insulin. Previous

studies on the topic were either affected by important biases, were outdated, or did not include degludec, the most recently marketed long-acting insulin analogue. In our third manuscript, we addressed these methodological issues by using contemporary data and sophisticated statistical methods. We found that long-acting insulin analogues were associated with a reduced risk of hospitalization for hypoglycaemia compared to NPH insulin. When molecule-specific analyses, we found that glargine reduced the risk of hospitalization for hypoglycaemia as compared to NPH, but not detemir. The analysis of degludec was inconclusive due to sparse data.

Overall, this thesis provides crucial information on the utilization, effectiveness, and safety of long-acting insulin analogues and NPH in a real-world setting. This evidence may be used to help inform treatment guidelines for type 2 diabetes and reimbursement policies for these drugs. The differential effects of long-acting insulin analogues and NPH insulin on the risk of cardiovascular outcomes and on the risk of hospitalization for hypoglycaemia may also be considered when physicians and patients decide on the most appropriate treatment strategy for type 2 diabetes.

I declare that I received guidance from my supervisor for my thesis objectives and clinical and methodological guidance from thesis committee members. The conception, execution, and drafting of the manuscripts were entirely my own.

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List of acronyms and abbreviations

ACE	Angiotensin-converting enzyme (inhibitors)
ADA	American diabetes association
AKI	Acute kidney injury
APC	Admitted patient care
ARB	Angiotensin-II receptor blockers
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CCB	Calcium-channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disorder
CPRD	Clinical practice research datalink
CT	Clinical terms
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trials
DAG	Directed acyclic graph
DBP	Diastolic blood pressure
DEVOTE	Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events
DOAC	Direct-acting oral anticoagulants
DOAC	Direct oral anticoagulants
DPP-4	Dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
ÉCM	Évènement cardiovasculaire majeur
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FFA	Free fatty acids
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
HES	Hospital episodes statistics

HR	Hazard ratio
IC	Intervalle de confiance
ICD	International Classification of Disease
IMD	Index of Multiple Deprivation
IPCW	Inverse probability of censoring weighting
IPTW	Inverse probability of treatment weighting
IR	Incidence rate
ITT	Intention to treat
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MICE	Multiple imputation by chained equations
MSM	Marginal structural model
NEFA	Non-esterified fatty acids
NHANES III	Third National Health and Nutrition Examination Survey
NHS	National health services
NICE	National Institute for Health Care Excellence
NPH	Neutral protamine Hagedorn
NSAID	Non-steroidal anti-inflammatory drugs
OAD	Oral antidiabetic drug
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys classification of interventions and procedures
OR	Odd ratio
ORIGIN	Outcome Reduction with an Initial Glargine Intervention
PCOS	Polycystic ovary syndrome
PPIC	Poids de probabilité inverse de censure
PPIT	Poids de probabilité inverse de traitement
RAMQ	Régie de l'Assurance Maladie du Québec
RCT	Randomized controlled trial
RR	Relative risk or rate ratio (paper 1)
RRI	Rapport des risques instantané
SBP	Systolic blood pressure
SD	Standard deviation

SGLT-2	Sodium-glucose co-transporter 2
TZD	Thiazolidinediones
UK	United Kingdom
UKPDS	United Kingdom prospective diabetes study
US	United States
WHO	World health organization

1. Chapter 1: Introduction

1.1 Overview

Diabetes is associated with substantial morbidity and mortality and affects more than 422 million people worldwide[1,2]. Approximately 85% of people with diabetes have type 2 diabetes, a complex disease that is caused by modifiable risk factors such as obesity and non-modifiable risk factors such as age, sex, and family history[3]. The aim of treatment for type 2 diabetes is to control glycaemic levels to prevent complications that can result from chronic hyperglycaemia, including macrovascular complications (myocardial infarction [MI] and ischaemic stroke) and microvascular complications (diabetic retinopathy, nephropathy, and neuropathy)[4,5]. Canadian[5] and International[4,6] guidelines recommend initiating treatment for type 2 diabetes with lifestyle modifications. Most patients will progress to the use of antidiabetic drugs, and approximately 20% of patients will require treatment with insulin[7]. Insulins can be broadly classified into 2 categories: human insulin and insulin analogues[5]. Human insulins include short-(regular) and intermediate-acting neutral protamine Hagedorn (NPH) insulin, whereas insulin analogues include rapid-(aspart, glulisine, lispro), long- (glargine, detemir), and ultra-long-acting (degludec) insulin. Patients with type 2 diabetes with poorly controlled glycaemia while using first or second-line therapies alone will be recommended to use basal insulin, namely NPH insulin, glargine, detemir, or degludec[4,5].

Long-acting insulin analogues were introduced as treatments for type 2 diabetes in the 2000s, with glargine entering the United Kingdom (UK) market in 2002, detemir in 2004, and degludec in 2013[8,9]. Due to the obesity epidemic, safety concerns regarding thiazolinediones,[10,11] and the marketing of newer antidiabetic therapies (sodium-glucose co-transporter 2 [SGLT-2] inhibitors, dipeptidyl-peptidase 4 [DPP-4] inhibitors, glucagon-like peptide 1 [GLP-1] receptor agonists), and

the changing characteristics of patients with type 2 diabetes,[12] the prescribing patterns of antidiabetic drugs, including insulin, have evolved over the last two decades[13]. While the use of basal insulins has been studied, few studies assessed the use of individual long-acting insulin analogues and NPH, and most studies on the use of basal insulins were conducted before the marketing of degludec[14]. Thus, it remains unclear how the patterns of use of long-acting insulin analogues and NPH have evolved over the last two decades. In addition, few studies have described treatment switching among users of long-acting insulin analogues and NPH insulin. Treatment switching may indicate presence of adverse events such as severe hypoglycaemia or other side effects, and it may affect adherence[15]. Thus, more insight into the utilization of long-acting insulin analogues and NPH insulin is needed to inform drug policies and clinical guidelines.

Randomized controlled trials (RCTs) and subsequent meta-analyses suggest that long-acting insulin analogues and NPH insulin have comparable efficacy with respect to glycaemic control, although some studies report differences between individual types of long-acting insulin analogues[16-19]. Although RCTs have evaluated the comparative efficacy of these insulins on measures of glycaemic control, few trials have examined their comparative efficacy at reducing cardiovascular events[20,21]. In addition, as patients included in RCTs seldom represent the patient population that is seen in routine clinical practice, the generalizability of results from RCTs is debatable[22]. A small number of observational studies have examined the real-world comparative effectiveness of long-acting insulin analogues and NPH at reducing the risk of cardiovascular events[23-26]. However, these studies had important methodological limitations, which limit the interpretation of their results. Furthermore, few studies have compared the different long-acting insulin analogues with respect to their risk of cardiovascular events. As such, the comparative

effectiveness of long-acting insulin analogues and NPH for the prevention of cardiovascular events in a real-world setting has yet to be fully understood.

As any pharmacological treatment, the use of long-acting insulin analogues and NPH insulin may lead to adverse events. Hypoglycaemia is a well-recognized adverse effect of insulin treatment[27]. Severe hypoglycaemia can result in serious consequences including hospitalization, diabetic coma, and death[28]. RCTs comparing the risk of hypoglycaemia between long-acting insulin analogues and NPH have shown mixed results, although generally reporting modestly reduced risks of hypoglycaemia with long-acting insulin analogues[18]. Although some observational studies have examined the risk of hypoglycaemia with the use of long-acting insulin analogues and NPH, they had important methodological limitations, including conclusion-altering biases such as differential exposure definitions between cases and non-cases[29], crude analyses only[30,31], were outdated, had no comparator group[32], or had limited generalizability[33]. There remains a need for high-quality, real-world studies on the comparative safety of long-acting insulin analogues and NPH for the risk of hypoglycaemia.

1.2 Research objectives

The overall purpose of my thesis is to address important knowledge gaps regarding the utilization and comparative effectiveness and safety of long-acting insulin analogues and NPH insulin among patients with type 2 diabetes. This overarching aim will be addressed in three objectives:

1 To describe the utilization of long-acting insulins and NPH insulin over time in the United Kingdom (UK), the characteristics of users of long-acting insulins (glargine, detemir, and degludec) and NPH insulin and to compare rates of treatment switching between these two types of insulin among patients with type 2 diabetes.

2 To compare the effectiveness of long-acting insulins and NPH insulin at reducing the risk of major adverse cardiovascular events (MACE), a composite endpoint of MI, ischaemic stroke, and cardiovascular death, among patients with type 2 diabetes.

3 To compare the to the risk of severe hypoglycaemia of long-acting insulins (glargine, detemir, degludec) and NPH insulin among patients with type 2 diabetes.

1.3 Thesis organization

This thesis is manuscript based. Chapter 2 presents the relevant background information for my thesis, including the epidemiology of type 2 diabetes, non-modifiable and modifiable risk factors for type 2 diabetes, the pathophysiology of type 2 diabetes, the diagnosis and management of type 2 diabetes, complications of type 2 diabetes, diagnosis and management of cardiovascular risk factors in patients with type 2 diabetes, treatments for type 2 diabetes (including insulin analogues and human insulins), the adverse events of treatment with insulin and the link between hypoglycaemia and cardiovascular events. Chapter 3 provides a detailed literature review for the specific objectives of my thesis described in Section 1.2. Chapter 4 presents a summary of the data sources used for my thesis, including the Clinical Practice Research Datalink (CPRD) Aurum, the Hospital Episodes Statistics (HES), and the Office for National Statistics (ONS) vital statistics data. This chapter also includes information on the methodology used and diagnostic codes for the creation of my study cohorts and provides additional details regarding the methods reported in the manuscripts. Chapter 5 consists of a drug utilization study on the utilization and treatment switching in users of long-acting insulin analogues and NPH in the UK from 2003 to 2018 (Manuscript 1). Chapter 6 describes a population-based retrospective cohort study on the comparative effectiveness of long-acting insulin analogues and NPH insulin on the risk of MACE (Manuscript 2). Chapter 7 presents a population-based retrospective cohort study on the risk of

severe hypoglycaemia of long-acting insulins analogues and NPH (Manuscript 3). Chapter 8 summarizes the findings of the thesis and provides an interpretation of the overall results, discusses the strengths and limitations of my thesis, and the implications of this work. Finally, Chapter 9 provides overall conclusions. References for Chapters 1 to 4 and Chapter 8 are provided at the end of this thesis. References for Chapters 5 to 7 are provided in the corresponding chapters.

2 Chapter 2: Study background

2.1 The epidemiology of type 2 diabetes

The global prevalence of diabetes quadrupled in only three decades, reaching 422 million people in 2014[2]; a number likely to continue to increase in the coming years due to the increased prevalence of risk factors for diabetes including obesity[12,34]. Diabetes is classified into two main categories: type 1 and type 2 diabetes[35]. Type 1 diabetes is generally diagnosed during childhood and early adolescence[36] and is the result of chronic autoimmune destruction of the ß-cells of the pancreas that produce insulin[36]. In contrast, type 2 diabetes is generally diagnosed in adulthood and is characterized by insulin resistance[37,38], where skeletal muscle cells and other tissues become unresponsive to the insulin produced by the pancreas[36]. Approximately 85% of people with diabetes have type 2 diabetes[5,6]. People with type 2 diabetes are at increased risk of many adverse health outcomes, including microvascular complications such as diabetic nephropathy and retinopathy, and macrovascular outcomes, such as MI and ischaemic stroke[39]. People with type 2 diabetes are also at increased risks of cancer and infection-related mortality[40]. Every year, 1.6 million deaths are directly attributed to diabetes worldwide[41]. In addition, the economic burden of type 2 diabetes continues to rise; the attributable cost of diabetes in 2011/2012 was estimated at $15.36 billion CAD[42] in Canada and $314.8 billion USD in 2014 in the United States (US)[43].

2.2 Non-modifiable risk factors for type 2 diabetes

Non-modifiable risk factors for type 2 diabetes include family history, sex, ethnicity/race, and increasing age[3]. The Framingham Offspring study assessed the parental transmission of type 2 diabetes to offspring and the genetic phenotypes associated with type 2 diabetes[44]. They reported a 3.5-fold increased risk of type 2 diabetes in offspring that had maternal diabetes (odds ratio [OR]: 3.4, 95% confidence interval [CI]: 2.3, 4.9) or paternal diabetes (OR: 3.5, 95% CI: 2.3, 5.2) compared to offspring whose parents did not have diabetes. This elevated risk increased to 6-fold

when both parents were diagnosed with type 2 diabetes (OR: 6.1, 95% CI: 2.9, 13.0)[44], suggesting an additive model of transmission (risk ratio $_{both} - 1 = [$risk ratio $_{mother} - 1 +$ risk ratio $_{father} - 1]$)[44]. However, the role played by intrauterine environments in mothers as opposed to purely genetic factors are difficult to separate in the transmission of type 2 diabetes and remain unclear[17]. Ethnicity/race also plays an important role in the risk of type 2 diabetes. The Third National Health and Nutrition Examination Survey (NHANES III) reported a 1.6-fold increased prevalence of type 2 diabetes among non-Hispanic African Americans than among Caucasians of comparable age[45]. In a 20-year follow-up study, the Nurses' Health study reported increased risk of type 2 diabetes among Asian (RR 2.26, 95% CI: 1.70, 2.99), Hispanic (RR: 1.86, 95% CI: 1.40, 2.47), and African American women (RR: 1.34, 95% CI: 1.12, 1.61) compared to Caucasian women, after adjustment for age and body mass index (BMI)[46]. Increased risks are also present among Native American populations, where they exhibit 2.8 times greater prevalence of diabetes than Caucasians[47,48]. While the genetic predisposition of certain ethnicity/race subpopulations is associated with an increased risk of diabetes[49], environmental factors such as lower socioeconomic status[50] and barriers to healthcare[51] are also important contributors to this increased risk. Racial differences also exist in the risk of mortality due to underlying diabetes, as studies have reported that African-Americans, Native Americans, Alaskan Natives, and Hispanic Americans with diabetes are between 1.5 and 2.3 times more likely to die from diabetes compared to non-Hispanic Whites with diabetes[49,52].

Older age is also a major risk factor for type 2 diabetes, while a lower age at diagnoses of type 2 diabetes is associated with a greater risk of complications from type 2 diabetes[53]. Most studies report a mean age at diagnosis of type 2 diabetes between 50-60 years [54]. Due to the obesity epidemic and modern sedentary lifestyles, the mean age at diagnosis has decreased in recent

years[54] and an alarming rise in adolescents diagnosed with type 2 diabetes has been observed in developed countries[55]. The age at which patients are diagnosed can have significant impacts on their daily lives due to use of antidiabetic drugs and insulin much earlier in life. In addition, patients diagnosed with type 2 diabetes at younger ages are also at increased risks of adverse cardiovascular outcomes compared to patients diagnosed with type 2 diabetes later on in life[53], which may reflect an increased prevalence of obesity in patients diagnosed with diabetes at younger ages.

2.3 Modifiable risk factors of type 2 diabetes

Modifiable risk factors are important in the development of type 2 diabetes[56]. Lifestyle factors associated with the risk of developing type 2 diabetes include socioeconomic status, smoking[57], excess alcohol consumption, poor dietary habits, lack of physical activity, and obesity[58]. Excess caloric intake and lack of physical inactivity[59] are associated with an increased risk of obesity, which is an independent risk factor for type 2 diabetes[46,55], with or without unhealthy lifestyle habits[60]. A recent study determined that the risk of type 2 diabetes increases by more than 5-fold for patients with a BMI ≥ 30 kg/m^2 compared to individuals with a BMI < 30 kg/m^2 [60]. It is believed that a prolonged elevation of free fatty acid levels that is seen in obese patients leads to constant utilization of stored lipids by the skeletal muscles, decreasing the amount of glucose uptake.

Unsurprisingly, high caloric intake and sedentary lifestyle are major risk factors associated with the increased prevalence of type 2 diabetes observed worldwide, with or without an elevated BMI[61]. As explained in detail below, excess caloric intake causes a surge in glycemia, which in turn increases the production of endogenous insulin. This constant over-production ultimately causes skeletal muscles cells and other tissues to become unresponsive to the insulin that is produced. Women with a diet of high-fibre cereal, marine n-3 fatty acids, folate, and a high polyunsaturated to saturated fat ratio were less likely to develop type 2 diabetes than women with

a high-risk diet, defined using composite dietary scores (RR: 0.38, 95% CI: 0.25, 0.58)[62], independently of BMI level.

Socioeconomic status is an important risk factor for type 2 diabetes, as it is also closely linked with lifestyle habits and obesity[63]. In women, level of education completed was inversely associated with incident diabetes, where women with more than 16 years of education were 74% less likely to develop diabetes compared to women with less than 9 years of education (hazard ratio [HR]: 0.26, 95% CI: 0.13, 0.54)[64].

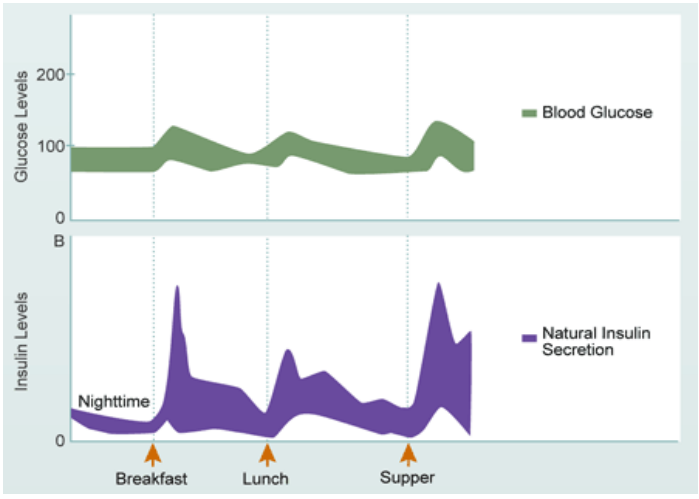
Several studies have reported on the increased risk of type 2 diabetes associated with smoking and alcohol, although these characteristics may also be proxies for poor lifestyle habits. One study reported a 74% increased risk of type 2 diabetes among current smokers compared to never smokers, after controlling for other risk factors such as BMI, physical activity, alcohol intake, social class, and history of coronary heart disease (HR: 1.74, 95% CI: 1.24, 2.43)[57]. Similarly, alcohol consumption is also independently associated with incident type 2 diabetes[65]. Andrea et al. reported that heavy alcohol consumption is associated with a 43% increased incidence (relative risk [RR]: 1.43, 95% CI: 1.01, 2.02) of type 2 diabetes compared to moderate alcohol intake[66].

2.4 Pathophysiology of type 2 diabetes

2.4.1 Healthy glucose homeostasis

Glucose and insulin homeostasis operate through a feedback loop between plasma glucose, insulin-sensitive tissues, and the pancreas [38]. In a healthy individual, endogenous insulin secretion is stimulated by a rise in circulating glucose levels following meal ingestion[67]. Endogenous insulin is a key hormone for the regulation of glucose levels and is secreted by the β cells located in the islets of Langerhans that make up approximately 1-2 % of the total pancreatic tissue[68]. These islets are responsible for most of the pancreatic endogenous hormonal secretion, including glucagon through α cells and ghrelin through ε cells among others. The liver is also partly responsible for glucose regulation. Glucokinase detects entry of glucose into the ß cell, which phosphorylates glucose leading to cell-membrane depolarization and activation of calcium channels, thus increasing the calcium concentration inside the cell and triggering insulin secretion[69]. Although glucose is the principal stimulus for insulin secretion, non-nutrient secretagogues, such as other

Figure 2.1: Normal daily (24h) serum glucose and insulin levels



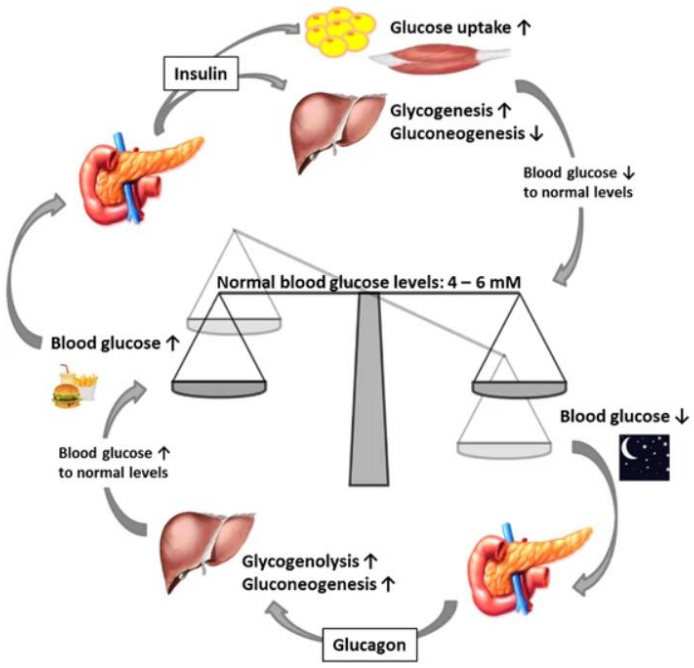
Source: Jacobs MAJM, et al. Diabetes Care. 1997;20(8):1279-86.

hormones, also play a role through various pathways including adrenergic pathways, peptide hormones, and cationic amino acids.

The release of insulin in response to glucose occurs in two phases[69] (**Figure 2.1*)***. The first "rapid" phase begins 1 minute after glucose detection and peaks around 3-5 minutes following glucose detection. The second phase begins 10 minutes after glucose detection and lasts for the duration of the hyperglycemia induced by meal ingestion[69]. The magnitude and duration of the second phase of insulin release will depend on the composition of the ingested meal: a meal high in carbohydrates and low in fiber, protein, and fat will induce a rapid and sharp peak and decline of insulin secretion, while meals containing greater amounts of complex carbohydrates, fiber, fat, and protein will induce a more gradual insulin peak and decline[70].

Insulin-sensitive tissues respond to the increased level of insulin in the bloodstream by increasing their uptake of glucose, amino acids, and fatty acids, as well as glycogenesis (glucose storage) and decreased gluconeogenesis (glucose release) by the liver (***Figure 2.2)***. In healthy patients, the ß cells of the pancreas adapt to the glucose concentrations in the blood and vice versa. When blood glucose levels do not decrease as expected following insulin secretion, insulin resistance is said to be present[69]. Another important hormone responsible for the maintenance of glucose homeostasis is glucagon, which is also produced by the pancreas. When blood glucose levels are low, for instance between meals or during the night, the pancreas secretes glucagon, which in turn signals to the liver to release glucose (glycogenolysis/gluconeogenesis) into the bloodstream. As depicted in ***Figure 2.2***, the maintenance of blood glucose is the result of the complex interplay between energy consumption, insulin secretion from pancreas, insulin sensitivity of skeletal muscles, glucose uptake by insulin-sensitive tissues, and glucose production by the liver.

Figure 2.2*:* Schematic representation of glucose homeostasis



Source: Röder, P., Wu, B., Liu, Y. *et al.* Pancreatic regulation of glucose homeostasis. *Exp Mol Med* 48**,** e219 (2016). https://doi.org/10.1038/emm.2016.6

2.4.2 Impaired glucose homeostasis and related complications among patients with type 2 diabetes

In patients with type 2 diabetes, several elements of blood glucose control may be impaired and lead to a state of chronic hyperglycemia. When insulin resistance is present, the increased output of insulin by the ß cells is not matched by an increase in glucose uptake by insulin-sensitive tissues. Thus, higher levels of serum glucose are observed[38]. The divergence of plasma glucose levels seen in people with insulin resistance from plasma glucose concentrations in people without insulin resistance is proportional to the impairment in ß-cell function. In addition to reduced ß-cell function, patients with type 2 diabetes have declining quantities of ß-cells compared to patients

without type 2 diabetes. This reduction is due to several factors including amyloid deposition, which leads to ß-cell apoptosis through oxidative and endoplasmic-reticulum stress and glucolipotoxicity[34]. The impaired release of glucagon by the α-cells also contributes to hyperglycemia. However, it is unclear if this impaired release of glucagon is a consequence or a cause of abnormal insulin levels due to ß-cell dysfunction[71]. Therefore, the progressive deterioration of α and ß-cell function, in addition to a decline in ß-cell numbers, contribute to progressive worsening of glucose and insulin homeostasis observed in people with type 2 diabetes.

Certain populations are at increased risk of ß-cell dysfunction, such as patients with a family history of type 2 diabetes, women with polycystic ovary syndrome, and women with a history of gestational diabetes. As ß-cell function is thought to be heritable, certain racial and ethnic groups are also at increased risk of ß-cell dysfunction[71]. In recent studies, more than 50 gene loci have been associated with type 2 diabetes[38], and 53 loci have been linked with insulin and glucose concentrations. Most of these loci are linked with ß-cell function, although some are also linked with obesity and insulin resistance. Adipose tissues release non-esterified fatty acids, hormones, and glycerol, all of which have an impact on insulin sensitivity and insulin resistance in people with obesity[71,72].

2.5 Diagnosis and management of type 2 diabetes in adults

Guidelines from Diabetes Canada recommend that adults should be evaluated once a year to assess their risk of type 2 diabetes, and individuals aged 40 or more years or at high risk should undergo screening for type 2 diabetes every 3 years[73]. Individuals with additional risk factors for type 2 diabetes should be screened earlier or more frequently (every 6 to 12 months). A diagnosis of type 2 diabetes can be made if the patient has a fasting plasma glucose (FPG) level ≥ 7.0 mmol/L has a plasma glucose ≥ 11.1mmol/L in a 2-hour 75g oral glucose tolerance test or has a glycated

haemoglobin level (HbA1c) ≥ 6.5%. Having results above diagnostic thresholds from two different tests confirms the diagnosis of type 2 diabetes. As the average lifespan of an erythrocyte is 120 days, HbA1c provides a measure of glycemia over the previous 8 to 12 weeks[74]. If a patient presents symptoms of hyperglycemia, such as polyuria (frequent urination), polydipsia (extreme thirst), acanthosis nigricans (a skin condition characterized by dark pigmentation in skin folds), and weakness[75], only one of these criteria must be met to provide the diagnosis.

The guidelines for the diagnosis of type 2 diabetes in adults are similar in the United Kingdom. The National Institute for Health and Care Excellence (NICE) recommends to suspect the presence of type 2 diabetes if a patient presents persistent hyperglycemia, defined as a HbA1c ≥ 48 mmol/mol (≥ 6.5%), a FPG ≥ 7.0 mmol/mol, or a random plasma glucose ≥ 11.1 mmol/mol in the presence of signs and symptoms of diabetes[76]. These guidelines also suggest that persistent hyperglycemia may be accompanied by clinical features such as polydipsia, polyuria, blurred vision, unexplained weight loss, acanthosis nigricans, recurrent infections, and tiredness. In addition, if a patient is symptomatic, a single HbA1c or FPG can be used to diagnose type 2 diabetes. Alternatively, if the patient is not symptomatic, repeat HbA1c and FPG testing is recommended[76]. In the UK, type 2 diabetes management and diagnosis in adults is managed by the general practitioner[77].

Following diagnosis, patients will be closely monitored to ensure adequate control of glycaemic levels and to prevent diabetes complications. NICE guidelines recommend measuring HbA1c levels every 3 months until the HbA1c is at target on unchanged treatment, at which point a 6-month assessment period may be sufficient[78]. In addition, it is recommended that patients be screened for diabetic retinopathy at diagnosis and every 2 years for people at low risk of retinopathy and every year for patient at higher risk. Patients should also be screened for diabetic

foot complications such as peripheral neuropathy, peripheral arterial disease, ulceration, infection, foot deformities, gangrene, or Charcot foot disease at the time of diagnosis and once a year thereafter[78].

2.6 Type 2 diabetes complications: cardiovascular outcomes

Patients with type 2 diabetes are at an increased risk of macro and microvascular complications. Macrovascular complications include cardiovascular outcomes such as heart failure[79], coronary heart disease, ischaemic stroke, and MI[80]. Microvascular complications include retinopathy, nephropathy, and neuropathy[9]. While the physiological effects of macro and microvascular complications are different, their pathogenesis is relatively similar. Chronic hyperglycemia seen in patients with type 2 diabetes is thought to cause oxidative stress to blood vessels. In smaller blood vessels such as those present in the kidneys, eyes, and limbs, oxidative stress can impair their functioning and lead to nephropathy, retinopathy, and neuropathy[81], respectively, which can lead to blindness, end stage renal disease, and amputation[82]. In larger blood vessels such as arteries, oxidative stress can lead to atherosclerosis, which is an important risk factor of cardiovascular events[83] including MI, ischaemic stroke, heart failure, and cardiovascular death[79,84]. Consequently, the overarching goal of treatment for type 2 diabetes is to prevent these complications through control of serum glucose levels with glucose lowering drugs and managing other cardiovascular risk factor levels[85].

Adverse cardiovascular events are the leading cause of death and morbidity in patients with type 2 diabetes[40]. Patients with type 2 diabetes are at between 2- and 8-times greater risk of cardiovascular mortality than patients without diabetes[86,87]. In addition, patients with diabetes experience stroke at younger ages, as well as greater mortality and slower recovery from ischaemic stroke,[88] than patients without diabetes. Similarly, the age-standardized incidence rates for MI are

greater in men and women with type 2 diabetes than in those without type 2 diabetes[89]. Comorbidities of patients with type 2 diabetes, such as hypertension and blood pressure variability, also contribute to the increased risk of cardiovascular outcomes observed in this population.[90]

The importance of cardiovascular events among patients with type 2 diabetes is well illustrated by the US Food and Drug Administration (FDA)'s requirement that manufacturers of glucose lowering drugs conduct post-marketing cardiovascular outcome trials (CVOT)s for all new therapies for type 2 diabetes [91]. This requirement was initiated in 2008 following the publication of a meta-analysis of 43 RCTs in 2007, which reported an increased risk of cardiovascular outcomes with randomization to rosiglitazone, a thiazolidinedione that was widely used by patients with type 2 diabetes at the time[92]. This controversial publication led the FDA's Endocrinologic and Metabolic Drugs Advisory Committee to recommend systematic post-marketing outcome trials of antidiabetic drugs to rule-out any potential increased cardiovascular risk. These non-inferiority trials are designed to rule out a HR of 1.3 for major cardiovascular events (cardiovascular death, nonfatal MI, and non-fatal stroke) for final regulatory approval (conditional approval is provided after demonstrating efficacy for glycaemic control while awaiting results of the CVOT). However, insulins are exempt from this requirement, which highlights the importance of observational studies evaluating the cardiovascular risk associated with their use.

2.7 Diagnosis and management of cardiovascular risk factors and complications in patients with type 2 diabetes

As patients with type 2 diabetes are at increased risk of cardiovascular complications, cardiovascular risk factors must be closely monitored in this population. NICE guidelines recommend assessing a person's 10-year cardiovascular risk using the QRISK[93] tool every 5 years for patients without established cardiovascular disease. In addition, these guidelines recommend

routinely measuring clinical cardiovascular risk factor levels in patients with type 2 diabetes and to treat hypertension, hyperlipidemia, and atherothrombotic events[78].

Approximately two thirds of patients with type 2 diabetes have hypertension[94]. Patients with type 2 diabetes who are already on antihypertensive treatment should aim to maintain systolic and diastolic blood pressure (SBP and DBP) levels below 140/90 mmHg if they are less than 80 years of age and below 150/90 if they are aged 80 or more years. In addition, patients with type 2 diabetes and chronic kidney disease (CKD) should maintain systolic blood pressure between 120-129 mmHg and diastolic blood pressure below 80 mm Hg. Patients not currently treated with antihypertensive drugs but who are newly diagnosed with hypertension should also aim for similar blood pressure targets. NICE recommends first-line treatment monotherapy for patients with diabetes and hypertension, which includes angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARB)s. If the patient's hypertension is not controlled through monotherapy with either of these drugs, a calcium-channel blocker or thiazide-like diuretic can be added to either medication.

Managing blood lipid levels is another effective measure to prevent cardiovascular complications among patients with type 2 diabetes, which is usually achieved by prescribing statins[95]. Patients with type 2 diabetes are also at a greater risk of atherothrombotic events, due to endothelial dysfunction, oxidative stress, and vascular inflammation, which cause atherosclerotic plaques to develop over time[96]. In addition, these plaques are more rupture-prone in patients with type 2 diabetes, which can lead to arterial thrombosis. Therefore, prevention of atherosclerotic plaques is crucial[96]. Antiplatelets are recommended for the prevention of atherothrombotic events among patients with type 2 diabetes[78]. They are recommended for treatment in patients with multiple cardiovascular risk factors and evidence of vascular inflammation such as having an

elevated C-reactive protein level. Recently, newer antidiabetic drugs such as SGLT-2 inhibitors and GLP-1 receptor agonists have also been shown to decrease the risk of cardiovascular events in this population[97,98].

2.8 Treatment for type 2 diabetes

Treatment for type 2 diabetes generally involves either increasing the production of endogenous insulin, increasing sensitivity to endogenous insulin, or providing exogenous insulin to reduce serum glucose levels[99]. This process begins with lifestyle education and modification[5,6] followed by treatment with oral antidiabetic drugs (OADs). Lifestyle modification includes adoption of a low-caloric, low-fat and high-fiber diet, in addition to achieving 150 minutes of physical activity per week[100]. The American Diabetes Association (ADA), Diabetes Canada, and the European Association for the Study of Diabetes (EASD) recommend beginning pharmacological treatment with metformin[5,6,101] (***Figure 2.3***). Subsequently, if the target HbA1c is not reached within 3 months, these guidelines recommend adding a second-line antidiabetic drug. These drugs include but are not limited to SGLT-2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 receptor agonists, thiazolidinediones, and sulfonylureas[5,6]. Finally, patients whose glycaemia remains poorly controlled after receiving maximum non-insulin antihyperglycaemic therapy will typically be prescribed insulin. Consequently, patients using insulin are at later stages of their disease, are older, and have more comorbidities[13,102-105] than patients with type 2 diabetes not using insulin.

Figure 2.3: American Diabetes Association 2020 clinical practice recommendations for pharmacological approaches to glycaemic treatment

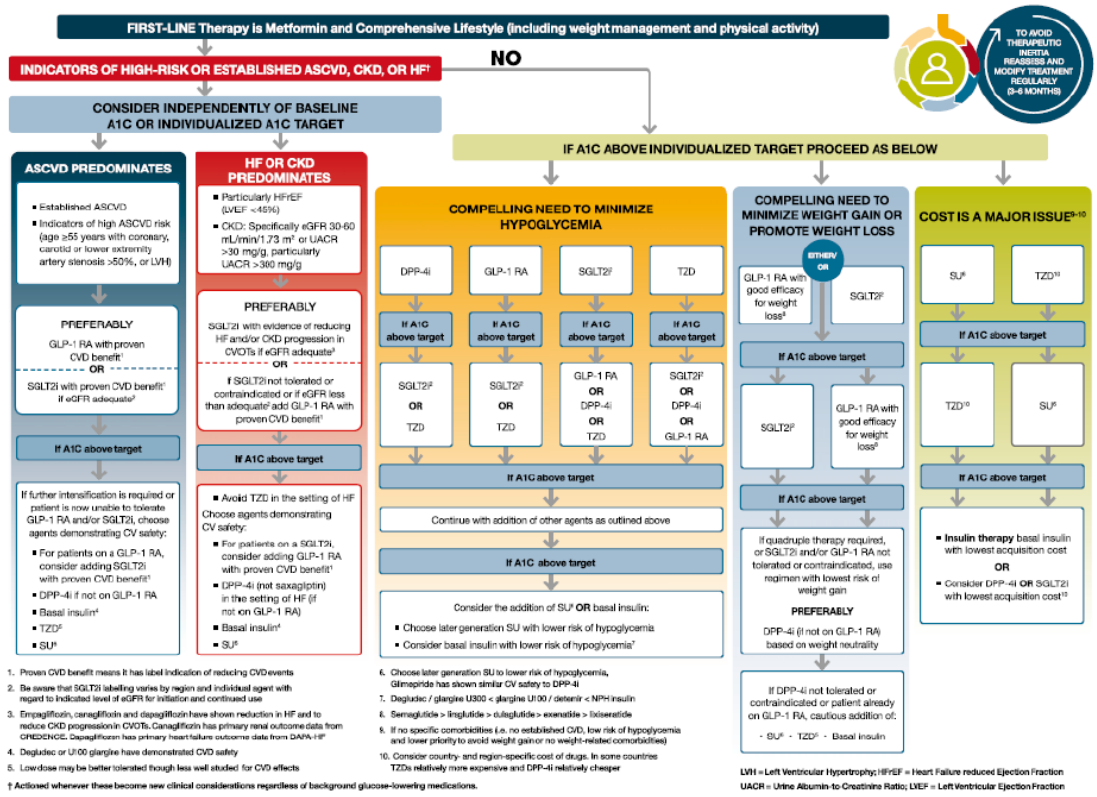


Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Source: American Diabetes Association. Addendum. 9. Pharmacologic approaches to glycaemic treatment: standards of medical care in diabetes-2020. Diabetes Care 2020;43(Suppl. 1):S98-S110.

2.9 Treatment with insulin analogues and human insulins

Basal insulins can be broadly classified into 2 categories: human insulin and insulin analogues (**Table 2.1**) [106,107]. Human insulin and insulin analogues may be further classified into rapid- (analogue: aspart, glulisine, lispro), short- (human: regular), intermediate- (human: NPH), long- (analogue: glargine, detemir), and ultra-long-acting (analogue: degludec). NPH insulin has been on the market since 1946 and is widely accepted as a safe and effective treatment to control hyperglycaemia[108]. It was added to the World Health Organization's (WHO) list of essential medicines in 1977 for the indication of type 1 and type 2 diabetes mellitus[109].

The differences between rapid-, short-, intermediate-, long-, and ultra-long acting insulins reside in the peak and duration of their action in the bloodstream[107,110]. Rapid- and short-acting insulins are used immediately before meals to control the glucose peak that will result from meal ingestion, triggering a quicker and stronger glucose absorption by skeletal muscles and other tissues. In contrast, intermediate and long-acting insulins maintain a constant level of insulin in the body, inducing gradual glucose absorption. Both human and analogue insulins function similarly, binding to α and β sub-units of insulin receptors present in the cells of skeletal muscles and other target tissues[38,111,112], ultimately resulting in glucose absorption in the cells of the body.

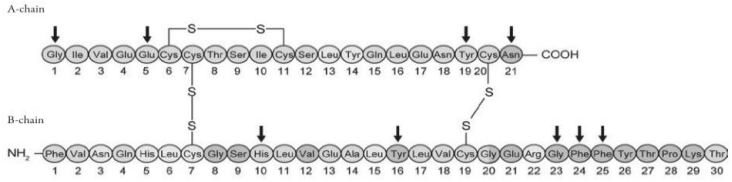
***Table 2.1**: Insulin types and timing of onset, peak and duration*

Insulin type [trade name]	**Onset**	**Peak**	**Duration**
Bolus (preprandial or mealtime) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart [NovoRapid ®] • Insulin glulisine [Apidra ®] • Insulin lispro [Humalog ®] U-100, U-200 • Faster-acting insulin aspart [Fiasp ®]	 9-20 min 10-15 min 10-15 min 4 min	 1-1.5h 1-1.5h 1-2h 0.5-1.5h	 3-5h 3.5-5h 3-4.75h 3-5h
Short-acting insulins (clear) • Insulin regular [Humulin ®-R, Novolin ® ge Toronto] • Insulin regular [Entuzity ®] U-500	 30 min 15 min	 2-3h 4-8h	 6.5h 17-24h
Basal insulins			
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn [Humulin ® -N, Novolin ® ge NPH]	1-3h	5-8h	up to 18h
Long-acting insulin analogues • Insulin detemir [Levemir ®] • Insulin glargine [Lantus ®] U-100 • Insulin glargine [Toujeo ®] U-300 • Insulin glargine biosimilar [Basaglar ®] • Degludec [Tresiba ®] U-100, U-200	90 min	N/A	 16-24h 24h >30h 42h
Premixed insulins			
Premixed regular insulin – NPH (cloudy) • Humulin ® 30/70 • Novolin ® ge 30/70, 40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart [NovoMix ® 30] • Insulin lispro/ lispro protamine [Humalog ® Mix25 and Mix50)	% of rapid-acting or short-acting insulin to % of intermediate-acting insulin		
Source: Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Booth G, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. Can J Diabetes 2018;42 Suppl 1:S88-S103.			

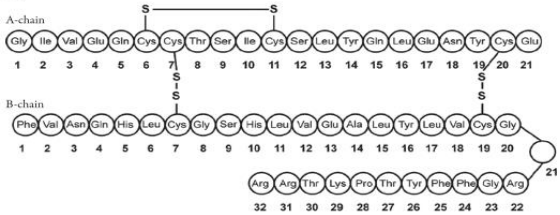
European[99], American[6], and Canadian[5] guidelines recommend treating patients with type 2 diabetes needing constant insulin control with either human NPH insulin or long- or ultra-long-acting insulin analogues[5,99]. These insulins are molecularly similar to human insulin[113] (***Figure 2.4***), and they thus exert their glucose lowering effects through similar mechanisms. As depicted in ***Figure 2.5***, NPH insulin begins to exert its effects in 1-3 hours (onset) and peaks between 5-8 hours, with a total duration of action of up to 18 hours[110,113]. In contrast, long-acting insulin analogues do not have a peak and present longer time-action profiles: glargine can last up to 24-32 hours (depending on insulin concentration), while detemir can last up to 24 hours and degludec up to 42 hours[110].

Figure 2.4*:* Molecular structure of human insulin, glargine, detemir and degludec

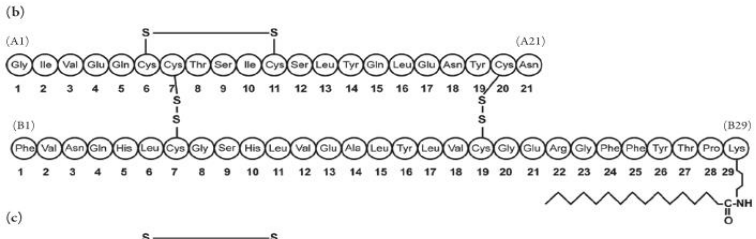
Human insulin



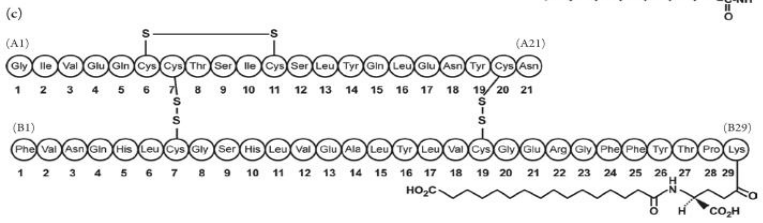
Glargine



Detemir



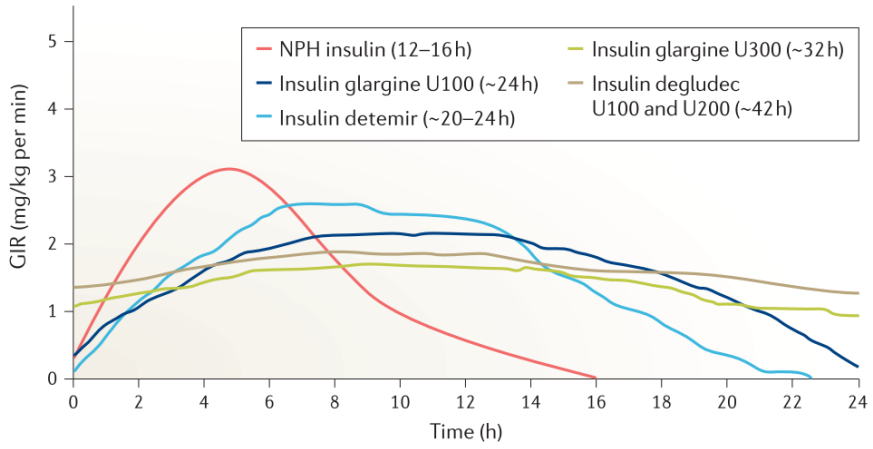
Degludec



Source: Tibaldi JM. Evolution of insulin development: focus on key parameters. Adv Ther 2012;29:590-619.

Substantial differences in price exist between long-acting insulin analogues and NPH. For instance, the Canadian Agency for Drugs and Technologies in Health (CADTH) estimates that degludec costs $7.19/day while NPH insulin costs $4.68/day[114,115]. With approximately 2.3 million Canadians diagnosed with diabetes and a prevalence of insulin use among those with type 2 diabetes of 7.4%[116], use of insulin degludec rather than NPH insulin would cost an additional ~$132 million per year in Canada.

***Figure 2.5**: Pharmacodynamic action profiles of intermediate and long-acting insulin analogues*



GIR: Glucose infusion rate
Source: Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nature Reviews Endocrinology 2017;13:385.

2.10 Adverse events of treatment with insulin: hypoglycaemia

Hypoglycaemia is a well-established adverse event of treatment with insulin[117,118]. It is characterized by abnormally low serum glucose levels, and severe hypoglycaemia can lead to serious consequences such as seizures, coma, and death[117,119-123]. It is often defined by clinical symptoms; for instance, the ADA and the EASD define severe hypoglycaemia as one that requires the assistance of another person for its treatment[124]. Diabetes Canada states that severe

hypoglycaemia typically occurs with plasma glucose values < 2.8 mmol/l, although they recommend not enforcing this as an absolute cut-off and leaving room for interpretation and clinical judgment[27]. Studies have reported that the incidence rate of severe hypoglycaemia requiring a hospitalization is between 150-200 hospitalizations for 10,000 person-years[125] among working-age patients with type 2 diabetes. Insulins are not the only treatment for type 2 diabetes to present greater risks of hypoglycaemia in patients with type 2 diabetes; studies have reported increased risks of hypoglycaemia with sulfonylureas as well[126]. In addition to its adverse effects on patient health, hypoglycaemia has substantial economic consequences: the total direct medical cost of hypoglycaemia in the US population was estimated at 1.84 billion USD in 2009[127].

2.11 Link between hypoglycaemia and cardiovascular events

Hypoglycaemia can have long-term effects on the health of patients with type 2 diabetes, including an increased risk of cardiovascular events and cardiovascular mortality[128]. In a post-hoc analysis of the *Outcome Reduction with an Initial Glargine Intervention* (ORIGIN) trial, severe hypoglycaemia, which was defined as hypoglycaemia requiring assistance or with serum glucose ≤ 36 mg/dL, was associated with an increased risk of major adverse cardiovascular events (MACE, a composite endpoint of MI, ischaemic stroke, and cardiovascular death; HR: 1.58, 95% CI: 1.24, 2.02), all-cause mortality (HR: 1.74, 95% CI: 1.39, 2.19), cardiovascular death (HR: 1.71, 95% CI: 1.27, 2.30), and arrhythmic death (HR: 1.77, 95% CI: 1.17, 2.67)[129]. Conversely, non-severe hypoglycaemia, defined as symptoms confirmed by glucose ≤ 54 mg/dL, was not associated with any of these outcomes[129]. Secondary analyses of the risk of cardiovascular outcomes associated with hypoglycaemia were also conducted in the *Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patient with Type 2 Diabetes at High Risk of Cardiovascular Events* (DEVOTE) trial[130]. These analyses revealed an increased risk of all-cause mortality (HR:

2.51, 95% CI: 1.79, 3.50) and potential increase in MACE (HR: 1.38, 95% CI: 0.96, 1.96) in participants who experienced severe hypoglycaemia compared to those who did not[130]. Observational studies have also reported increased risks of cardiovascular outcomes in patients experiencing hypoglycaemia. In a meta-analysis of retrospective and prospective cohort studies, patients who experienced hypoglycaemia were twice as likely to suffer from cardiovascular outcomes (i.e., MI, ischaemic stroke, surgical intervention for vascular disease) compared to patients with type 2 diabetes who did not experience hypoglycaemia (HR: 2.05, 95% CI: 1.74, 2.42)[131]. The timing of hypoglycaemia also seems important, as the risk of cardiovascular events and all-cause mortality appears to be greatest shortly after the hypoglycaemic event[130,132]. In addition, hypoglycaemia at the time of MI has been reported a predictor of mortality[133].

The relationship between hypoglycaemia and cardiovascular outcomes may impact rates of cardiovascular events with different insulins, where insulins with a lower risk of hypoglycaemia may also display lower risks of cardiovascular events[134]. As hypoglycaemia can be seen as either a confounder or a mediator on the causal pathway between insulin use and cardiovascular outcomes[135], observational studies using methods that take this complex relationship into consideration are needed to better understand the effectiveness and safety profiles of these drugs.

3. Chapter 3: Literature review

3.1 Drug utilization studies of basal insulin

There is a vast body of literature on the utilization of antidiabetic agents in patients with type 2 diabetes. Although the discussion of the totality of this evidence goes beyond the scope of this literature review, I summarize studies that highlight trends in the use and prescribing of basal insulins in the context of the evolving availability of newer antidiabetic drugs and changing characteristics of patients with type 2 diabetes. In addition, I also describe the few studies that have assessed treatment switching and discontinuation in patients with type 2 diabetes using basal insulin.

Basal insulin in commonly used in patients with type 2 diabetes. More than 20% of patients with type 2 diabetes will eventually require treatment with insulin[7]. Patients using basal insulin are at an advanced stage of type 2 diabetes, as insulins are typically recommended for treatment when glycaemic control has failed with other glucose-lowering therapies. Recently, several new glucose lowering agents have entered the market, including SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists[13,15], and their availability has changed the prescribing patterns of antidiabetic drugs (including insulin). Prescribing patterns have also been affected by the changing characteristics of patients with type 2 diabetes (e.g., younger age at diagnosis, increased obesity), especially for those drugs that also have weight loss benefits such as GLP-1 receptor agonists[136] and SGLT-2 inhibitors[137]. Finally, safety concerns with thiazolidinediones reported in 2008[10,11] also had an impact on the utilization of antidiabetic agents.

Several previous studies have examined the utilization of all insulins (basal and short-acting combined) among patients with type 2 diabetes. A study evaluating the use of insulin in type 2 diabetes using NHANES in the US reported a prevalence of insulin use of 29.1% (95% CI: 26.7,

31.5) among patients with type 2 diabetes during the 2005-2012 cycle[138]. In the UK, the crude prevalence of insulin use among patients with type 2 diabetes increased from 0.67 (95% CI: 0.64, 0.70) to 4.34 (95% CI: 4.29, 4.39) per 1000 population between 1991 and 2010[103]. In the US, one study reported an increased use of insulin from 23.0% to 31.0% among individuals with diabetes (both type 1 and type 2) between 2008 and 2015[139]. Wilkinson et al. evaluated the rates of antidiabetic drug treatment initiation in the UK among patients with type 2 diabetes from 2000 to 2017 and reported that 2% of all initiators of antidiabetic drugs did so on insulin monotherapy and 5% on dual insulin-metformin combination therapy[13]. Although most studies on insulin utilization in type 2 diabetes report increased rates of use with time[140], one study based on self-reported insulin use in US adults with type 2 diabetes reported decreased age-standardized proportions of insulin use, from 36% in 1995 to 22% in 2007[141]. Use of insulin also differs in different populations, where insulin use seems to be greater in patients with impaired renal function than in patients with normal renal function[142], which might reflect contraindications of other antihyperglycaemic agents in patients with impaired renal function.

Relatively sparse data are available on the utilization of different insulin classes such as long-acting insulin analogues and NPH. Lipska et al. reported a 65% decrease in NPH insulin use and a 55% increase in the use of insulin analogues among patients with type 2 diabetes in the US from 2000 to 2010[14]. Importantly, the data used in this study are now over 10 years old and did not include degludec, which had not yet entered the market. A study of trends in ambulatory insulin use in the US found that long-acting insulins accounted for two thirds of all physician/patient encounters where treatment was the primary reason for the visit from 2009 to 2020 in patients with type 2 diabetes[143]. However, the authors considered that each insulin use as a separate encounter. Thus, a patient that is prescribed two types of insulin in one encounter will be counted as 2 insulin

encounters, which renders these results difficult to interpret, as the number of physician/patient encounters for insulin does not reflect the number of insulin prescriptions. Idris et al. assessed the trends in high-dose insulin use (>200 units per day) among patients with type 1 and type 2 diabetes in the UK between 2009 and 2013 and found that 83.7% of patients with type 2 diabetes initiating insulin did so with a high-dose insulin analogue[144]. However, this study did not report overall long-acting insulin and NPH insulin use trends, and only reported on insulin initiators; thus, trends in all users of antidiabetic drugs were not evaluated.

Few studies have evaluated switching and discontinuation between NPH insulin and long-acting insulins. Patrick et al. reported that 27% of patients with type 2 diabetes who initiated insulin discontinued their treatment within 90 days of initiation, although their definition of discontinuation is unclear, and their data only covered the period from 2003 to 2008[145]. Wei et al. created two separate cohorts of patients initiating treatment on glargine, and one cohort of patients initiating treatment on detemir. They found that the patients in the glargine initiator cohort were less likely to switch to detemir in both cohorts (41 - 44.5%, $p < 0.0002$), and that those in the detemir initiator cohort were more likely to switch to glargine (52.9%, $p=0.14$)[146]. However, this study did not report on switching from NPH or degludec[146]. One meta-analysis of RCTs, which included 28 RCTs totalling 12,669 patients, reported a 60% reduced risk of adverse events leading to treatment discontinuation for glargine compared to detemir (RR: 0.40, 95% CI: 0.24, 0.69)[147]. However, as this meta-analysis only included RCTs, the generalizability of this study is unclear due to the highly selected patients and greatly protocolized care of RCTs. Given the limitations of this existing literature and that switching and discontinuation of insulin treatment may reflect non-adherence and poorly controlled glycaemia, increasing the risk of diabetes complications[148,149],

there remains a need for additional studies on the prescribing patterns and switching in patients using human insulin or insulin analogues in patients with type 2 diabetes.

3.2 RCTs on the efficacy of long-acting insulin analogues and human NPH insulin

RCTs and subsequent meta-analyses have demonstrated that long-acting insulins and NPH insulin have comparable efficacy in terms of HbA1c control among patients with type 2 diabetes[16,150]. A meta-analysis of RCTs comparing the efficacy of insulin glargine and NPH insulin reported similar proportions of patients who reached target HbA1c levels (30.8% and 32.1%, respectively)[18]. A subsequent Cochrane review and meta-analysis of RCTs, which included 6 trials with a duration of at least 24 weeks, also reported similar glycaemic control with long-acting insulin analogues and NPH insulin[19], finding a similar mean difference for change in HbA1c for glargine vs NPH (mean difference (%): -0.00 , 95% CI: -0.10, 0.09) and for detemir vs NPH (mean difference (%): 0.15, 95% CI: -0.02, 0.32). Another meta-analysis of RCTs by Monami et al., which included 14 trials with durations of at least 12 weeks, also suggested that glycaemic control was similar for glargine and NPH but found that NPH resulted in a greater reduction in HbA1c than detemir (0.1%, 95% CI 0.0%, 0.2%) [151]. In a network meta-analysis that included 57 trials, indirect comparisons between glargine U300, glargine U100, detemir, and degludec also did not reveal important differences in glycaemic control between long-acting insulin analogues at 24 weeks[152]. However, they reported better glycaemic control for detemir compared to glargine U100 at 52 weeks (weighted mean difference 0.11%, 95% CI: 0.00%, 0.22%)[152].

The overarching objective of controlling one's serum glucose is to prevent diabetes complications, including MACE[85]. However, clinical trials conducted to obtain regulatory approval are designed to evaluate the efficacy of antidiabetic drugs at reducing serum glucose levels only. Surprisingly, few RCTs have evaluated the efficacy of insulin therapy at reducing the

risk of cardiovascular outcomes. The UK Prospective Diabetes Study (UKPDS) randomized 3867 newly diagnosed patients with type 2 diabetes to intensive treatment, which included insulin or sulfonylureas, or to standard treatment, which included diet and metformin if the patient was overweight. This trial found a reduced risk of MI among patients randomized to the intensive treatment arm over a 10-year follow-up period (HR: 0.84, 95% CI: 0.71, 1.00)[153,154]. However, the UKPDS was carried out in the 1990s, which renders the applicability of its results to contemporary practice unclear given the availability of newer long-acting insulin analogues and changes in standard of care since this time. The ORIGIN trial evaluated the cardiovascular safety of long-acting insulins (glargine) compared to standard of care (diet therapy, sulfonylurea, or metformin if the patient was obese, or non-glargine insulin). This trial, which included 12,500 patients and had a mean follow-up duration of 6.2 years, found no difference between both groups for MACE (HR 1.02, 95% CI: 0.94, 1.11)[155]. However, the ORIGIN trial included patients diagnosed with pre-diabetes only,[155] and the standard of care included treatments that are not used at the same point in the management of type 2 diabetes. The DEVOTE trial evaluated the cardiovascular safety of degludec versus glargine U100 among 7,637 patients with type 2 diabetes, of which 85% had established cardiovascular disease[21]. After a median follow-up of 1.99 years, degludec was found to be non-inferior to glargine U100 with respect to MACE among patients with type 2 diabetes (8.5% vs 9.3%, HR: 0.91, 95% CI: 0.78, 1.06), with a non-inferiority margin of 1.3. In secondary outcomes, degludec was found to be non-inferior to glargine U100 for the risk of death from any cause (5.3% vs 5.8%, HR: 0.91, 95% CI: 0.76, 1.11), cardiovascular death (3.6% vs 3.7%, HR: 0.96, 95% CI: 0.76, 1.21), non-fatal MI (3.8% vs 4.4%, HR: 0.85, 95% CI: 0.68, 1.06), and non-fatal stroke (1.9% vs 2.1%, HR: 0.90, 95% CI: 0.65, 1.23)[21].

Although the UKPDS, ORIGIN, and DEVOTE provide important information on the cardiovascular risk of long-acting insulin analogues and NPH, these trials were conducted in highly selected patient populations that may not represent the patients seen in routine clinical practice[156]. In addition, evidence suggests that a minority of patients seen in everyday clinical practice meet the inclusion criteria of cardiovascular outcome trials of antidiabetic medications[22]. As evidence from RCTs has limited generalizability to everyday clinical practice, there is a need for real-world evidence for the risk of MACE with long-acting insulins compared to NPH insulin.

3.3 Observational studies on the effectiveness of long-acting insulin analogues and NPH insulin

To date, four observational studies have compared the effectiveness of long-acting insulins and NPH insulin, and these studies provided mixed results (**Table 3.1**)[25,157]. Rhoads et al. compared the risk of MI with NPH insulin vs glargine using administrative data from the US in a cohort of 20,191 patients with type 2 diabetes using either NPH or glargine[23]. The authors reported that NPH was associated with an increased risk of MI (HR 1.39, 95% CI: 1.14, 1.81) compared to glargine[23]. However, the authors imposed a minimum duration of insurance coverage of 1 year during follow-up, which may have introduced immortal time bias as patients were, by definition, unable to experience the outcome during the first year of their follow-up[158,159]. Furthermore, this study had substantial bias due to misclassification of exposure due to the use of an intention-to-treat exposure definition and a follow-up duration of over 5 years. Although the authors reported analyses restricted to shorter follow-up times, the substantial treatment effects observed (e.g., odds ratio: 2.27 in analyses restricted to 1 month) underscore the potential presence of immortal time bias (although it typically biases downward, immortal time bias can bias the estimate in either direction in the presence of an active comparator).

Cammarota et al. also compared the risk of macrovascular complications, with insulin glargine versus basal human insulins in a cohort of 1,921 patients using administrative data from local health authorities in Italy[24]. Their composite outcome of macrovascular complications included ischaemic heart disease, MI, arrhythmia, heart failure, atherosclerosis, peripheral vascular disease, and lower limb complications. The authors found that glargine was associated with a reduced risk of macrovascular complications (HR 0.61, 95% CI: 0.44, 0.84). However, the authors required users in the glargine group to use it throughout follow-up, likely inducing immortal time bias, as users in the comparator group did not have the same requirement. In addition, the authors did not exclude prevalent users and thus may have been affected by prevalent user bias[160].

Strandberg et al. conducted a retrospective cohort study using administrative data from Finland comparing glargine and NPH insulin in 23,751 individuals aged 40+ years with type 2 diabetes[25]. The authors reported reduced risks of all-cause mortality among users of insulin glargine (HR 0.55, 95% CI: 0.44, 0.69) and detemir (HR 0.39, 95% CI: 0.30, 0.50) compared to users of NPH insulin. When comparing long-acting insulins amongst themselves, the authors reported that insulin detemir reduced the risk of all-cause mortality compared to insulin glargine (HR 0.71, 95% CI: 0.54, 0.93). In their propensity-matched sub-cohort, the authors found that both detemir (HR 0.42, 95% CI: 0.28, 0.61) and glargine (HR 0.65, 95% CI: 0.47, 0.91) were protective relative to NPH, with greater benefits with detemir than glargine (HR 0.64, 95% CI: 0.43, 0.95). However, as with other studies in this area, immortal time bias appears to be present and is a likely explanation for these large treatment effects. In addition, this study did not control for several important confounders that are associated with cardiovascular risk, such as use of other antidiabetic drugs (except for sulfonylureas), statins, antiplatelets, anticoagulants, and clinical measures such as obesity.

Most recently, Neugebauer et al. conducted a retrospective cohort study comparing the risk of mortality and cardiovascular events with long-acting insulins versus NPH insulin among 127,600 US patients with type 2 diabetes between 2000 and 2013[26]. Compared with the continuous use of NPH insulin, long-acting insulins were not associated with the risks of overall mortality (HR 1.15, 95% CI: 0.97, 1.34), cardiovascular mortality (HR 1.26, 95% CI: 0.86, 1.66), MI (HR 1.11, 95% CI: 0.77, 1.45), stroke (HR 1.30, 95% CI: 0.81, 1.78), or heart failure hospitalization (HR 0.93, 95% CI: 0.75, 1.11), although some estimates were accompanied by wide 95% CIs that included clinically important treatment effects. The study period ranged from 2000 to 2013 and thus did not include degludec and contained only a limited amount of detemir. In addition, with inclusion restricted to US patients with health insurance, the study population was not a representative of US patients with a lower socioeconomic status, which are disproportionately affected by type 2 diabetes[161] and its results therefore are of unclear generalizability. Thus, despite the increasing use of insulin among patients with type 2 diabetes and the high risk of cardiovascular events in this population, there is limited real-world evidence of the cardiovascular effects of long-acting insulins.

***Table 3.1**: Observational studies of long-acting insulins versus NPH insulin and the risk of adverse cardiovascular events among patients with type 2 diabetes.*

Study (year)	Design	Location	Sample size	Study period	Exposure	Comparator	Outcome	Adjusted HR	Main limitations
Rhoads (2009)	Retrospective cohort	USA	20,191	2001-2005	Glargine	NPH	MI	0.65 (0.55, 0.78)*	Immortal time bias
Cammarota (2014)	Retrospective cohort	Italy	1,921	2005	Glargine	Human	Macrovascular complications	0.61 (0.44, 0.84)	Immortal time bias, prevalent user bias
							Cardiovascular disease	0.68 (0.45, 1.02)	
							Cerebrovascular disease	0.51 (0.28, 0.94)	
Strandberg (2016)	Retrospective cohort	Finland	23,751	2006-2009	Detemir	NPH	All-cause mortality	0.39 (0.30, 0.50)	Immortal time bias, did not adjust for important confounders
							Cardiovascular death	0.42 (0.28, 0.61)	
					Glargine	NPH	All-cause mortality	0.55 (0.44, 0.69)	
							Cardiovascular death	0.65 (0.47, 0.91)	
Neugebauer (2020)	Retrospective cohort	USA	127,600	2000-2013	Long-acting insulins	Human	All-cause mortality	1.15 (0.97, 1.34)	Outdated, unclear generalizability, no degludec
							MI	1.11 (0.77, 1.45)	
							Stroke	1.30 (0.81, 1.78)	
							Cardiovascular death	1.26 (0.86, 1.66)	
							Heart failure hospitalization	0.93 (0.75, 1.11)	

Abbreviations: HR: hazard ratio; MI: myocardial infarction; USA: United States of America.
* The reference group in the published study was insulin glargine, and the reported estimate was a HR of 1.39 (95% CI: 1.14, 1.81). It has been inverted here to facilitate comparisons across studies.

3.3 RCTs on risk of hypoglycaemia of long-acting insulin analogues and NPH insulin

Several RCTs reported on the safety of long-acting insulins as compared to NPH insulin regarding hypoglycaemia risk[16,17,162-167], although most were not designed to assess this safety endpoint. A meta-analysis of individual patient data including 6 trials revealed a lower risk of severe nocturnal hypoglycaemia (odds ratio [OR] 0.44, 95% CI: 0.25, 0.76), and suggested a lower risk of daytime hypoglycaemia (OR 0.64, 95% CI: 0.39, 1.04) with insulin glargine vs NPH insulin[168]. In a separate meta-analysis including 14 RCTs, Monami et. al reported a decreased risk of nocturnal (OR: 0.46, 95% CI: 0.38, 0.55) and severe hypoglycaemia (OR: 0.69, 95% CI: 0.60, 0.80) with long-acting insulins vs NPH insulin. Similar results were reported in a Cochrane review that included 6 RCTs comparing glargine to NPH and 2 RCTs comparing detemir to NPH[19]. In a systematic review and meta-analysis that included 67 RCTs, Pontiroli et al. reported similar glycaemic control with detemir and glargine vs comparators (which included other insulin as well as other antidiabetic treatments) but lower risks of hypoglycaemia with detemir (OR: 0.46, 95% CI: 0.35, 0.60) and glargine (OR: 0.76, 95% CI: 0.65, 0.88) than comparators[169].

RCTs have compared the risk of hypoglycaemia between long-acting insulin analogues[170,171]. Swinnen et al. reported rates of severe hypoglycaemia with determir (0.16 ± 1.42 events per person-year) and glargine (0.08 ± 0.63 events per person-year)[172]. In the DEVOTE trial, a reduced risk of severe hypoglycaemia was reported for degludec compared to glargine (RR: 0.60, 95% CI: 0.48, 0.76)[21]. Wysham et al. also reported a reduced risk of severe symptomatic hypoglycaemia (an episode requiring third party assistance or where blood glucose was <56 mg/dL) with degludec compared to glargine (RR: 0.70, 95% CI: 0.61, 0.80)[173]. In contrast, Zinman et al. reported decreased rates of hypoglycaemia for degludec compared to glargine (RR: 0.82, 95% CI: 0.64, 1.04). In a meta-analysis of seven phase 3a RCTs, Russel-Jones et al. reported lower risks of

hypoglycaemia with degludec than with glargine (RR: 0.62, 95% CI: 0.49, 0.78). However, the highly selected patient populations of these trials limit their generalizability and interpretability to a real-world setting[22].

3.4 Observational studies on the risk of hypoglycaemia of long-acting insulin analogues and NPH

Observational studies evaluating the risk of hypoglycaemia of long-acting insulins compared to NPH insulin also provided mixed results (**Table 3.2**). Wang et al. conducted a retrospective cohort study on the risk of hypoglycaemia with glargine and NPH using US MarketScan data and found similar rates of hypoglycaemia between the two groups (both 4.4%, p=1.0)[30]. However, the authors only conducted descriptive and crude analyses, and they did not conduct adjusted analyses, only compared proportions between glargine and NPH for the risk of hypoglycaemia. In addition, only 24 hypoglycaemic events occurred during the study period, which ranged from 2003 to 2009, making the study difficult to generalize to current practice. Tentolouris et al. also found similar rates of severe hypoglycaemia between glargine and NPH in a retrospective cohort study which included 301 patients (0.007 episodes per month for NPH vs 0.002 episodes per month for glargine, p=0.83)[174]. Due to their limited sample size and the absence of adjustment for confounders, these results are difficult to interpret. In contrast, Solomon et al. reported an increased risk of severe hypoglycaemia with NPH insulin vs glargine (HR: 2.02, 95% CI: 1.25, 3.26), but not detemir (HR: 1.20, 95% CI: 0.71, 1.78)[29]. However, exposure definitions differed in patients with and without hypoglycaemia: patients with hypoglycaemia were classified into the exposure category corresponding to the type of insulin they used most recently, while patients who did not experience hypoglycaemia were classified according to the insulin type that they cumulatively used the most. Thus, important bias was introduced with this differential exposure definition. In addition, this study did not adjust for HbA1c or duration of treated diabetes. Rhoads et. al[23] and Cammarota et

al. [24] reported lower rates of hypoglycaemia for glargine compared to NPH insulin, but were affected by immortal time bias (as described in Section 3.2). In contrast, Strandberg et al. did not find a reduced risk of severe hypoglycaemia with glargine versus NPH insulin (HR: 0.92, 95% CI: 0.74, 1.15) , but did find a reduced risk with detemir versus NPH (HR 0.70, 95% CI: 0.51, 0.94)[175] and detemir versus glargine (HR 0.76, 95% CI: 0.58, 0.99). Lipska et al. conducted a retrospective cohort study with propensity score matching and found no difference in hypoglycaemia risk between long-acting insulins and NPH insulin (HR 1.16, 95% CI:0.71, 1.78)[176]. However, this study did not include degludec and was unable to rule out a 78% increased risk of hypoglycaemia due to imprecise confidence intervals. In an uncontrolled retrospective cohort, Pfohl et al. reported low rates of confirmed symptomatic hypoglycaemia with the use of glargine (0.03, 95% CI: 0.02, 0.04 per person-year), but these rates were not compared with the rates of hypoglycaemia with other insulin, which makes these results difficult to interpret[32]. Finally, Bradley et al. conducted a retrospective new-user cohort study comparing the risk of severe hypoglycaemia with glargine, detemir, and NPH among 575,008 people with type 2 diabetes in the US between 2007 and 2019[33]. The authors found a reduced risk of hypoglycaemia with the use of glargine (HR: 0.71, 95% CI: 0.63, 0.80) and detemir (0.72, 95% CI: 0.63, 0.82) compared to NPH. However, this study had a very limited follow up duration (median: 0.37 years, interquartile range: 0.20, 0.76 years) and was conducted using Medicare data, which only include patients aged 65 years or older. In addition, it did not address time-varying confounding. Given the conflicting results of these studies, there is no consensus for the risk of hypoglycaemia for NPH insulin and long-acting insulin analogues in observational studies.

***Table 3.2**: Observational studies of long-acting insulins versus NPH insulin and the risk of hypoglycaemia*

Study (year)	Design	Location	Sample size	Study period	Exposure	Comparator	Outcome	Estimate	Main limitations
Wang (2013)	Retrospective cohort	US	534	2003-2009	Glargine	NPH	Hypoglycaemia	4.4% vs 4.4%	Crude analysis, total of 24 hypoglycaemic events only, outdated
Tentolouris (2013)	Retrospective cohort	Greece	301	Not reported	Glargine	Human	Number of mild/moderate episodes of hypoglycaemia per month Number of nocturnal episodes of hypoglycaemia per month Number of serious episodes of hypoglycaemia per month	0.71 vs 0.76 (p=0.93) 0.05 vs 0.08 (p=0.96) 0.007 vs 0.017 (p=0.833)	Crude analysis, limited sample size
Solomon (2013)	Retrospective cohort	US	8,626	1997-2009	Glargine Detemir	NPH Glargine	Severe hypoglycaemia	0.45 (0.28, 0.74)* 1.11 (0.40, 3.08)	Different exposure definitions among patients with and without hypoglycaemic events
Rhoads (2009)	Retrospective cohort	US	20,191	2001-2005	Glargine	NPH	Hypoglycaemia	0.85 (p=0.004)**	Immortal time bias
Cammarota (2014)	Retrospective cohort	Italy	1,921	2005	Glargine	Human	Hypoglycaemia	0.47 (0.16, 1.40)	Immortal time bias
Strandberg (2017)	Retrospective cohort study	Finland	16,985	2006-2009	Glargine Detemir	NPH	Severe hypoglycaemia	0.92 (0.74, 1.15) 0.70 (0.51, 0.94)	Non-diabetic coma included

									in outcome, outdated
Lipska (2018)	Propensity-matched retrospective cohort	US	4,428	2006-2015	Long-acting insulin	NPH	Hypoglycaemia-related emergency department visit	1.16 (0.71, 1.78)	Did not include degludec, wide CIs
Pfohl (2020)	Uncontrolled retrospective cohort	Germany and Switzerland	1,153	2015-2017	Glargine	-	Symptomatic hypoglycaemia within 12 months of initiation Confirmed symptomatic hypoglycaemia within 12 months of initiation Nocturnal hypoglycaemia within 12 months of initiation	0.04 (0.03, 0.06) per person-year 0.03 (0.02, 0.04) per person-year 0.01 (0.00, 0.02) per person-year	No comparison group
Bradley (2021)	Retrospective new-user cohort study	US	575,008	2007-2019	Glargine Detemir	NPH NPH	First emergency department visit or hospitalization for hypoglycaemia	0.71 (0.63, 0.80) 0.72 (0.63, 0.82)	Did not address time-varying confounding, only included patients above 65 years of age

Abbreviations: HR: hazard ratio; USA: United States of America
* The reference group in the published study was insulin glargine, and the reported estimate was a HR of 2.02 (95% CI: 1.25, 3.26). It has been inverted here to facilitate comparisons across studies.
** The reference group in the published study was insulin glargine, and the reported estimate was an odds ratio of 1.18. It has been inverted here to facilitate comparisons across studies.

In summary, previous studies on insulin utilization either did not differentiate between insulin classes, did not evaluate treatment switching rates between these classes, or are outdated. Efficacy on glycaemic control has been shown to be similar between long-acting insulins and NPH insulin in RCTs, but very few RCTs have examined their efficacy in terms of prevention of cardiovascular events. In addition, inferences made on these highly selected patient populations provide limited information regarding the real-world effectiveness regarding the prevention of cardiovascular outcomes associated with these medications among patients seen in actual clinical practice. Observational studies evaluating the effectiveness of these medications in routine practice had several important limitations related to study design and analysis. Available evidence is also inconclusive regarding the risk of hypoglycaemia of these insulins; both RCTs and observational studies provided mixed results. In addition, none of the previous studies addressed time-varying confounding. Methodologically rigorous observational studies with sufficient sample size are needed to accurately evaluate the utilization and the real-world effectiveness and safety of long-acting insulins in comparison to NPH insulin.

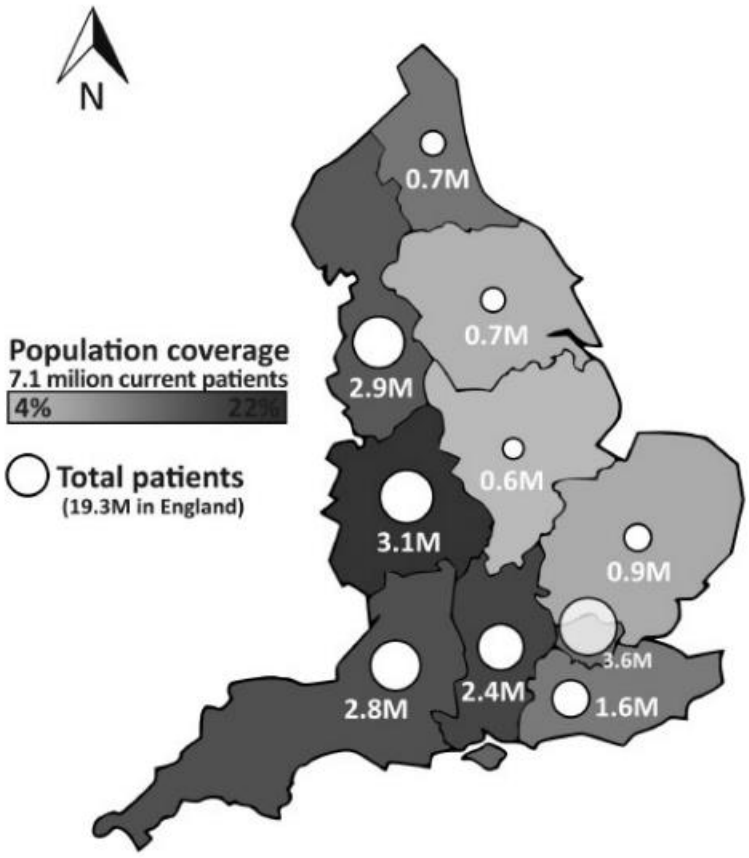
4. Chapter 4: Data Sources and Thesis Methods

4.1 Data sources

4.1.1 Overview of the Clinical Practice Research Datalink Aurum

The data source for this thesis is the Clinical Practice Research Datalink (CPRD) Aurum It contains routinely collected information such as diagnoses, prescription information, referrals, and tests from primary care practices in the UK. The CPRD Aurum was launched in 2017, which was added as a parallel database to the CPRD Gold. CPRD Gold has been in place since 2012, when it replaced the General Practice Research Database (GPRD) that was established in 1987[177,178]. The CPRD Aurum and Gold differ mainly by the software used by the practices to collect patient information. As of September 2018, 19 million patients from 738 general practices (10% of English practices) are included in the CPRD Aurum, of which 7 million were alive, representing 13% of the population of England[178]. Citizens of the UK have access to free healthcare with the National Health Service (NHS), and 98% of the population are registered with a primary care general practitioner[177]. General practitioners are the primary point of contact for non-emergency health conditions and refer patients to secondary care when needed, making them the "gatekeepers" of the healthcare system. A unique NHS number is assigned to each patient, and this number is used across the NHS databases[177]. The population included in the CPRD is representative of the general population in the UK, both in terms of geographical location (**Figure 4.1**) and in terms of age and sex (**Figure 4.2**).

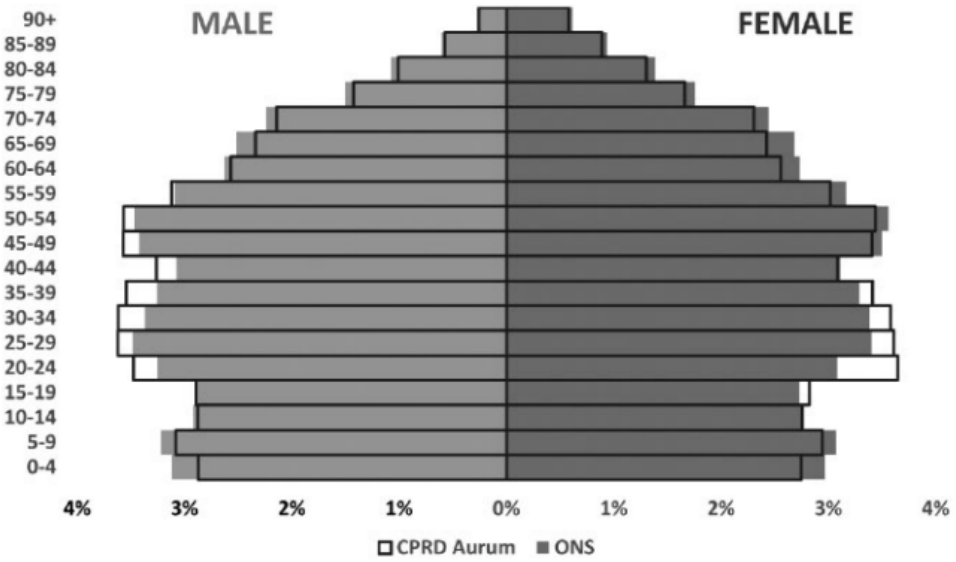
Figure 4.1: Geographical coverage of the CPRD Aurum as of September 2018



Source: Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol 2019;48:1740-g.

Note: circles represent total patients in CPRD Aurum in each region. Shading represents population coverage of current patients as a proportion of total regional population.

Figure 4.2: Population pyramids for CPRD Aurum and ONS data, based on mid-2017 data



Source: Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol 2019;48:1740-g.

Data are collected from primary care practices that agree to contribute to the CPRD. When practices consent to share information, the CPRD receives the full history of the practices' electronic health records, including information on deceased patients and those who are no longer registered with that practice. Individuals can opt-out of sharing their patient information, and approximately 2.7% have done so as of September 1st, 2018[178]. De-identified data are collected on a daily basis by practice staff and processed to create monthly data "cuts" for observational research purposes[177]. Clinical diagnoses in the CPRD Aurum are captured using Snomed Clinical Terms (CT; UK edition) codes[179] and Read Version 2 codes[180]. Prescription information is recorded using the Dictionary of Medicines and Devices, which lies within the SNOMED CT terminological structure. Information on prescriptions includes product names and codes from the British National Formulary, days of supply, quantity, and dose. In addition, the CPRD contains information on lifestyle variables and clinical measurements that are typically not available in

other healthcare administrative databases, including BMI, smoking, systolic and diastolic blood pressure measurements, as well as laboratory measurements such as HbA1c and estimated glomerular filtration rate (eGFR)[178].

4.3.1 National Health Services (NHS) linked databases

Data from patients in the CPRD can be linked with other patient-level health data by NHS Digital using the NHS number, date of birth, sex, and patient residence postcode[181]. Linked data are available for approximately 93% of English practices contributing to CPRD Aurum from April 1st, 1997 onwards. For Objectives 2 and 3, we linked CPRD data to Hospital Episodes Statistics (HES) and Office for National statistics (ONS) data. HES Admitted Patient Care (APC) data include detailed records on all hospitalizations at English NHS Health care providers. Diagnoses are recorded in the HES using the International Classification of Disease 10th revision (ICD-10) codes, and procedures are recorded using the Office of Population Censuses and Surveys classification of interventions and procedures (OPCS) 4th revision.

ONS Death Registration data are considered the gold standard for vital statistics data in the UK and include information on the time, place, and cause of death[182]. Causes of death are recorded using ICD-9 (1979 to 2001) and ICD-10 (since 2001) codes. Up to 15 codes can be reported to take into account contributing and underlying causes of death.

The English Index of Multiple Deprivation (IMD; 2010 version) is a proxy for socioeconomic status[183]. The IMD ranks each small area (there are 32,844 small areas in England) at a population level based on 7 domains of deprivation including income, employment education, health, crime, barriers to housing and services and living environment. A lower score indicates greater deprivation and thus lower socioeconomic status[183]. These scores are attributed using the patient's postal code.

4.3.2 Data quality and validation

The CPRD Aurum provides quality assurance metrics in the form of a binary "acceptability" flag for patients. This metric is based on the internal consistency of important variables such as date of birth, practice registration date, and transfer out date[177].

Data in the CPRD Aurum have been validated by several sources. In a recent validation study using the CPRD Aurum, Read codes for type 2 diabetes were validated using laboratory and prescription drug data; the authors found a sensitivity of 99% and a specificity ranging from 94-98%[184]. Linkage between the CPRD Aurum, HES, and ONS has also been well validated. A recent study compared diagnoses of pulmonary embolism in the CPRD Aurum and HES and found 79% sensitivity for primary hospitalized pulmonary embolism events[185]. In addition, the linked population in CPRD Aurum was shown to be representative of the larger CPRD population in terms of age, sex, geographical distribution, and deprivation[178].

4.2 Thesis Methods

4.2.1 Study Population

We used CPRD Aurum data for Objective 1, and we used CPRD Aurum data linked with HES and ONS for Objectives 2 and 3. For Objective 1, we created 3 study cohorts. First, we created a cohort of individuals who received a prescription for a pharmacological treatment for type 2 diabetes among metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, human insulin (NPH and short acting), insulin analogues (rapid, long-acting) between January 1st, 2003 and December 31st, 2018. We initiated our cohort in 2003 to ensure that all included individuals had the opportunity to receive a long-acting insulin analogue, as the first long-acting insulin analogue glargine was added to the British National Formulary in September 2002[186]. We refer to this cohort as the all-user cohort as it included initiators and

prevalent users of antidiabetic drugs. Cohort entry was defined by their first eligible prescription for an antidiabetic drug after January 1st, 2003. Second, we created a cohort of initiators of antidiabetic drugs that included all patients with a first-ever prescription for an antidiabetic drug (listed above), with the date of cohort entry defined by the date of this first prescription. Third, we created a cohort of initiators of either long-acting insulin analogues (glargine [U100, U300], detemir, degludec) or NPH insulin between January 1st, 2003 and December 31st, 2018 (the product codes used for these definitions are reported in **Table 4.1**). The date of this first-ever basal insulin prescription defined entry into the insulin initiator cohort. Exclusion criteria applied to all 3 cohorts were: 1) age less than 18 years to ensure that we are only capturing adults with type 2 diabetes; 2) a database history of less than 365 days to adequately assess comorbidities and previous medication use; 3) a diagnosis of polycystic ovary syndrome at any time prior to cohort entry, as this is another indication for metformin[187]; 4) a diagnosis of gestational diabetes in the year before cohort entry to avoid including patients who used insulin or metformin for an indication other than type 2 diabetes; and 5) a diagnosis of type 1 diabetes, as it represents a different pathophysiology than type 2 diabetes[188].

For Objectives 2 and 3, we created cohorts of HES and ONS linkable patients who initiated treatment with basal insulin between September 1st, 2002, and November 30th, 2018. For these objectives, we restricted our cohorts to linkable patients as the outcomes were measured using hospitalization and vital statistics data. For both objectives, cohort entry was defined by the date of the first basal insulin prescription. As for Objective 1, we excluded patients who, at the time of their cohort entry defining prescription, were aged less than 18 years, had less than 1 year of recorded medical history, had a previous diagnosis of polycystic ovary syndrome (as these patients may also present insulin resistance[189] and are at elevated risks of cardiovascular outcomes[190-192]

and of hypoglycaemia[193]), or had a previous diagnosis of type 1 diabetes (any time) or a diagnosis of gestational diabetes (in the previous year). We also excluded patients at cohort entry who initiated two different insulins on the same day as concomitant treatment with two basal insulins is not recommended for type 2 diabetes[5].

4.2.2 Exposure Definitions

In Objective 1, we used an intention to treat (ITT) approach as the primary exposure definition for the outcome of insulin switching. In this approach, individuals were considered as exposed to their cohort entry defining insulin from their date of cohort entry until a first prescription for a different basal insulin type (a treatment switch) or censoring due to end of registration with the CPRD, death, or December 31st, 2018, whichever occurred first. In sensitivity analyses, we used an as-treated exposure definition in which patients were considered as exposed for the duration of the insulin prescription (typically 28-30 for antidiabetic drugs in the CPRD) + a 60-day grace period to take into account non-adherence.

For Objectives 2 and 3, we used a time-varying exposure definition. We defined prescription duration using days of supply of each prescription. A 30-day grace period was applied following the last day of each prescription during which the patient was still considered as exposed to the type of insulin that was previously prescribed. Follow-up time was divided in 30-day intervals. Each person-month of follow-up was classified into one of two mutually exclusive categories: 1) current use of long-acting insulin analogues (glargine, detemir, or degludec); or 2) current use of NPH insulin. Concomitant use of other antidiabetic drugs (listed above) was permitted in both exposure categories. Patients were censored upon treatment discontinuation or upon combination use of both long-acting insulin analogues and NPH (or upon combination use of multiple long-acting insulin analogues for molecule-specific analyses). Combination use was defined as a

prescription for two different types of insulin within the same 30-day interval. Discontinuation was defined by non-use of basal insulin in a person-month.

4.2.3 Outcome definition

For Objective 1, we assessed insulin switching as an outcome. Switching was defined with a prescription for a new insulin type that was not previously prescribed. The date of this new prescription defined the event date.

For Objective 2, we studied 6 outcomes, which were assessed separately in the analyses, with separate follow-up times estimated for each. These outcomes included MACE as our primary outcome, and MI, ischaemic stroke, cardiovascular death, hospitalization for heart failure, and all-cause mortality as secondary outcomes. We chose MACE as the primary outcome as this is the outcome that is used in FDA-mandated CVOTs of antidiabetic medications[91]. In previous validation studies of HES, diagnoses of MI were shown to have a positive predictive value of 91.5% (95% CI: 90.8, 92.1), diagnoses of stroke were shown to have negative predictive value and specificity of 100% (95% CI: 99, 100), and diagnoses of coronary heart disease were shown to have a negative predictive value and specificity of 96% (95% CI: 96, 96)[194,195]. For Objective 3, we assessed the outcome of hospitalization for hypoglycaemia. The ICD-10 codes for all outcomes are provided in **Table 4.2**. Diagnoses of hypoglycaemia have not been formally validated in HES but have been used in previous studies[126,196,197]. In both Objectives, the event date was defined as the date of hospital admission for HES-defined events and the date of death for ONS-defined events, and patients were followed until the outcome, death, end of registration with the CPRD, end of the study period (November 30th, 2018), or censoring due to concomitant insulin therapy or discontinuation, whichever occurred first.

4.2.4 Potential Confounders

We assessed several potential confounders for Objectives 1, 2, and 3, based on variables that were present in the database that were potentially associated with the exposure and were predictors of the outcome. These included demographic information (age, sex, ethnicity [Caucasian, other, missing], smoking status, Index of Multiple Deprivation quintile[198] [score from 1: least deprived to 5: most deprived, missing], comorbidities (duration of treated diabetes, previous history of alcohol-related disorders [alcoholism, cirrhosis, hepatitis, liver failure], atrial fibrillation, a previous diagnosis of cancer [other than non-melanoma skin cancer], chronic obstructive pulmonary disease, coronary artery disease, dyslipidaemia, hypertension, peripheral vascular disease, stroke, MI, coronary revascularization, acute kidney injury, chronic kidney disease, retinopathy, neuropathy, hypoglycaemia and dialysis, clinical measurements (BMI, HbA1c, SBP, DBP, eGFR), use of other antidiabetic drugs and use of other drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, statins, direct oral anticoagulants, antiplatelets, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], use of oral anticoagulants [vitamin K antagonists, direct-acting oral anticoagulants], and antiplatelets [clopidogrel, ticagrelor, prasugrel]). Clinical measurements were assessed using the latest measure in the year before cohort entry. Duration of treated diabetes was defined as the time between the first-ever prescription for an antidiabetic drug and cohort entry date.

For Objectives 2 and 3, age, diabetes duration, clinical measurements, comorbidities, and prescription drug use were assessed at baseline and in a time-varying manner. Details on the assessment windows and definitions are included in **Table 4.3**. In Objective 3, we measured the following additional covariates: dementia, and use of fibrates, opioids, and digoxin. Continuous

variables such as age, duration of treated diabetes and month of follow-up were modelled using restricted cubic splines with 5 knots, including 3 interior knots at the 25th, 50th and 75th percentiles, to reduce potential model misspecification that could arise with a linear model[199,200] and to decrease the variance of the estimator[201].

4.2.5 Construction of variable definitions

Variable definitions must be created for all the exposures, outcomes, and covariates from the CPRD Aurum. This database records patient information using the SnomedCT codes (diagnoses) the Product Codes (prescription information), which are very granular and thus can be grouped for wider disease and prescription definitions. For instance, the diagnosis of cancer, which was used as a covariate in our studies, can be expressed using 2,228 different SnomedCT codes in the CPRD Aurum according to different types of cancers and different terminologies. Similarly, our covariate of statin use was defined using 88 Product codes, which express the different types of statins as well as dosages. The definitions were constructed using the CPRD Aurum code browser, which allows users to search for codes based on clinical terms and descriptors for diagnoses and based on generic and brand names for drugs[202]. The definitions of exposures, outcomes, and important confounders were reviewed by Dr. Yu and other staff with clinical expertise.

***Table 4.1**: Product codes for basal insulins in the CPRD Aurum.*

Type of insulin	Product code	Description
Detemir	3137241000033111	Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
Detemir	3136941000033116	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
Detemir	3137041000033115	Insulin detemir 100units/ml solution for injection 3ml cartridges
Detemir	3137141000033116	Levemir Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
Detemir	4126541000033110	Levemir InnoLet 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
Glargine	2780841000033118	Lantus 100units/ml solution for injection 3ml cartridges (Sanofi)
Glargine	2798941000033111	Insulin glargine 100units/ml solution for injection 3ml cartridges
Glargine	2780941000033114	Lantus 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
Glargine	2799041000033119	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
Glargine	2798841000033115	Insulin glargine 100units/ml solution for injection 10ml vials
Glargine	2780741000033111	Lantus 100units/ml solution for injection 10ml vials (Sanofi)
Glargine	10600641000033118	Abasaglar 100units/ml solution for injection 3ml cartridges (Eli Lilly and Company Ltd)
Glargine	3869341000033114	Lantus 100units/ml solution for injection 3ml OptiClik cartridges (Sanofi)
Glargine	10600741000033110	Abasaglar KwikPen 100units/ml solution for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
Glargine	12686641000033112	Semglee 100units/ml solution for injection 3ml pre-filled pen (Mylan)
Glargine	4258541000033111	Lantus 100units/ml solution for injection 3ml pre-filled SoloStar pen (Sanofi)
Glargine	10494241000033110	Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices
Glargine	10494441000033111	Toujeo 300units/ml solution for injection 1.5ml pre-filled SoloStar pen (Sanofi)
NPH	724041000033112	Humulin I 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
NPH	2953241000033110	Insulatard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
NPH	779141000033111	Insulin isophane human 100units/ml suspension for injection 10ml vials
NPH	2035241000033118	Insuman Basal 100units/ml suspension for injection 5ml vials (Sanofi)
NPH	2035441000033117	Insuman Basal 100units/ml suspension for injection 3ml cartridges (Sanofi)
NPH	1615941000033113	Humulin I 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
NPH	2953341000033117	Insulatard Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	6389641000033111	Insuman Basal 100units/ml suspension for injection 3ml pre-filled SoloStar pen (Sanofi)
NPH	2953141000033115	Insulatard NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)

NPH	2644641000033113	Insulatard InnoLet 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
NPH	2796741000033112	Insulatard FlexPen 100units/ml suspension for injection (Novo Nordisk Ltd)
NPH	2266841000033110	Insuman Basal 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
NPH	2182441000033113	Humulin I Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
NPH	5911541000033119	Humulin I KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
NPH	2158541000033117	Insuman Comb 15 100units/ml suspension for injection 3ml cartridges (Sanofi)
NPH	2267041000033118	Insuman Comb 15 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
NPH	2158441000033118	Insuman Comb 15 100units/ml suspension for injection 5ml vials (Aventis Pharma)
NPH	2035641000033115	Insuman Comb 25 100units/ml suspension for injection 3ml cartridges (Sanofi)
NPH	2267141000033119	Insuman Comb 25 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
NPH	6011841000033112	Insuman Comb 25 100units/ml suspension for injection 3ml pre-filled SoloStar pen (Sanofi)
NPH	2035541000033116	Insuman Comb 25 100units/ml suspension for injection 5ml vials (Sanofi)
NPH	725341000033110	Humulin M3 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
NPH	1616341000033118	Humulin M3 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
NPH	727341000033117	HumaJect M3 Pen 100units/ml suspension for injection (Eli Lilly and Company Ltd)
NPH	5910741000033117	Humulin M3 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
NPH	2158741000033113	Insuman Comb 50 100units/ml suspension for injection 3ml cartridges (Sanofi)
NPH	2267241000033114	Insuman Comb 50 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
NPH	2158641000033116	Insuman Comb 50 100units/ml suspension for injection 5ml vials (Aventis Pharma)
NPH	1818141000033110	Human Mixtard 10 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	2953541000033112	Mixtard 10 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	2953441000033111	Mixtard 10 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
NPH	1818241000033115	Human Mixtard 20 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	2953741000033116	Mixtard 20 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	1616241000033111	Humulin M2 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
NPH	2953641000033113	Mixtard 20 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)

NPH	1818341000033113	Human Mixtard 30 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	2953941000033118	Mixtard 30 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
NPH	2954041000033116	Mixtard 30 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	2644741000033116	Mixtard 30 InnoLet 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
NPH	2953841000033114	Mixtard 30 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
NPH	3333841000033113	Humulin M3 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
NPH	1818441000033119	Human Mixtard 40 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	2954241000033112	Mixtard 40 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	2954141000033117	Mixtard 40 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
NPH	1818541000033118	Human Mixtard 50 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	722841000033112	Humulin M5 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
NPH	2954541000033114	Mixtard 50 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
NPH	2954341000033119	Mixtard 50 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
NPH	1714041000033116	Human Insulatard Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
NPH	779841000033117	Isophane Insulin Injection 100 units/ml
NPH	1621141000033118	Isophane Insulin (Human Pyr) Penfill Cartridges (1.5 Ml) 100 units/ml
NPH	1621341000033115	Isophane Insulin (Human Pyr) Preloaded pen 100 units/ml
NPH	779641000033118	Isophane Insulin Injection (Evans) Injection 100 units/ml
NPH	776041000033117	Isophane Insulin (Human, Prb) Cartridges 100 units/ml
NPH	1620641000033115	Isophane Insulin (Human Pyr) Injection 100 units/ml, 10 ml vial
NPH	1621241000033113	Isophane Insulin (Human Pyr) Penfill cartridges (3 ml) 100 units/ml
NPH	11493341000033110	Actraphane Hm (Ge) Suspension For Injection 100 units/ml, 10 ml vial
NPH	725041000033113	Human Actraphane(Nova) Injection
NPH	721341000033112	Human Protaphane Penfill Injection 100 units/ml
NPH	725641000033119	Human Protaphane Injection 100u/ml
NPH	727241000033110	Humaject (Humulin M2) Preloaded pen
NPH	727541000033112	Humaject (Humulin M5) Preloaded pen

NPH	719841000033112	Humulin I Cartridges (1.5 Ml) 100 units/ml
NPH	720141000033119	Humulin M3 (Lilly) Cartridges (1.5 Ml)
NPH	1616441000033112	Humulin M4 Cartridges (3 Ml)
NPH	720041000033118	Humulin M2 Cartridges (1.5 Ml)
NPH	724141000033111	Humulin M1 Injection
NPH	727441000033111	Humaject (Humulin M4) Preloaded pen
NPH	2868341000033113	Humulin 60/40 Injection 100 units/ml, 10 ml vial
NPH	719941000033116	Humulin M1 Cartridges (1.5 Ml)
NPH	724241000033116	Humulin M2 Injection
NPH	2868141000033110	Humulin 80/20 Injection 100 units/ml, 10 ml vial
NPH	727141000033115	Humaject (Humulin M1) Preloaded pen
NPH	1616141000033116	Humulin M1 Cartridges (3 Ml)
NPH	2867741000033110	Humulin N Injection 100 units/ml, 10 ml vial
NPH	721141000033114	Humulin M5 50/50 Cartridges
NPH	721541000033117	Humulin M3 (Lilly) Injection 100 units/ml, 10 ml v
NPH	725241000033117	Humulin M4 Injection
NPH	727641000033113	Humaject (Humulin I) Preloaded pen 100 units/ml
NPH	720241000033114	Humulin M4 Cartridges (1.5 Ml)
NPH	2868041000033111	Humulin 90/10 Injection 100 units/ml, 10 ml vial
NPH	720441000033110	Humulin M5 Cartridges (1.5 Ml)
NPH	2868241000033115	Humulin 70/30 Injection 100 units/ml, 10 ml vial
NPH	2868441000033119	Humulin 50/50 Injection 100 units/ml, 10 ml vial
NPH	721641000033116	Human Insulatard Ge Injection 100 units/ml
NPH	726641000033110	Human Insulatard Ge Penfill cartridges (3 ml) 100
NPH	726941000033115	Human Insulatard Ge Preloaded pen 100 units/ml
NPH	726141000033117	Human Mixtard 10 Penfill cartridges (3 ml)
NPH	726541000033114	Human Mixtard 50 Penfill cartridges (3 ml)
NPH	1062041000033112	Human Mixtard 50 Preloaded pen
NPH	2954441000033113	Mixtard 50 Injection 100 units/ml, 10 ml vial
NPH	1052941000033117	Human Mixtard 10 Injection
NPH	1053241000033119	Human Mixtard 50 Injection

NPH	1061941000033118	Human Mixtard 40 Preloaded pen
NPH	1053041000033110	Human Mixtard 20 Injection
NPH	1061641000033113	Human Mixtard 30 Preloaded pen
NPH	722941000033116	Human Mixtard 30 Ge Injection
NPH	726441000033113	Human Mixtard 40 Penfill cartridges (3 ml)
NPH	726341000033119	Human Mixtard 30 Penfill cartridges (3 ml)
NPH	1053141000033114	Human Mixtard 40 Injection
NPH	1061841000033114	Human Mixtard 20 Preloaded pen
NPH	1053541000033117	Human Mixtard 30 Injection (cartridges) 100 u/ml
NPH	1061741000033116	Human Mixtard 10 Preloaded pen
NPH	726041000033116	Human Mixtard 30 Injection 10 ml vial
NPH	726241000033112	Human Mixtard 20 Penfill cartridges (3 ml)
Degludec	8264341000033118	Insulin degludec 100units/ml solution for injection 3ml cartridges
Degludec	8264441000033112	Tresiba Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
Degludec	8264141000033116	Tresiba FlexTouch 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
Degludec	8263941000033117	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
Degludec	8264041000033115	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
Degludec	8264241000033111	Tresiba FlexTouch 200units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
Degludec	10044541000033113	Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices
Degludec	10044641000033114	Xultophy 100units/ml / 3.6mg/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)

***Table 4.2**: List of ICD-10 diagnostic codes used in HES and ONS for the outcomes of major adverse cardiovascular events and severe hypoglycaemia*

Study Outcome	ICD-10 code
MI	I21.x
Ischaemic stroke	I63.x, I64.x
Cardiovascular death	I00-I77.x, excluding I46.9
Hospitalization for heart failure	I50.x
Severe hypoglycaemia	E16.2

Abbreviation: MI: Myocardial infarction.

***Table 4.3**: List of covariates and assessment windows for Objectives 2 and 3*

Characteristic	**Description**	**Baseline lookback**	**Time varying assessment**	**IPTW**	**IPCW$_A$**	**IPCW$_B$**	**Outcome model**
Demographic							
Age	continuous and categorical: <40, 40-49.9, 50-59.9, 60-69.9, 70-79.9, ≥80	Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sex	women, men	N/A	N/A	yes	yes	yes	yes
Ethnicity	Caucasian, other, missing	N/A	N/A	yes	yes	yes	yes
Index of multiple deprivation quintile	1 (least deprived) to 5 (most deprived), missing	N/A	N/A	yes	yes	yes	yes
Duration of treated diabetes	Defined as time between the first prescription of antidiabetic drugs and cohort entry or month of follow-up	Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Smoking status	ever/never	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Clinical measurements							

Body mass index	kg/m^2 continuous and categorical: <25, 25-29.9, 30-34.9, 35-39.9, ≥40	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
HbA1c	% continuous and categorical: <6.5, 6.5-8, ≥8	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
eGFR	$ml/min/1.73m^2$ continuous and categorical: <60, ≥60	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Systolic blood pressure	mmHg continuous	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Diastolic blood pressure	mmHg continuous,	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Comorbidities							
Alcohol related disorders: alcoholism, cirrhosis, hepatitis, and liver failure	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only

Atrial fibrillation	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Cancer	other than non-melanoma skin cancer yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
COPD	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Coronary artery disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dyslipidaemia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypertension	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Peripheral vascular disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Stroke	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals, except where stroke or MACE is the outcome	yes*	yes	yes	yes, baseline only
Myocardial infarction	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals (except where MI or MACE is the outcome)	yes*	yes	yes	yes, baseline only
Coronary revascularization	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acute kidney injury	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Chronic kidney disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Retinopathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only

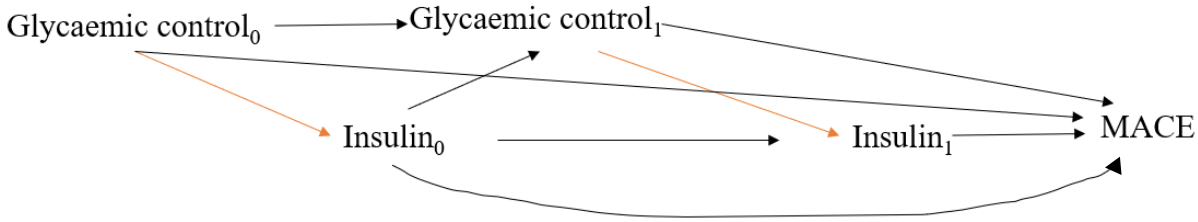
Neuropathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dialysis	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypoglycaemia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dementia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of antidiabetic drugs							
Metformin	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Sulfonylureas	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Thiazolidinediones	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
DPP-4 inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
SGLT-2 inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
GLP-1 receptor agonists	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Alpha-glucosidase inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Meglitinides	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Non-basal insulin	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Use of other drugs							
Angiotensin-converting enzyme inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Angiotensin II receptor blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only

Beta-blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Calcium channel blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Diuretics	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Oral anticoagulants	vitamin K antagonists, direct-acting oral anticoagulants yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Antiplatelets	clopidogrel, ticagrelor, prasugrel yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Statins	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Acetylsalicylic acid	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Nonsteroidal anti-inflammatory drugs	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Glucagon	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Fibrates	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Opioids	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only

Abbreviations: IPTW: Inverse probability of treatment weight, IPCW: Inverse probability of censoring weight, BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, COPD: chronic obstructive pulmonary disorder, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2

4.2.6 Marginal Structural Models

For Objectives 2 and 3, we constructed marginal structural models (MSM)[203] to estimate the marginal HRs and 95% CIs for the risk of adverse cardiovascular events (Objective 2) and severe hypoglycaemia (Objective 3) with the current use of long-acting insulin analogues versus the current use of NPH. MSMs are used to obtain unbiased estimates for associations where time-varying covariates that are risk factors for (or predictors of) the outcome and of subsequent exposure or in situations where past exposure history predicts the value of the covariate[204]. Type 2 diabetes is a lifelong progressive disease and as such, physicians typically modify treatment according to changing patient characteristic (time-varying confounders) that will affect future outcomes. The use of an MSM allowed us to overcome limitations in the existing literature. As explained in Section 2.11, glycaemic control is a risk factor for cardiovascular outcomes. In addition, it is also a predictor of future treatment as it may influence physicians' decisions to prescribe certain insulins. A visual representation of this association is depicted in the simplified directed acyclic graph (DAG) below.



A similar situation occurs for the outcome of hypoglycaemia in Objective 3. For instance, time-varying confounders such as other antidiabetic drug use can influence the choice of treatment by the physician[75,205], as well as the risk of the event (severe hypoglycaemia)[206]. The use of a MSM allows us to control for the association between the time-varying confounder and the treatment (orange arrow), if certain assumptions (described below) are met[204].

The parameters of the MSM were estimated using stabilized weights[203], using inverse probability of treatment weights (IPTW) and two inverse probability of censoring weights ($IPCW_A$ and $IPCW_B$) to account for right censoring. $IPCW_A$ was used to account for possible informative administrative censoring caused by death (by other causes than the outcome, other than for the outcome of all-cause mortality), end of registration with the CPRD, or end of the study period. $IPCW_B$ was used to account for potential informative censoring due to censoring related to our exposure definition (i.e., concomitant treatment with long-acting insulin analogues and NPH) or due to treatment discontinuation. The equations for the IPTW, $IPCW_A$, and $IPCW_B$ are as follows:

IPTW:

$$\prod_{k=0}^{t} \frac{pr[A(k) = a_i(k) | \overline{A}\,(k-1) = \overline{a}_i(k-1), V]}{pr[A(k) = a_i(k) | \overline{A}\,(k-1) = \overline{a}_i(k-1), L(k)]}$$

$IPCW_A$:

$$\prod_{k=0}^{t} \frac{pr[C_A(k+1) = 0 | \overline{C}_A\,(k) = 0, \overline{A}\,(k), V]}{pr[C_A(k+1) = 0 | \overline{C}_A(k) = 0, \overline{A}(k), \overline{L}(k)]}$$

$IPCW_B$:

$$\prod_{k=0}^{t} \frac{pr[C_B(k+1) = 0 | \overline{C}_B\,(k) = 0, \overline{A}\,(k), V]}{pr[C_B(k+1) = 0 | \overline{C}_B(k) = 0, \overline{A}(k), \overline{L}(k)]}$$

where $A(k)$ denotes the treatment at time k, and $\overline{A}\,(k-1)$ denotes the treatment history prior to time k. V represents a vector of baseline covariates, and $\overline{L}(k)$ represents a vector of time-varying covariates through time k, which also includes the baseline vector V. $\overline{C}\,(k)$ denotes the censor status at time k [203]. In our study, time k was defined by the month of follow-up, each lasting 30 days. Therefore, the numerator of the IPTW represents the probability of observed treatment for

each patient-month, given the prior treatment history and baseline covariates. The denominator represents the probability of observed treatment given prior treatment history, baseline, and time-varying covariates. Similarly, the numerators of the IPCWs represent the probability of censoring due to prior treatment history and baseline covariates, while the denominators of the IPCWs represent the probability of censoring due to prior treatment history, baseline covariates, and time-varying covariates. The IPTW was obtained using logistic regression with exposure status as the outcome, while the censoring models were obtained using logistic regression with censoring status as the outcomes (these models are described in detail in subsequent chapters). Each person-month of follow-up was assigned a different stabilized weight.

These time-varying stabilized weights allowed us to estimate the average causal treatment effects[207]. Four assumptions must be met to use MSMs. The first, *conditional exchangeability*, refers to the absence of unmeasured confounders, i.e., all variables that are to be included in the IPTW, IPCW, and outcome models are measured and can be used in the analysis[207]. Although this is difficult to verify in observational studies, we adjusted for more than 45 covariates and used an active comparator to minimize this potential issue. The second, *positivity*, refers to the presence of a positive probability of each treatment and each set of covariates, i.e., that each patient is at risk of receiving each of the treatments of interest. This means there must be a count ≥ 1 in every cell of exposure and covariate combinations. Our inclusion and exclusion criteria allowed us to reduce the probability of violating this assumption, as we aimed to include patients with type 2 diabetes who are at risk of receiving any of the four insulins under study. The third assumption, *consistency*, requires that each individual's observed outcome is the causal outcome with their treatment history, i.e., no outcome misclassification. The fourth assumption is the use of the correct models for weighting and for the outcome models. We evaluated model fit with the Akaike Information

Criterion and the Bayesian Information Criterion[208], and we used robust variance estimators in the model to account for potential within-subject correlation[209,210].

4.2.7 Missing data

We used multiple imputation by chained equations[211] (MICE) for variables with missing data, including BMI, HbA1c, ethnicity, IMD, SBP, and DBP for Objectives 2 and 3. We used separate logistic regression models with the variables to be imputed as the outcome and with all the variables that can predict the value of these variables as covariates, including the exposures and outcomes. We then created 5 imputed datasets that were analysed separately and pooled using Rubin's rules[211].

5. Chapter 5: Manuscript 1- Initiation of four basal insulins and subsequent treatment modification in people treated for type 2 diabetes in the United Kingdom: changes over the period 2003-2018

5.1 Preface

Previous studies have examined the utilization of all insulins (short-acting and basal) in patients with type 2 diabetes. However, relatively few studies have assessed the utilization of different insulin classes, such as long-acting insulin analogues and NPH, and the studies that did were carried out before the marketing of degludec. In addition, few studies have evaluated the rates of treatment switching among users of long-acting insulin analogues and NPH. Thus, the aims of the first study of this thesis were to assess the utilization of long-acting insulin analogues and NPH insulin among patients with type 2 diabetes, to describe the characteristics of these patients, and to compare the rates of insulin treatment switching between these two types of insulin.

To do so, we evaluated the utilization of long-acting insulin analogues and NPH in 3 separate cohorts of patients with type 2 diabetes between 2003 and 2018 1) an all-user cohort, comprised of all patients using antidiabetic drugs (prevalent users and initiators) during the study period; 2) an antidiabetic initiator cohort, comprised of all patients initiating an antidiabetic drug during the study period; and 3) an insulin initiator cohort comprised of all patients initiating long-acting insulin analogues or NPH during the study period. We also assessed the characteristics of patients initiating basal insulin and stratified prescription rates of long-acting insulin analogues and NPH by sex, by subgroups defined by CVD history, and by BMI category. Overall, this study provides a comprehensive assessment of the utilization of long-acting insulin analogues and NPH in a real-world clinical setting. This manuscript was published in *Diabetic Medicine* (2021; 38:e14603).

5.2 Title Page

Initiation of four basal insulins and subsequent treatment modification in people treated for type 2 diabetes in the United Kingdom: changes over the period 2003-2018
Running title: Utilization of Basal Insulins in Type 2 Diabetes in the UK

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Novelty statement

What is already known?

- The use of antidiabetic drugs has changed in recent years, due in part to the marketing of newer glucose-lowering agents.

What has this study found?

- Prescription rates of neutral protamine Hagedorn (NPH) insulin decreased between 2003-2018, while prescription rates of glargine increased during this period.
- Individuals initiating insulin treatment on detemir were more likely to change treatment compared to those initiating on NPH or glargine.

What are the clinical implications of the study?

- The use of insulin in the management of type 2 diabetes has evolved during the last two decades.
- Differences in the rates of insulin treatment change may suggest poorer glycaemic control or the occurrence of adverse events.

Key words: Insulin, type 2 diabetes, drug utilization, epidemiology, insulin analogues.

5.3 ABSTRACT

Aims: To describe changes in the utilization of basal insulins (glargine, detemir, degludec, neutral protamine Hagedorn [NPH]) among individuals with type 2 diabetes between 2003 and 2018 in the United Kingdom (UK).

Materials and Methods: Using the UK Clinical Practice Research Datalink (CPRD) Aurum, we created three study cohorts of individuals with type 2 diabetes: 1) all users of antidiabetic drugs (n=686,170); 2) initiators of antidiabetic drugs (n=382,247); and 3) initiators of basal insulins (n=85,369). Trends in prescription rates were determined using Poisson regression overall and stratified by sex, cardiovascular disease history, and obesity. Crude and adjusted Cox proportional hazards models were used to obtain hazard ratios (HRs) and confidence intervals (CI) comparing rates of treatment change between classes of basal insulins, with an intention-to-treat exposure definition.

Results: During the study period, prescription rates of insulin analogues increased in the all user cohort from 118.3 (95% CI: 116.4, 120.2) prescriptions per 1000 person-years in 2003 to 579.4 (95% CI: 576.9, 582.0) in 2018. Prescription rates of NPH decreased from 770.5 (95% CI: 765.0, 775.3) in 2003 to 457.7 (95% CI: 455.5, 460.0) in 2018. Compared to initiators of NPH, initiators of detemir were more likely to change treatment (adjusted HR: 1.31, 95% CI: 1.25, 1.37) while glargine initiators were less likely to change treatment (adjusted HR: 0.85, 95% CI: 0.82, 0.88).

Conclusions: Basal insulin prescription evolved between 2003 and 2018. Our study provides insight into the evolving use of basal insulin among individuals with type 2 diabetes in the UK.

5.4 INTRODUCTION

Type 2 diabetes mellitus is a disease characterized by increased levels of blood glucose due to insulin resistance and pancreatic beta-cell dysfunction (1), as opposed to type 1 diabetes, which is characterized by an inability to produce endogenous insulin. Due to the decline in beta-cell function causing progressive worsening of hyperglycemia, individuals with type 2 diabetes require treatment with exogenous insulin to maintain glycaemia within recommended targets and to avoid macrovascular and microvascular complications. European (2), American (3), and Canadian (4) guidelines recommend treating people with type 2 diabetes with basal insulins such as human neutral protamine Hagedorn (NPH) or long-acting insulin analogues (2, 4), which include glargine, detemir, and degludec, if their glycaemic levels remain uncontrolled with other antidiabetic drugs. NPH insulin is an intermediate acting human insulin, while long-acting insulin analogues were developed synthetically and provide glucose-lowering effects for longer time periods (5). More than 20% of people with type 2 diabetes will eventually require treatment with insulin (6).

Prescribing patterns of antidiabetic drugs including insulin have greatly changed in recent years (7), largely due to the obesity epidemic, safety concerns with thiazolidinediones (8, 9), and the recent marketing of new oral antidiabetic drugs (OADs i.e., sodium-glucose co-transporter 2 [SGLT-2] inhibitors, dipeptidyl peptidase 4 [DPP-4] inhibitors), and newer insulin analogues (7, 10). Prescription rates of insulins have been described until 2010 (11), but limited contemporary population-level data are available. In addition, no study to date has examined prescription rates for the different classes of long-acting insulin analogues or have compared the rates of treatment change between basal insulins. As treatment changes may reflect non-adherence, the occurrence of adverse events such as severe hypoglycaemia (12, 13), or poorly controlled glycaemia (which

increases the risk of diabetes complications), it is important to understand these patterns in this population (14). Our study objective was to describe the characteristics of initiators of basal insulins and to compare prescription rates and treatment switching between basal insulins among people with type 2 diabetes in the United Kingdom (UK).

5.5 METHODS

5.5.1 Data source

We conducted a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD) Aurum, which contains the primary care records of over 19 million individuals in over 700 general practitioner practices in the UK (15). The CPRD includes information on diagnoses and prescriptions distributed by general practitioners, and lifestyle and laboratory information not typically found in administrative databases, including body mass index (BMI) and glycated haemoglobin (HbA1c) levels. Diagnoses and non-prescription information are recorded using SnomedCT (16, 17) (UK edition) and Read Version 2 codes, and prescriptions are assigned a ProdCode based on the Dictionary of Medicines and Devices and classified according to the British National Formulary. The CPRD is well suited for the study of diabetes, as long-term management of people with type 2 diabetes is primarily handled by general practitioners in the UK (18). In addition, a recent study revealed 99% correctness and 94-98% completeness for diagnoses related to type 2 diabetes in CPRD Aurum (19), and other laboratory measures have also been validated in the CPRD (20).

This study was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital (protocol number: 19_217R). This protocol was made available to journal reviewers.

5.5.2 Study population

We created three separate cohorts to evaluate the utilization of insulins in subgroups of people with type 2 diabetes. First, we formed a cohort of individuals who received ≥ 1 prescription for any of the following pharmacological treatment for type 2 diabetes between January 1st, 2003 and December 31st, 2018: metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors,

glucagon-like peptide-1 (GLP-1) receptor agonists, alpha-glucosidase inhibitors, meglitinides, SGLT-2 inhibitors, human insulin (NPH and short-acting), and insulin analogues (rapid, long-acting). The first long-acting insulin analogue glargine was added to the British National Formulary in 2002 (21, 22); consequently, initiating our cohort in 2003 ensured that all included individuals had the opportunity to receive a long-acting insulin analogue. This cohort included prevalent users as well as initiators of antidiabetic drugs, and individuals entered the cohort upon their first eligible prescription for an antidiabetic drug after January 1st, 2003. We refer to this cohort as the all user cohort. Second, we created a cohort of initiators of antidiabetic drugs, which included all individuals who received a first-ever prescription for an antidiabetic drug. The date of this first prescription defined entry into this cohort. Finally, we created a third cohort restricted to initiators of either long-acting insulin analogues (glargine [U100, U300], detemir, degludec) or NPH insulin between January 1st, 2003 and December 31st, 2018. The date of this first-ever basal insulin prescription defined entry into this cohort. In all 3 cohorts, we excluded individuals with 1) < 18 years of age, 2) a database history of < 365 days (to measure comorbidities and assess previous use), 3) a diagnosis of polycystic ovary syndrome (another indication for metformin) at any time before cohort entry, 4) a diagnosis of gestational diabetes in the year before cohort entry, and 5) a diagnosis of type 1 diabetes any time before cohort entry to ensure that we capture only individuals with type 2 diabetes. We focused on basal insulins as they are the most clinically relevant type of insulin among individuals with type 2 diabetes initiating insulin in contemporary practice (14, 23, 24). In all cohorts, individuals were followed until end of registration with the CPRD, death, or December 31st, 2018, whichever occurred first.

5.5.3 Prescription rates

For all three cohorts, we considered four exposure categories based on current use of 1) glargine, 2) detemir, 3) degludec, or 4) NPH insulin. We considered treatment durations of 30 days for each of the 4 categories. Yearly prescription counts were measured to compute yearly overall and subgroup-specific prescription rates.

5.5.4 Treatment change

We examined the time to treatment change in the insulin initiator cohort using two approaches. First, we used an intention-to-treat approach, where individuals were considered as exposed to their cohort entry defining insulin (glargine, detemir, degludec, or NPH) from their date of cohort entry until a first prescription for a different basal insulin type (a treatment change) or censoring (defined above). The date of this new prescription defined the outcome date. Second, we used an as-treated approach, where individuals were considered exposed for the duration of the insulin prescription (30 days) + 60-day grace period to account for non-adherence and discontinuation (i.e., a treatment gap that exceeded the 60-day grace period) resulted in censoring. In both analyses, individuals initiating two different basal insulins on the same date were excluded at cohort entry, as this is generally not recommended in diabetes treatment guidelines (2-4).

5.5.5 Covariates

Baseline characteristics included age at cohort entry (mean ± standard deviation [SD] and categorical [≤40, 41-50, 51-60, 61-70, 71-80, ≥80 years]), sex, year of study cohort entry, duration of treated diabetes (time since first ever prescription for an antidiabetic drug), smoking status (never, ever), alcohol use (alcohol-related diseases: alcoholism, cirrhosis, hepatitis, liver failure), history of acute kidney injury, chronic kidney disease, cardiovascular disease (CVD), or dialysis, and previous use of other antidiabetic drugs and other drugs (ever use; at any time prior to cohort

entry). We also measured the following characteristics using the most recent measure in the past 5 years: BMI (mean ± SD and categorical: <25, 25-29, ≥ 30 kg/m^2), HbA1c (mean ± SD and categorical: <48 mmol/mol [<6.5%], 48 – 64 mmol/mol [6.5 – 8.0%], > 64 mmol/mol [>8.0%]), and estimated glomerular filtration rate (eGFR, mean ± SD and categorical: <60, ≥60 ml/min/1.73 m^2).

5.5.6 Statistical analysis

We summarized the characteristics of initiators of long-acting insulin analogues and NPH insulin using mean and SD for continuous variables and proportions for categorical variables. Annual prescription rates and corresponding 95% confidence intervals (CI) for long-acting insulin analogues and NPH (overall and by class) were obtained using Poisson regression in all 3 cohorts. To study the change in the distribution of basal insulin use over the period 2003-2018, Poisson regression was used to calculate crude and age-adjusted rate ratios, using 2005 as the reference year, in the insulin initiator cohort. We chose 2005 as the reference category as it provided individuals sufficient time to be exposed to long-acting insulins following the marketing of glargine in the UK in 2002 and provided more stable estimates than using 2003 as the reference period. We also stratified annual prescription rates of long-acting insulins (overall and by molecule) and NPH insulin by subgroups defined by sex, previous history of CVD, and obesity status (≥30 kg/m^2, <30 kg/m^2).

We estimated crude rates of treatment change for long-acting insulins and NPH and corresponding 95% CIs using the Poisson distribution. We used Cox proportional hazards models to obtain HRs and 95% CIs to compare the rate of incident treatment change between glargine, detemir, degludec, and NPH (25). Models were adjusted for the above-mentioned baseline covariates to control for potential confounding of the association between type of basal insulin and

treatment change. In sensitivity analyses, we varied the grace period to 30 and 90 days in the as-treated approach. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

5.6 RESULTS

Our cohorts included 686,170 users (prevalent and initiators) of antidiabetic drugs, 382,247 initiators of antidiabetic drugs, and 85,369 initiators of insulin (**Figure 5.1**). The insulin initiator cohort included 32,154 glargine initiators, 11,703 detemir initiators, 616 degludec initiators, and 40,896 NPH initiators.

Baseline characteristics

In the insulin initiator cohort, the mean ± SD age of initiators of insulins was similar between groups, ranging from 61 ± 14 to 65 ± 15 years (**Table 5.1**). Most characteristics were similar between initiators of long-acting insulin analogues and NPH, but differences were observed when comparing the characteristics of individuals using different long-acting insulin analogues. While BMI, smoking status, baseline HbA1c, and eGFR were similar between groups, initiators of degludec were more likely to have a history of CVD (69%) compared to initiators of glargine (50%) and detemir (47%). Initiators of degludec were also more likely to have previously used each class of OADs compared to initiators of NPH, glargine, and detemir. In addition, initiators of degludec were less likely to use antiplatelets but more likely to use statins compared to initiators of NPH, glargine, and detemir.

Prescription trends

In the all user cohort, overall prescription rates of basal insulins overall increased slightly during the study period, increasing from 888.7 (95% CI: 883.5, 894.0) prescriptions per 1000 person-years in 2003 to 1037.1 (95% CI: 1033.7, 1040.6) in 2018 (**e-Table 5.1**, **Figure 5.2**). Rates of prescriptions for insulin analogues generally increased while those of NPH insulin decreased over time in all three cohorts (**Figures 5.2A, 5.2B, 5.2C**). The most widely used insulin analogue

among all users and initiators of antidiabetic drugs in 2018 remained glargine. After adjusting for age at cohort entry, the prescription rate of long-acting insulin analogues increased by 28% (RR: 1.28, 95% CI: 1.27, 1.29) from 2005 to 2018 while the rate of NPH decreased by 25% during this period (RR: 0.75, 95% CI: 0.74, 0.76) in the insulin initiator cohort (**e-Table 5.2**).

Prescription rates by subgroup

All individuals were included in the stratified analyses by subgroups of sex and CVD, and 80,779 (95%) of the cohort was included in the stratified analyses by subgroups of obesity after excluding 4,593 individuals (5.4%) with missing information on BMI. Trends in prescription rates were similar for both sexes (**e-Figure 5.1A** & **B**) for long-acting insulins and NPH. Similar prescription trends were observed for all insulins within subgroups defined by CVD history and obesity, although rates of NPH were greater at the beginning of the study period for individuals with a history of CVD and those with obesity (**e-Figures 5.2A** & **B**, **e-Figures 5.3A** & **B**).

Incidence of insulin treatment change

A total of 85,307 individuals were included in these analyses (62 individuals who initiated two different types of insulin on the day of cohort entry were excluded), and their mean follow-up duration ± SD was 5.1 ± 4.2 years. A total of 14,936 treatment changes occurred in the intention-to-treat analyses over 435,908 person-years of follow-up (overall incidence rate: 33.7, 95% CI: 33.2, 34.2 per 1000 person-years). After adjusting for covariates, initiators of glargine were less likely to change insulin treatment compared to initiators of NPH (HR: 0.85, 95% CI: 0.82, 0.88) while initiators of detemir were more likely to change insulin treatments compared to initiators of NPH (HR: 1.31, 95% CI: 1.25, 1.37) (**Table 5.2**). In direct comparisons, individuals using detemir were more likely to change treatment than those on glargine (HR: 1.54, 95% CI: 1.47, 1.62). In our as-treated analyses, initiators of detemir and degludec were more likely to change insulin

treatment compared to NPH, while initiators of glargine had similar rates as initiators of NPH. In sensitivity analyses, initiators of detemir were more likely to change treatment as compared to initiators of glargine for all grace period durations.

5.7 DISCUSSION

The results of this large retrospective cohort study demonstrate that prescribing of long-acting insulin analogues increased between 2003 and 2018 among individuals with type 2 diabetes in the UK, while prescribing of NPH decreased during this period. Initiators of degludec were more likely to have a history of CVD and to have used other OADs prior to initiating insulin than initiators of NPH, glargine, or detemir. In stratified analyses, prescription rates were similar within subgroups defined by sex, history of CVD, and obesity status. Overall, initiators of detemir were more likely to change insulin treatment and initiators of glargine were less likely to change insulin treatment, compared to initiators of NPH.

The literature on the use of basal insulin in individuals with type 2 diabetes remains relatively sparse. Although some studies have examined prescription patterns of insulins (7) over time, few have compared the prescription rates of individual basal insulins. Similarly to our study, Lipska et al. reported an increase in the use of long-acting insulin analogues in the US between 2000 and 2010 (11). The present study, with an additional 8 years of data, provides a more contemporary view of prescribing patterns. The observed rise in insulin analogue utilization may be explained by their convenience: long-acting insulin analogues typically require fewer injections than NPH to reach glycaemic control, making them easier to use (26). Initiators of degludec seem to have more advanced diabetes compared to other insulin groups, which is demonstrated by their greater use of OADs and DOACs at baseline, and greater prevalence of CVD. The inclusion of Xultophy (combination of degludec and liraglutide) as part of the degludec group may also explain these observations, as it may be preferentially prescribed to individuals at higher CVD risk.

Previous studies on treatment change among insulin users have reported similar results. Wei et al. reported that individuals initiating insulin treatment on detemir were more likely to

switch to glargine and those initiating on glargine were less likely to switch to detemir (27). In addition, one meta-analysis of RCTs reported a 60% reduced risk of treatment switching for glargine compared to detemir (28). The increased likelihood of treatment change observed in detemir initiators may be explained by its pharmacokinetics. Although earlier research suggested that detemir presented a similar pharmacodynamic action profile to glargine (29), recent reports suggest that the duration of action of detemir is shorter and contains a greater insulin peak as compared to glargine and degludec (30). As such, individuals using detemir may require multiple injections to achieve glycaemic control, which may be challenging for individuals with limitations (31, 32), those who are reluctant to self-inject (26) and those with complex therapy regimens (33). Thus, physicians may prefer glargine over detemir to ensure appropriate glycaemic control.

Several factors may lead to delayed insulin treatment initiation (referred to as insulin clinical inertia) (34-37), including personal and clinician barriers (36), and marketing of newer OADs which provide additional treatment options to individuals who would have otherwise initiated insulin treatment. While this is unlikely to have impacted our insulin initiator cohort, it may have affected the cohort of initiators of antidiabetic drugs. There remains a need for further studies focused on factors influencing insulin clinical inertia in this population.

Insulin prescription in the UK seems to follow treatment guidelines for type 2 diabetes to varying degrees. NICE guidelines in place during the study period, summarized in **e-Table 3**, recommend initiating insulin-based therapy with NPH following failing to control blood glucose with OADs, and considered long-acting insulin analogues as alternatives to NPH for individuals at a greater risk of hypoglycaemia or for whom target HbA1c was not reached (14). The majority of insulin initiators in our study had previously used metformin and sulfonylureas, thus agreeing with NICE guidelines on treatment intensification (14). However, more than a third of individuals

in our study initiated insulin treatment with glargine without prior use of NPH. In addition, the use of degludec may have been influenced by the NICE guidelines; insulin degludec is considered as an alternative to glargine and detemir in a NICE "advice" (38) and will be added to the upcoming updated guidelines. Physicians may be hesitant to prescribe degludec until it is fully integrated in the guidelines for the management of type 2 diabetes.

Our results provide important reassurance regarding clinical practices during the study period, particularly in the context of changing guidelines for the treatment of a growing population of individuals with type 2 diabetes. This study also has valuable policy implications, providing policy makers and drug plan managers evidence regarding the real-world use of basal insulins and the characteristics of individuals using them, which may help guide policy changes.

Strengths and limitations

Our study has several strengths. It provides important insight into the use of basal insulins in a representative sample of the UK population. The data used covers 15 years, which allowed us to comprehensively assess the patterns of basal insulin use over time and to describe the changes in prescribing patterns since the marketing of new OADs. By creating three different cohorts, we were able to examine differences in prescribing patterns in individuals with type 2 diabetes at various stages of their disease. In addition, the CPRD contains information on clinical measurements not typically found in administrative databases, such as HbA1c, BMI, and eGFR, which allowed us to adjust and stratify our models.

Our study also has some limitations. As in any observational study, some amount of residual confounding may remain. However, we have stratified and adjusted our models for a variety of comorbidities and concomitant use of other drugs, thus reducing potential confounding. As the CPRD only records prescriptions from general practitioners and not dispensing, we were

unable to assess treatment adherence or to capture specialist prescriptions. In addition, the available data on degludec was limited, as it only entered the UK market in 2015. When assessing treatment change, some misclassification may have occurred. However, the use of two analytical approaches (intention-to-treat, as-treated) and the use of varying durations of grace periods allowed us to evaluate the robustness of our findings. Although we explored how several factors may affect treatment choice, we were unable to measure how mental health may affect these choices or subsequent change of insulin treatments. Although our results were consistent across several sensitivity analyses, we cannot rule out the possibility of chance findings resulting from multiple comparisons.

5.8 CONCLUSIONS

We found that the prescription rates of long-acting insulin analogues have increased in the UK between 2002 and 2018, while prescription rates of NPH insulin have decreased during this time. In addition, individuals initiating detemir were more likely to change treatments than those initiating on other basal insulins. Our study provides important insight into the changing prescription patterns and characteristics of insulin users and provides information on the incidence of treatment change in this population.

5.9 CONFLICT OF INTEREST STATEMENT

Dr. Platt has received personal fees from Amgen, Analysis Group, Biogen, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser, all outside the submitted work. The other authors have no relationships to disclose.

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5.11 AUTHOR CONTRIBUTIONS

Ms. Brunetti and Dr. Filion conceived the study idea. Ms. Brunetti drafted the manuscript and performed statistical analyses. All authors contributed to the study design, were involved in the interpretation of the data, and reviewed the manuscript for intellectual content. Dr. Filion is the guarantor of this study.

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5.13 TABLES

Table 5.1: Baseline characteristics of initiators of basal insulins among individuals with type 2 diabetes in the United Kingdom between 2003 and 2018.

Characteristics[1]	Initiators of NPH	Initiators of Long-Acting Insulin Analogues			
		Glargine	Detemir	Degludec	All analogues
N (%)	40,896 (48)	32,154 (38)	11,703 (14)	616 (0.7)	44,473 (52)
Women	18,935 (46)	13,863 (43)	5,252 (45)	277 (45)	19,392 (44)
Age, years	65 ± 15	64 ± 15	61 ± 15	61 ± 14	64 ± 15
≤40	2,889 (7)	2,068 (6.4)	1,152 (9.8)	41 (6.7)	3,261 (7.3)
41-50	3,961 (10)	3,972 (12)	1,747 (15)	80 (13)	5,799 (13)
51-60	7,485 (18)	6,718 (21)	2,563 (22)	185 (30)	9,466 (21)
61-70	9,981 (24)	7,264 (23)	2,684 (23)	166 (27)	10,114 (23)
71-80	10,179 (25)	6,933 (22)	2,219 (19)	95 (15)	9,247 (21)
≥80	6,401 (16)	5,199 (16)	1,338 (11)	49 (8.0)	6,586 (15)
Year of cohort entry					
2003	3,578 (8.8)	1,794 (5.6)	0 (0.0)	0 (0.0)	1,794 (4.0)
2004	3,191 (7.8)	2,407 (7.5)	229 (2.0)	0 (0.0)	2,636 (5.9)
2005	5,001 (12)	2,083 (6.5)	649 (5.6)	0 (0.0)	2,732 (6.1)
2006	1,768 (4.3)	2,389 (7.4)	699 (6.0)	0 (0.0)	3,088 (6.9)
2007	1,511 (3.7)	2,495 (7.8)	884 (7.6)	0 (0.0)	3,379 (7.6)
2008	1,109 (2.7)	2,158 (6.7)	996 (8.5)	0 (0.0)	3,154 (7.1)
2009	1,024 (2.5)	2,011 (6.3)	1,148 (9.8)	0 (0.0)	3,159 (7.1)
2010	950 (2.3)	1,967 (6.1)	1,155 (9.9)	0 (0.0)	3,122 (7.0)
2011	1,565 (3.8)	1,934 (6.0)	984 (8.4)	0 (0.0)	2,918 (6.6)
2012	2,432 (6.0)	1,607 (5.0)	969 (8.3)	0 (0.0)	2,576 (5.8)
2013	2,820 (6.9)	1,445 (4.5)	922 (7.9)	12 (2.0)	2,379 (5.4)
2014	3,194 (7.8)	1,576 (4.9)	802 (6.9)	17 (2.8)	2,395 (5.4)
2015	3,521 (8.6)	1,897 (5.9)	699 (6.0)	50 (8.1)	2,646 (6.0)
2016	3,143 (7.7)	1,946 (6.1)	612 (5.2)	10 (18)	2,668 (6.0)

2017	3,113 (7.6)	2,165 (6.7)	523 (4.5)	91 (31)	2,879 (6.5)
2018	2,976 (7.3)	2,280 (7.1)	432 (3.7)	236 (38)	2,948 (6.6)
Duration of treated diabetes, years, mean (SD)	7.0 (8.3)	6.9 (7.4)	6.5 (6.2)	8.7 (7.2)	6.8 (7.1)
BMI, kg/m^2	30.9 ± 6.7	30.5 ± 6.7	31.4 ± 7.1	33.7 ± 7.8	30.8 ± 6.8
≤25	6,781 (17)	6,070 (19)	1,922 (16)	66 (11)	8,058 (18)
25 – 29	12,019 (29)	9,693 (30)	3,288 (28)	132 (21)	13,113 (30)
≥30	19,541 (48)	14,765 (46)	6,107 (52)	401 (65)	401 (65)
Missing	2,555 (6.3)	1,635 (5.1)	386 (3.3)	17 (2.8)	17 (2.8)
Smoking (ever)	29,480 (72)	23,262 (72)	8,494 (73)	474 (77)	32,230 (73)
Comorbidities					
Alcohol-related illness	9,091 (22)	6,762 (21)	2,660 (23)	157 (26)	9,579 (22)
AKI	2,162 (5.3)	1,546 (4.8)	352 (3.0)	73 (12)	1,971 (4.4)
CKD	8,043 (20)	6,650 (21)	2,543 (22)	117 (19)	9,310 (21)
CVD	22,674 (55)	16,151 (50)	5,529 (47)	424 (69)	22,104 (50)
Dialysis	271 (0.7)	152 (0.5)	57 (0.5)	S	213 (0.5)
HbA1c					
mmol/mol [%]	80 ± 6.0 [9.5 ± 2.2]	83 ± 5.1 [9.7 ± 2.1]	83 ± 5.1 [9.7 ± 2.1]	87 ± 5.1 [10.1 ± 2.1]	83 ± 5.1 [9.7 ± 2.1]
<48 [<6.5]	2,434 (6.0)	1,200 (3.7)	501 (4.3)	11 (1.8)	1,712 (3.9)
48 – 64 [6.5 – 8.0]	7,657 (19)	5,102 (16)	1,610 (14)	82 (13)	6,794 (15)
>64 [>8.0]	27,245 (67)	23,808 (74)	8,836 (76)	505 (82)	33,149 (75)
Missing	3,560 (8.7)	2,044 (6.4)	756 (6.5)	18 (2.9)	2,818 (6.3)
eGRF, ml/min/1.73 m^2	68 ± 21	67 ± 21	69.1 ± 21	72 ±19	68 ± 21
<60	6,709 (16)	5,916 (18)	2,104 (18)	101 (16)	8,121 (18)
≥60	14,722 (36)	13,149 (40)	5,738 (49)	415 (67)	19,302 (43)
Missing	19,465 (49)	13,089 (41)	3,861 (33)	100 (16)	17,050 (38)
Previous use of other antidiabetic drugs					

Metformin	33,130 (81)	27,769 (86)	10,136 (87)	561 (91)	38,466 (87)
Sulfonylureas	30,494 (75)	25,655 (80)	9,155 (78)	476 (77)	35,286 (79)
TZD	19,336 (47)	17,521 (55)	6,708 (57)	510 (83)	24,739 (56)
DPP-4	10,824 (27)	7,954 (25)	3,063 (26)	379 (62)	11,396 (26)
GLP-1 RA	3,958 (9.7)	2,670 (8.3)	1,496 (13)	273 (44)	4,439 (10)
Alpha-glucosidase inhibitors	2,124 (5.2)	1,511 (4.7)	496 (4.2)	15 (2.4)	2,022 (4.6)
SGLT-2	1,987 (4.9)	1,470 (4.6)	342 (2.9)	209 (34)	2,021 (4.5)
Previous use of other drugs[2]					
ACE inhibitors	27,415 (67)	21,289 (66)	7,720 (66)	435 (71)	29,444 (66)
Angiotensin-receptor blockers	16,104 (39)	12,436 (39)	4,529 (39)	264 (43)	17,229 (39)
Antiplatelets	23,366 (57)	18,683 (58)	6,559 (56)	307 (50)	25,549 (58)
Beta-blockers	17,746 (43)	13,321 (41)	4,715 (40)	256 (42)	18,292 (41)
Calcium-channel blockers	17,822 (44)	13,459 (42)	4,722 (40)	256 (42)	18,437 (42)
Diuretics	21,248 (52)	16,198 (50)	5,663 (48)	296 (48)	22,157 (50)
Direct oral anti-coagulants	720 (1.8)	468 (1.5)	130 (1.1)	38 (6.2)	636 (1.4)
NSAIDs	29,260 (72)	22,783 (71)	8,385 (72)	487 (79)	31,655 (71)
Statins	30,466 (75)	24,918 (78)	9,284 (79)	526 (85)	34,728 (78)

Abbreviations: NPH: neutral protamine Hagedorn, SD: standard deviation. BMI: body mass index, AKI: acute kidney injury, CKD: chronic kidney disease, CVD: cardiovascular disease, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, NSAID: non-steroidal anti-inflammatory drugs, ACE: angiotensin-converting enzyme.

[1.] Data are presented as mean ± SD and N (%)

[2.] Ever/never use

Table 5.2: Rates of treatment change among initiators of glargine, detemir, degludec, and NPH among individuals with type 2 diabetes.

Exposure	Events	Person-years	Crude IR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)†
Overall	14,963	435,908	33.7 (33.2, 34.2)	-	-
Intention-to-treat					
NPH	6,756	199,660	33.8 (33.0, 34.7)	1.00 (Ref)	1.00 (Ref)
Analogues					
Glargine	5,103	171,746	29.7 (28.9, 30.5)	0.87 (0.84, 0.90)	0.85 (0.82, 0.88)
Detemir	2,777	63,625	43.6 (42.0, 45.3)	1.39 (1.33, 1.45)	1.31 (1.25, 1.37)
Degludec	57	877	65.0 (49.2, 84.2)	1.68 (1.30, 2.19)	1.19 (0.92, 1.56)
As-treated					
60-day grace period					
NPH	2,435	60,049	40.6 (39.0, 42.2)	1.00 (Ref)	1.00 (Ref)
Analogues					
Glargine	1,732	46,194	37.5 (35.8, 39.3)	0.96 (0.90, 1.02)	0.97 (0.91, 1.03)
Detemir	1,052	16,797	62.6 (59.0, 66.5)	1.67 (1.55, 1.80)	1.62 (1.50, 1.75)
Degludec	43	518	83.0 (61.6, 111.9)	1.84 (1.36, 2.50)	1.39 (1.02, 1.90)
Sensitivity analyses (as-treated)					
30-day grace period					
NPH	1,346	30,761	43.8 (41.4, 46.2)	1.00 (Ref)	1.00 (Ref)
Analogues					
Glargine	937	20,397	45.9 (43.1, 49.0)	1.07 (0.98, 1.17)	1.04 (0.95, 1.13)
Detemir	563	7,667	73.4 (67.6, 79.8)	1.75 (1.58, 1.94)	1.67 (1.50, 1.85)
Degludec	35	324	108.0 (77.6, 150.4)	2.20 (1.56, 3.09)	1.78 (1.29, 2.52)
90-day grace period					

NPH	3,253	80,522	40.4 (39.0, 41.8)	1.00 (Ref)	1.00 (Ref)
Analogues					
Glargine	2,364	67,840	34.8 (33.5, 36.3)	0.90 (0.85, 0.95)	0.91 (0.86, 0.96)
Detemir	1,361	23,576	57.7 (54.7, 60.9)	1.55 (1.45, 1.66)	1.49 (1.39, 1.60)
Degludec	48	631	76.0 (57.3, 100.9)	1.73 (1.30, 2.30)	1.31 (0.98, 1.75)

Abbreviations: CI: confidence interval, HR: hazard rate, IR: Incidence rate, NPH: neutral protamine Hagedorn

* Per 1000 person-years

† Models adjusted for age, sex, year of study cohort entry, duration of treated diabetes, haemoglobin A1c (HbA1c), body mass index, smoking status, history of cardiovascular disease, history of acute kidney injury, diagnosis of chronic kidney disease.

5.14 FIGURE LEGENDS

Figure 5.1: Flow chart of people with type 2 diabetes included in the antidiabetic prevalent user cohort, the antidiabetic initiator cohort, and the insulin initiator cohort.

Figure 5.2: Prescription rates of insulin in the three study cohorts of patients with type 2 diabetes in the United Kingdom between 2003 and 2018

A) Prescription rates of insulin among users of antidiabetic drugs with type 2 diabetes in the United Kingdom between 2003 and 2018.

B) Prescription rates of insulin among initiators of antidiabetic drugs with type 2 diabetes in the United Kingdom between 2003 and 2018.

C) Prescription rates of insulin among initiators of basal insulin with type 2 diabetes in the United Kingdom between 2003 and 2018.

5.15 FIGURES

Figure 5.1

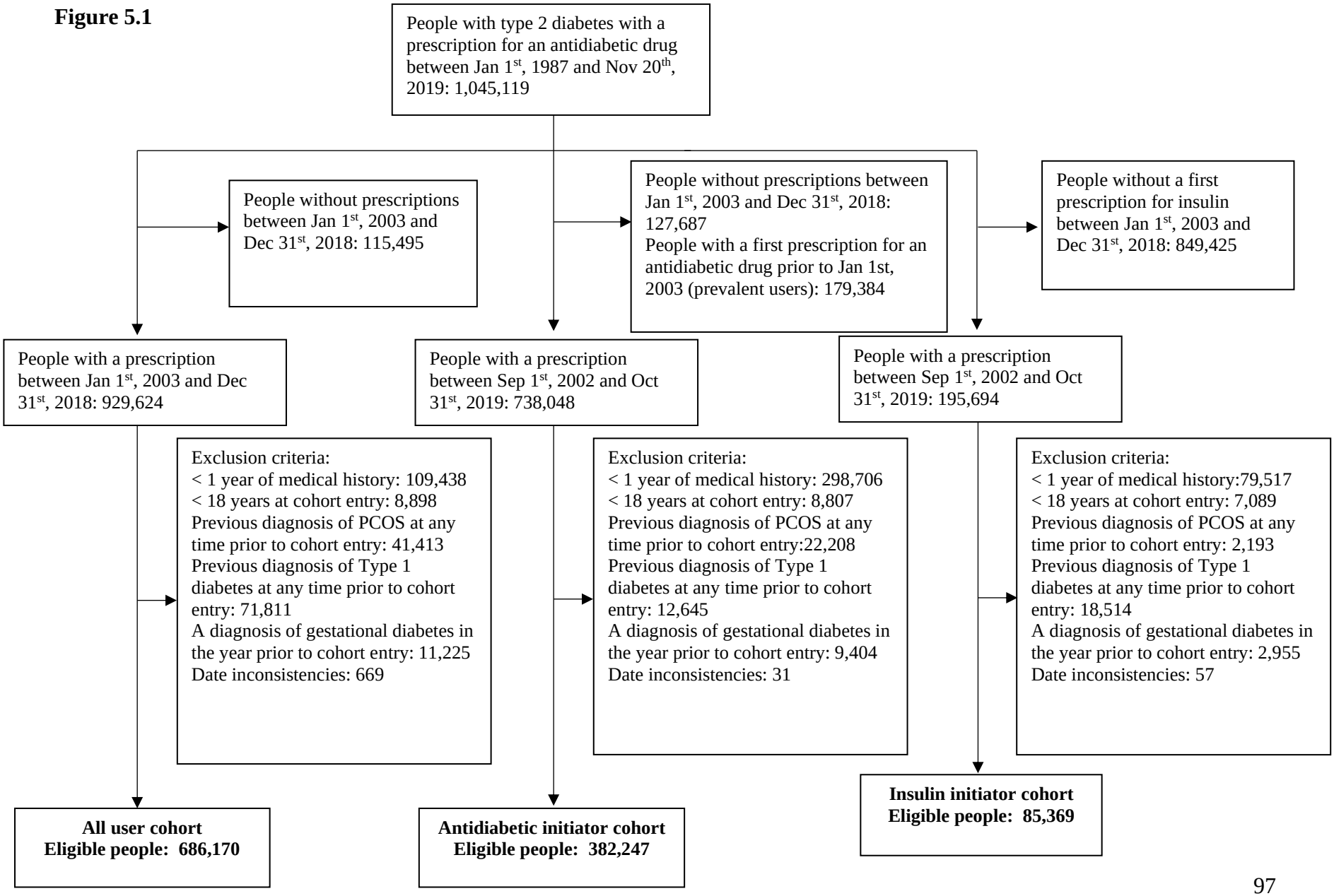
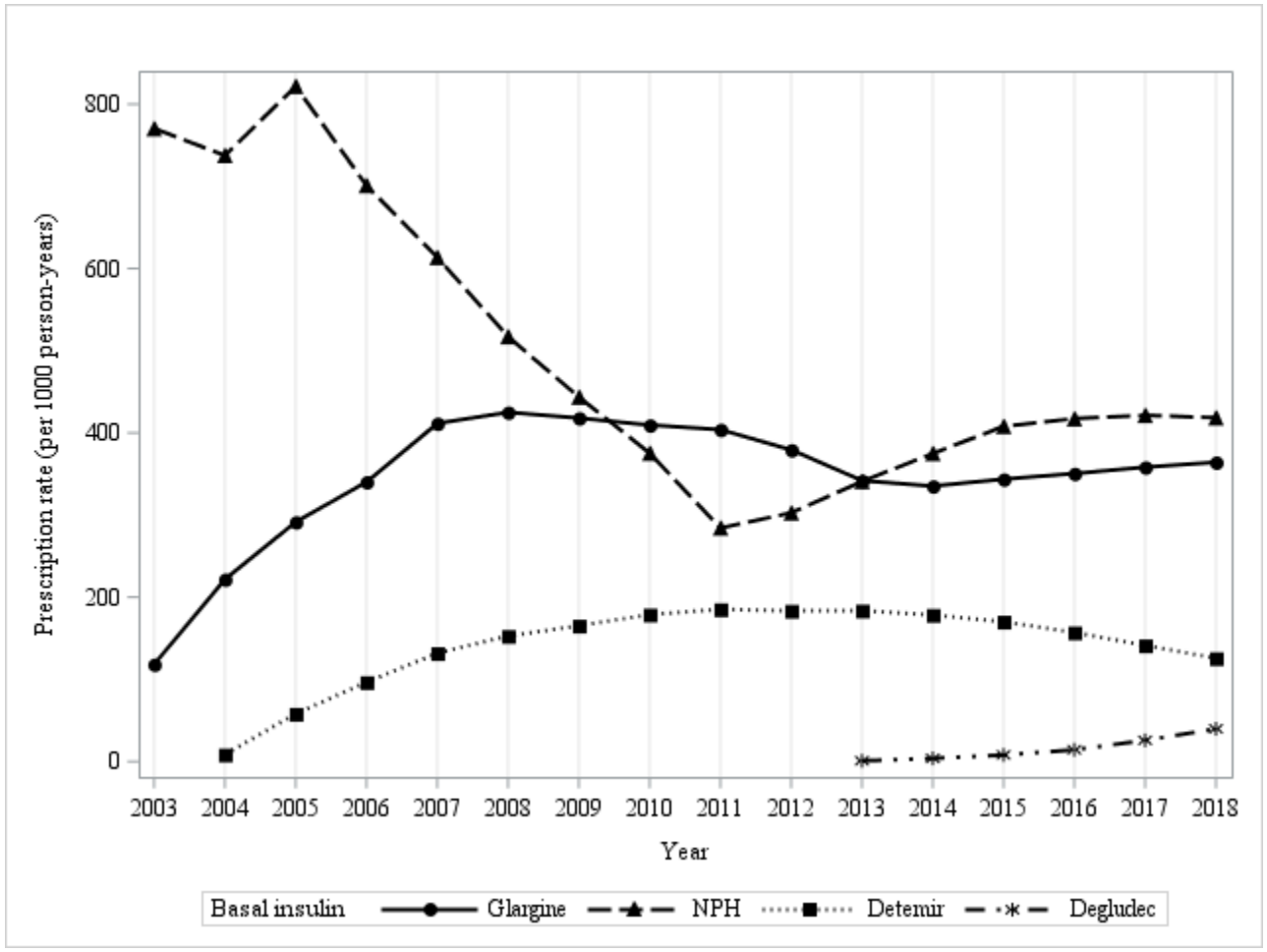
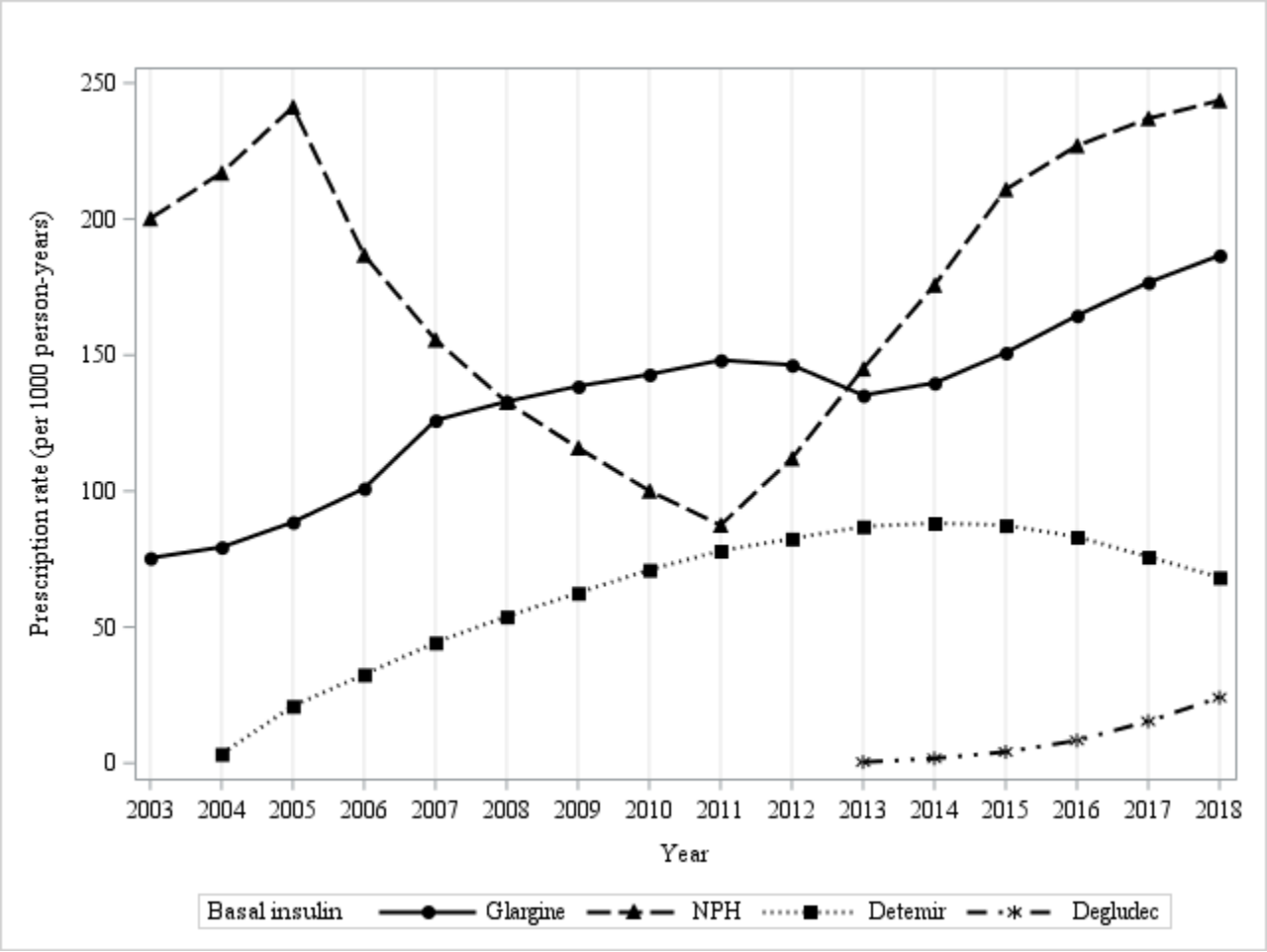


Figure 5.2

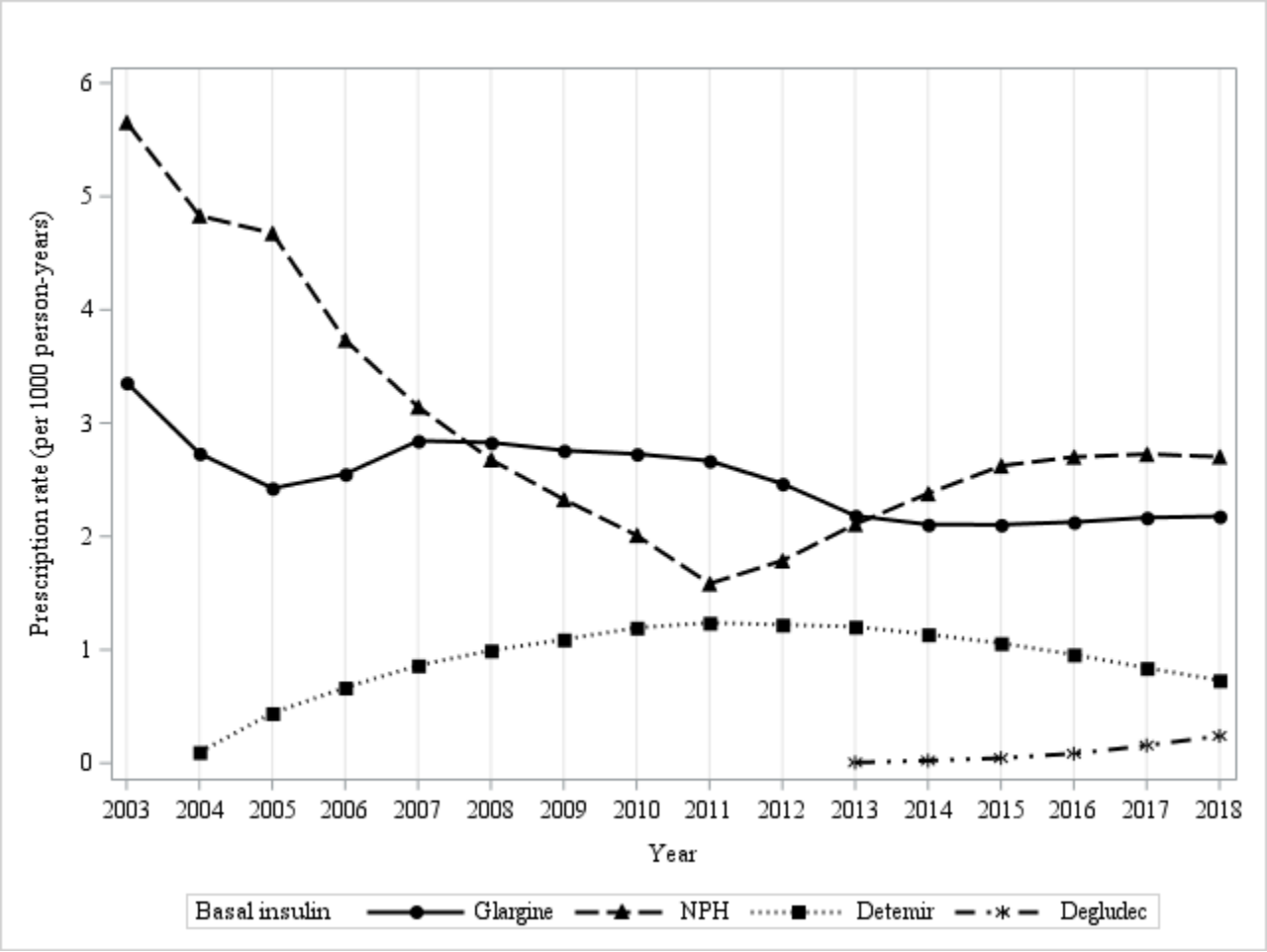
A


800
600
400
200
0
Prescription rate (per 1000 person-years)
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year
Basal insulin
Glargine
NPH
Detemir
Degludec

B


Prescription rate (per 1000 person-years)
250
200
150
100
50
0
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year
Basal insulin
Glargine
NPH
Detemir
Degludec

C


Prescription rate (per 1000 person-years)
0
1
2
3
4
5
6
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year
Basal insulin
Glargine
NPH
Detemir
Degludec

5.16 ONLINE SUPPLEMENTARY MATERIAL

e-Table 5.1: Yearly prescription rates of NPH and long-acting insulin analogs among all users of antidiabetic drugs from 2003-2018.

Year	Person-years	NPH		Analogues		All basal insulin	
		N of prescriptions	Rate* (95% CI)	N of prescriptions	Rate* (95% CI)	N of prescriptions	Rate* (95% CI)
2003	134197	96,519	770.5 (765.6, 775.3)	14,885	118.3 (116.4, 120.2)	111,404	888.7 (883.5, 894.0)
2004	152069	115,096	755.0 (750.7, 759.4)	36,092	235.7 (233.2, 238.1)	151,188	990.7 (985.7, 995.7)
2005	169187	143,690	846.5 (842.1, 850.9)	61,228	360.2 (357.4, 363.1)	204,918	1,206.7 (1,201.5, 1,212.0)
2006	184290	134,237	726.1 (722.2, 730.0)	83,749	452.4 (449.3, 455.5)	217,986	1,178.4 (1,173.5, 1,183.4)
2007	199313	127,510	637.6 (634.1, 641.1)	112,974	564.6 (561.3, 567.9)	240,484	1,202.2 (1,197.4, 1,207.0)
2008	214660	116,225	539.8 (536.7, 542.9)	129,947	603.3 (600.0, 606.6)	246,172	1,143.1 (1,138.6, 1,147.6)
2009	229790	107,068	464.6 (461.8, 467.4)	140,875	611.1 (607.9, 614.3)	247,943	1,075.7 (1,071.4, 1,079.9)
2010	245262	97,015	394.3 (391.8, 396.8)	152,069	618.1 (615.0, 621.2)	249,084	1,012.4 (1,008.4, 1,016.4)
2011	258522	77,853	300.0 (297.9, 302.1)	161,248	621.9 (618.9, 625.0)	239,101	921.9 (918.2, 925.6)
2012	270937	87,187	321.0 (318.8, 323.1)	162,058	596.6 (593.7, 599.5)	249,245	917.6 (914.0, 921.2)
2013	282173	102,530	362.7 (360.5, 365.0)	158,483	560.2 (557.5, 563.0)	261,013	922.9 (919.4, 926.5)
2014	293147	117,627	400.7 (398.5, 403.0)	162,556	553.2 (550.5, 555.9)	280,183	954.0 (950.4, 957.5)
2015	306094	134,145	437.8 (435.5, 440.2)	171,873	560.2 (557.5, 562.8)	306,018	998.0 (994.5, 1,001.6)
2016	322070	145,006	449.8 (447.5, 452.2)	181,596	562.5 (559.9, 565.1)	326,602	1,012.4 (1,008.9, 1,015.9)
2017	332541	152,237	457.5 (455.2, 459.8)	190,199	570.7 (568.1, 573.3)	342,436	1,028.2 (1,024.8, 1,031.7)
2018	343271	157,244	457.7 (455.5, 460.0)	199,277	579.4 (576.9, 582.0)	356,521	1,037.1 (1,033.7, 1,040.6)

Abbreviations: NPH: neutral protamine Hagedorn, CI: confidence interval
* Per 1000 person-years

e-Table 5.2: Crude and age-adjusted risk ratios (RRs) comparing rates of NPH and long-acting insulin analogue use in the insulin initiator cohort using 2005 as the reference.

	NPH		**Analogues**	
Year	Crude RR (95% CI)	Age-adjusted* RR (95% CI)	Crude RR (95% CI)	Age-adjusted* RR (95% CI)
2003	1.08 (1.06, 1.10)	1.08 (1.07, 1.10)	0.96 (0.94, 0.98)	0.95 (0.93, 0.97)
2004	1.02 (1.00, 1.03)	1.02 (1.01, 1.03)	0.96 (0.95, 0.98)	0.96 (0.94, 0.97)
2005	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2006	0.85 (0.84, 0.85)	0.85 (0.84, 0.86)	1.19 (1.17, 1.20)	1.18 (1.17, 1.20)
2007	0.73 (0.72, 0.74)	0.74 (0.73, 0.75)	1.40 (1.39, 1.42)	1.39 (1.38, 1.41)
2008	0.64 (0.63, 0.65)	0.65 (0.64, 0.66)	1.49 (1.47, 1.50)	1.47 (1.46, 1.49)
2009	0.57 (0.56, 0.58)	0.58 (0.57, 0.59)	1.54 (1.52, 1.56)	1.52 (1.50, 1.54)
2010	0.50 (0.50, 0.51)	0.52 (0.51, 0.52)	1.60 (1.59, 1.62)	1.58 (1.56, 1.60)
2011	0.42 (0.42, 0.43)	0.44 (0.43, 0.44)	1.71 (1.70, 1.73)	1.68 (1.66, 1.70)
2012	0.48 (0.48, 0.49)	0.50 (0.49, 0.51)	1.63 (1.61, 1.65)	1.59 (1.57, 1.61)
2013	0.57 (0.57, 0.58)	0.60 (0.59, 0.61)	1.52 (1.50, 1.54)	1.48 (1.46, 1.49)
2014	0.63 (0.63, 0.64)	0.67 (0.66, 0.67)	1.43 (1.42, 1.45)	1.38 (1.37, 1.40)
2015	0.68 (0.67, 0.69)	0.72 (0.71, 0.73)	1.37 (1.36, 1.39)	1.32 (1.31, 1.34)
2016	0.70 (0.69, 0.70)	0.74 (0.73, 0.75)	1.35 (1.34, 1.36)	1.30 (1.28, 1.31)
2017	0.70 (0.69, 0.71)	0.75 (0.74, 0.76)	1.34 (1.33, 1.36)	1.29 (1.27, 1.30)
2018	0.70 (0.69, 0.70)	0.75 (0.74, 0.76)	1.34 (1.33, 1.35)	1.28 (1.27, 1.29)

Abbreviations: CI: confidence interval, NPH: neutral protamine Hagedorn, RR: risk ratios
***** Age was measured at baseline, i.e., on the date of the first-ever insulin prescription

e-Table 5.3: Summary of National Institute for Health and Care Excellence (NICE) guidelines for the management of type 2 diabetes in the United Kingdom.

	Past guidelines published in 2009, updated in 2014 [1]	**Current guidelines (issued in 2015, updated in 2020) [2, 3]**
First-line therapy	• Metformin (if individual is overweight or obese) OR • Sulfonylurea if individual is not overweight or does not tolerate metformin	• Metformin OR • DPP-4 inhibitor, pioglitazone (if the individual is not at risk of heart failure, bone fracture or bladder cancer) or sulfonylurea OR • SGLT-2 inhibitor instead of DPP-4 inhibitor if pioglitazone and sulfonylureas are not appropriate. Monitor for adverse effects of canagliflozin (lower-limp amputation) and of all SGLT-2 inhibitors (diabetic ketoacidosis).
First intensification	Dual therapy with • Metformin + sulfonylureas • Metformin + DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea OR • Sulfonylurea + DPP-4 inhibitor if the individual does not tolerate first-line metformin OR • Metformin + pioglitazone instead of a sulfonylurea if the individual is at higher risk of hypoglycaemia or does not tolerate sulfonylurea and if the individual does not have heart failure or is at higher risk of fracture.	Dual therapy with: • Metformin + DPP-4 inhibitor • Metformin + pioglitazone • Metformin + sulfonylureas • Metformin + SGLT-2 inhibitor If the individual does not support Metformin, initiate dual therapy with: • DPP-4 inhibitor + pioglitazone • DPP-4 inhibitor + sulfonylureas • Pioglitazone + sulfonylureas

Second intensification	Triple therapy with: • Metformin + sulfonylurea + DPP4 inhibitor (Sitagliptin) • Metformin + sulfonylurea + GLP-1 receptor agonist (exenatide) if the individual is obese or is unable to use insulin OR • Basal insulin	Triple therapy with: • Metformin + DPP-4 inhibitor + sulfonylurea • Metformin + pioglitazone + sulfonylurea • Metformin + pioglitazone or sulfonylurea + SGLT-2 inhibitor OR • Insulin-based treatment
Insulin-based treatment	Continue metformin or sulfonylurea and: • Offer NPH insulin once or twice daily • As an alternative to NPH, consider using insulin analogues (detemir, glargine) if the person needs assistance or experiences frequent hypoglycaemia • Consider switching to a long-acting insulin analogue from NPH in people who experience hypoglycaemia, need help from a caregiver or do not reach their target HbA1c • Consider pre-mixed human insulin if needed	Continue metformin or sulfonylurea and: • Offer NPH insulin once or twice daily • Consider NPH insulin and a short-acting insulin either separately or as pre-mixed • As an alternative to NPH, consider using insulin detemir or glargine • Consider pre-mixed preparations that include short-acting insulin analogs and long-acting insulin analogs if needed • SGLT-2 inhibitor in combination with insulin with or without other antidiabetic drugs is an option • Only offer a GLP-1 receptor agonist with insulin under the advice of a specialist.

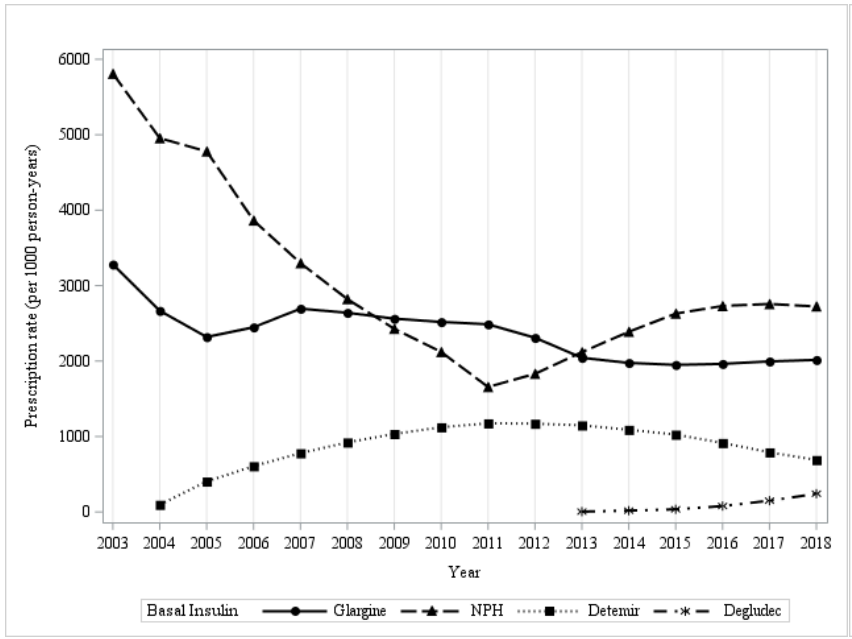
Abbreviations: DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; NPH: neutral protamine Hagedorn; SGLT-2: sodium-glucose co-transporter 2.

[1] National Institute for Health and Care Excellence. (2009) *Type 2 diabetes: the management of type 2 diabetes* [NICE clinical guideline 87] https://www.nice.org.uk/guidance/cg87

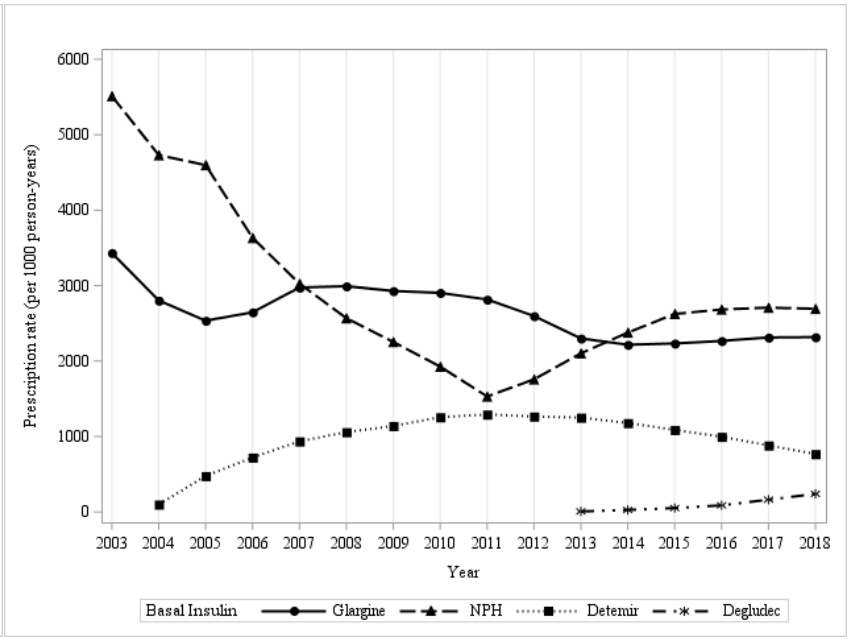
[2] National Institute for Health and Care Excellence. (2015) *Type 2 diabetes in adults: management* [NICE clinical guideline 28] https://www.nice.org.uk/guidance/ng28

[3] National Institute for Health and Care Excellence. (2013) *Type 2 diabetes: insulin degludec* [NICE advice ESNM5] https://www.nice.org.uk/guidance/esnm5

e-Figure 5.1A & B: Prescription rates of basal insulins by subgroups of sex

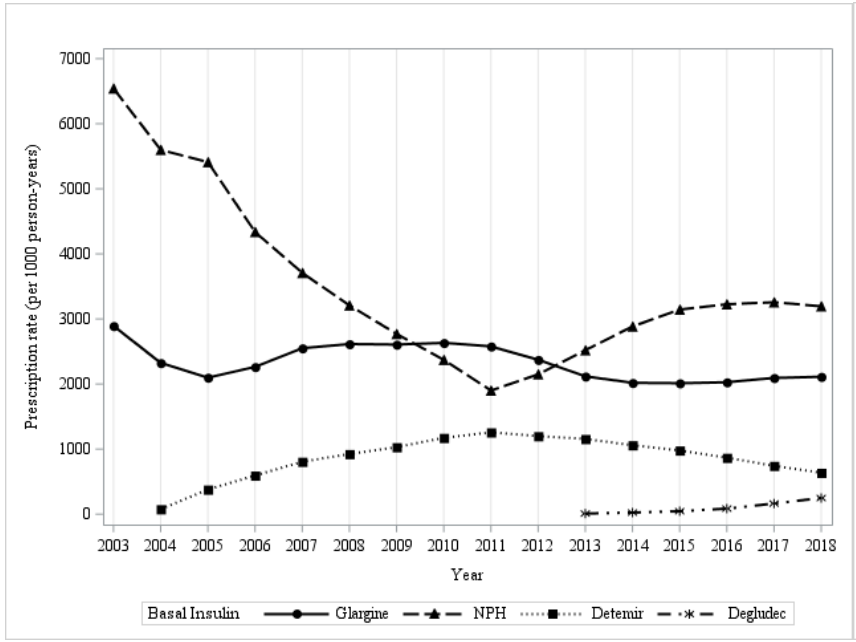


A: Women

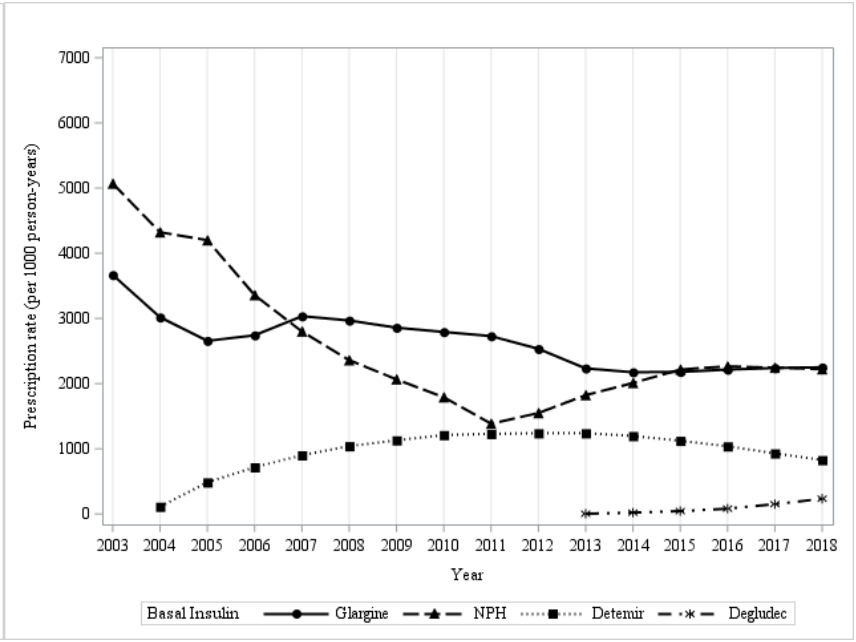


B: Men

e-Figure 5.2A & B: Prescription rates of basal insulins by subgroups of CVD history

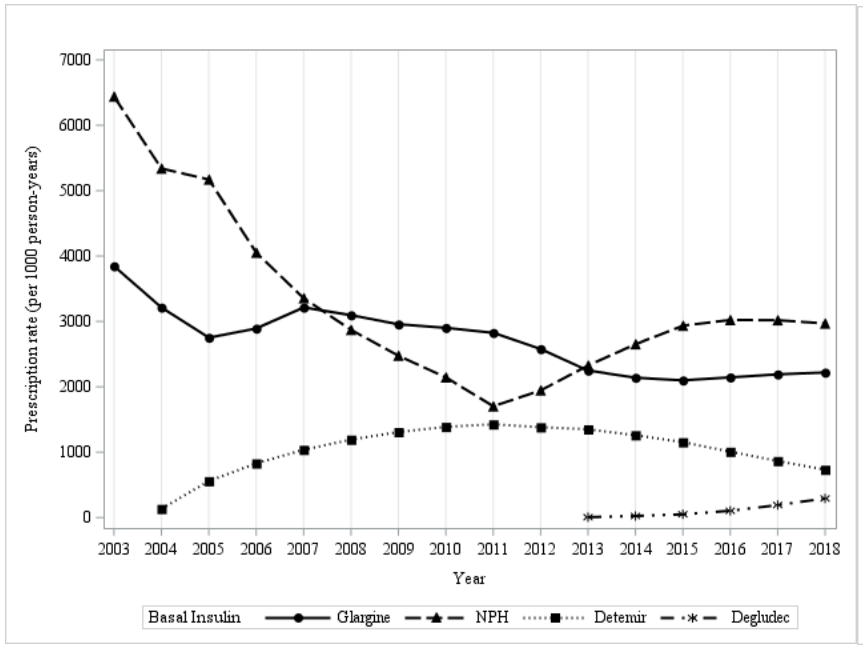


A: History of cardiovascular disease

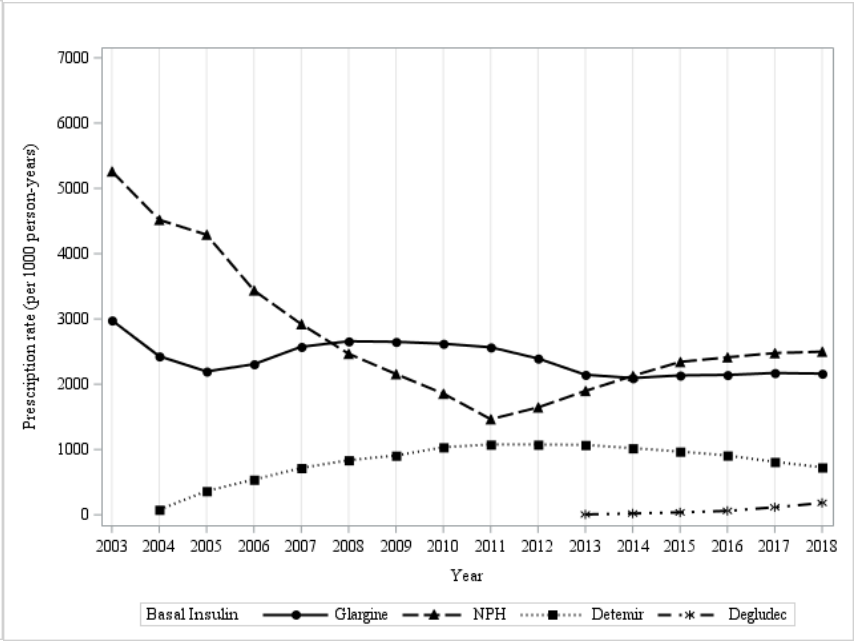


B: No history of cardiovascular disease

e-Figure 5.3A & B: Prescription rates of basal insulins by subgroups of obesity category



A: Patients with obesity (body mass index ≥ 30 kg/m^2)



B: Patients without obesity (body mass index < 30 kg/m^2)

6. Chapter 6: Manuscript 2- Comparative Effectiveness of Long-Acting Insulin Analogues versus Neutral Protamine Hagedorn Insulin for the Prevention of Major Adverse Cardiovascular Events among Individuals with Type 2 Diabetes: A Population-based Cohort Study

6.1 Preface

In Chapter 5, we observed an increase in the use of long-acting insulin analogues between 2003 and 2018 and a decrease in the use of NPH during this period. Given these observed trends and the underlying risk of cardiovascular events among patients with type 2 diabetes, it is important to understand how these drugs compare in terms of effectiveness in real-world clinical settings. Previous RCTs have evaluated the efficacy of long-acting insulin analogues and NPH with respect to glycaemic control and found similar efficacy for these drugs. However, few trials have assessed their efficacy at preventing cardiovascular outcomes in patients with type 2 diabetes, which is one of the overarching goals of treatment for type 2 diabetes. In addition, due strict selection criteria, patients enrolled in trials differ greatly from patients seen in routine clinical practice.

Four observational studies have assessed the comparative effectiveness of long-acting insulin analogues and NPH at preventing cardiovascular outcomes. However, these studies were affected by important limitations including immortal-time bias[23-25], prevalent-user bias[24], or did not include newer long-acting insulin types such as degludec[23-26]. Therefore, there remains a need for methodologically rigorous large observational studies on the comparative effectiveness of long-acting insulin analogues and NPH. The objective of our second manuscript was to compare the risk of cardiovascular outcomes with long-acting insulin analogues and NPH insulin among patients with type 2 diabetes in the UK. This manuscript has been submitted to Diabetes, Obesity and Metabolism.

6.2 Title Page

Comparative Effectiveness of Long-Acting Insulin Analogues versus Neutral Protamine Hagedorn Insulin for the Prevention of Major Adverse Cardiovascular Events among Individuals with Type 2 Diabetes: A Population-based Cohort Study

Running Title: Basal Insulins and Risk of Cardiovascular Events

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Word Count: 3,640; **Abstract Count:** 291; **Tables**: 2; **Figures**: 2; **Supplemental Tables**: 5; **Supplemental Figures**: 6

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Ms. Brunetti holds a Doctoral Training Scholarship from the *Fonds de recherche du Québec – Santé* (FRQS; Quebec Foundation for Research - Health). Dr. Yu holds a Junior I clinical research salary support from the FRQS. Dr. Platt holds the inaugural Albert Boehringer Chair in Pharmacoepidemiology at McGill University. Dr. Filion holds a Senior salary support award from the FRQS and a William Dawson Scholar award from McGill University. This study was supported by a Canadian Institutes of Health Research Project Grant (grant number PJT-175280).

6.3 ABSTRACT

Objectives: To compare the risk of cardiovascular outcomes with long-acting insulin analogues versus Neutral Protamine Hagedorn (NPH) insulin among patients with type 2 diabetes.

Design: Population-based retrospective cohort study.

Setting: United Kingdom Clinical Practice Research Datalink Aurum, linked with hospitalization and vital statistics data.

Population: Patients with type 2 diabetes who initiated basal insulin treatment between 2002 and 2018.

Main outcome measures: The primary outcome was major adverse cardiovascular events (MACE, a composite endpoint of myocardial infarction [MI], ischaemic stroke, and cardiovascular death). The secondary outcomes were the individual components of MACE, hospitalization for heart failure, and all-cause mortality. Exposure was defined using a time-varying approach. We used a marginal structural Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for MACE with current use of long-acting insulin analogues versus NPH insulin, and we subclassified long-acting insulins by molecule in secondary analyses.

Results: Our cohort included 57,334 patients. A total of 3,494 MACE events occurred over a mean follow-up of 1.6 years (incidence rate: 37.4, 95% CI: 36.2 to 38.7 per 1000 person-years). Long-acting insulin analogues were associated with a decreased risk of MACE compared to NPH insulin (HR: 0.89, 95% CI: 0.83 to 0.96). Long-acting insulin analogues were also associated with decreased risks of myocardial infarction (HR:0.85, 95% CI: 0.74 to 0.99), cardiovascular death (HR: 0.90, 95% CI: 0.82 to 0.99), all-cause mortality (HR: 0.88, 95% CI: 0.82 to 0.94), and hospitalization for heart failure (HR: 0.82, 95% CI: 0.77 to 0.88) but not associated with ischaemic stroke (HR: 0.95, 95% CI: 0.81 to 1.13).

Conclusions: Current use of long-acting insulin analogues is associated with a modestly reduced risk of MACE compared to current use of NPH insulin among patients with type 2 diabetes.

6.4 INTRODUCTION

Approximately 20% of patients with type 2 diabetes will be treated with insulin therapy in their lifetime[1,2]. European[3], American[4], and Canadian[5] guidelines recommend treating patients with type 2 diabetes who require insulin therapy with basal insulin, which can be broadly classified into two categories: 1) long-acting insulin analogues, which include glargine, detemir, and degludec; and 2) Neutral Protamine Hagedorn (NPH) human insulin. Randomized controlled trials (RCTs) have shown similar efficacy profiles for long-acting insulin analogues and NPH for glycaemic control[6-9], although some evidence suggests potential variation in the efficacy of different long-acting insulins[10]. Long-acting insulin analogues and NPH insulin exert their glucose lowering effects through similar mechanisms[11], but differences exist in their pharmacokinetic properties, with longer time-action profiles for long-acting insulin analogues compared to NPH[12]. Differences also exist in their price, as long-acting insulins can cost several folds more than NPH insulin.[13]

The overarching goal of glycaemic control among patients with type 2 diabetes is to prevent the complications of diabetes, including microvascular (neuropathy, retinopathy, nephropathy) and macrovascular (myocardial infarction [MI], ischaemic stroke)[14,15] complications resulting from hyperglycemia[16]. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial found no difference in cardiovascular outcomes among patients randomized to glargine and those randomized to standard of care, which included diet therapy, metformin, sulfonylureas, and non-glargine insulin[17]. A small number of observational studies have evaluated the real-world comparative effectiveness of basal insulins for the prevention of cardiovascular events[18-21]. However, these studies had important methodological limitations including immortal time bias[18-20] and prevalent-user bias[20] that render their results difficult to interpret, and they did

not include newer long-acting insulin types such as degludec[18-21]. Given these limitations and the differences observed between populations enrolled in RCTs and those seen in clinical practice[22], uncertainty remains regarding the real-world cardiovascular effects of long-acting insulin analogues compared to NPH insulin. The objective of our study was therefore to compare the effectiveness of long-acting insulin analogues and NPH insulin at reducing the risk of major adverse cardiovascular events (MACE) among patients with type 2 diabetes.

6.5 METHODS

6.5.1 Data source

We conducted a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD) Aurum[23]. CPRD Aurum (referred to as CPRD hereafter) contains the primary care records of >19 million individuals in >700 general practitioner practices in the United Kingdom (UK)[23]. This database includes information on diagnoses and prescriptions issued by general practitioners, as well as clinical measures including systolic and diastolic blood pressure (SBP, DBP), body mass index (BMI), laboratory test results (e.g., glycated haemoglobin [HbA1c] levels, estimated glomerular filtration rate [eGFR]). Diagnoses and non-prescription information are recorded using Read Version 2 codes and Snomed Clinical Terms[24,25] (UK edition) codes, and prescriptions are assigned a product code based on the Dictionary of Medicines and Devices and classified according to the British National Formulary. CPRD data were linked to the Hospital Episode Statistics (HES) data repository[26], which contains complete records for hospitalization, and data from the Office for National Statistics (ONS) vital statistics data, which include the date and cause of death. Linkage with HES and ONS was available for approximately 78% of patients in the CPRD. Linkage between CPRD, HES, and ONS has been well validated [27,28]. As long-term management of people with type 2 diabetes is primarily handled by general practitioners in the UK[29], the CPRD is well suited for the study of diabetes. A recent study revealed a 99% sensitivity and 94-98% specificity for diagnoses related to type 2 diabetes in CPRD Aurum[27]. Laboratory measures have also been validated in the CPRD[30].

This study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number: 19_217RA) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada. This protocol was made available to journal reviewers.

6.5.2 Study population

We created a cohort of all patients with type 2 diabetes who initiated basal insulin treatment with either long-acting insulin analogues (including insulin glargine, detemir, and degludec) or NPH insulin between September 1st, 2002, and November 30th, 2018. Cohort entry was defined by the date of the first basal insulin prescription. We then excluded patients who, at the time of their first basal insulin prescription, had 1) less than 1 year of recorded medical history; 2) age < 18 years; 3) any previous recorded diagnosis of polycystic ovary syndrome (another indication for metformin and a different pathophysiology of type 2 diabetes); 4) a previous diagnosis of type 1 diabetes; and 5) a diagnosis of gestational diabetes in the previous year, 6) zero days of follow-up and 7) with a first prescription for both long-acting insulin analogues and NPH at cohort entry. Patients were followed from cohort entry until the occurrence of the outcome (defined below), end of registration with the CPRD, death, or November 30th, 2018, whichever occurred first.

6.5.3 Exposure

We defined exposure using a time-varying approach, where each person-month of follow-up was classified into one of two mutually exclusive categories: 1) current use of long-acting insulin analogues (glargine, detemir, degludec); or 2) current use of NPH insulin. Use of other antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide-1 [GLP-1] receptor agonists, alpha-glucosidase inhibitors, meglitinides, sodium-glucose co-transporter 2 [SGLT-2] inhibitors, dipeptidyl-peptidase 4 [DPP-4] inhibitors, other insulin) was permitted in both exposure categories. Current use was defined using days of supply of each prescription. We applied a 30-day grace period following the last day of each prescription during which the patient was still considered as exposed to the previously prescribed insulin type. Patients were censored upon treatment discontinuation or upon combination use of both long-acting insulin and NPH

insulin. Discontinuation was defined by no use of basal insulin in a person-month. Combination use was defined as a prescription for at least two different insulin types within the same person-month.

6.5.4 Outcomes

The primary outcome was time to major adverse cardiovascular event (MACE), a composite endpoint of MI, ischaemic stroke, and cardiovascular death. This 3-point MACE definition is also used by the United States Food and Drug Administration for their mandated cardiovascular outcome trials of new treatments for type 2 diabetes[31]. We also evaluated 5 secondary outcomes, which included the individual endpoints of MACE, hospitalization for heart failure, and all-cause mortality. MI (ICD-10: I21.x) and ischaemic stroke (ICD-10: I63.x–I64.x) were defined using ICD-10 codes in HES. Cardiovascular death (ICD-10: I00.x-I78.x) was defined using ONS and all-cause mortality was defined using CPRD, HES and ONS. The event date was defined by the date of admission for HES-defined events and the date of death for ONS-defined events. These outcomes have been validated in the HES[32]. MI was shown to have 92% positive predictive value using electrocardiogram and troponin T as gold standards in a previous validation study in the CPRD and HES[33].

6.5.5 Covariates

We assessed 46 time-fixed and time-varying covariates using both the CPRD and HES data (additional details on covariate definitions are described in **e-Table 6.1**). These covariates included demographic information (age, sex, ethnicity, Index of Multiple Deprivation quintile, comorbidities (duration of treated diabetes, smoking status, previous history of alcohol-related disorders, atrial fibrillation, a previous diagnosis of cancer, chronic obstructive pulmonary disease, coronary artery disease, dyslipidaemia, hypertension, peripheral vascular disease, stroke [only at

baseline for analyses where stroke or MACE was the outcome], MI [only at baseline for analyses where MI or MACE was the outcome], coronary revascularization, acute kidney injury, chronic kidney disease, retinopathy, neuropathy and dialysis; assessed any time prior to cohort entry and updated at 30-day intervals thereafter), clinical measurements (BMI, HbA1c, SBP, DBP, eGFR; using the latest measure in the year before cohort entry at baseline and updated at 30-day intervals thereafter), use of other antidiabetic drugs (assessed in the year prior to cohort entry and updated at 30-day intervals thereafter) and use of other drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, statins, direct oral anticoagulants, antiplatelets, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], use of oral anticoagulants, and antiplatelets; assessed in the year prior to cohort entry and updated at 30-day intervals thereafter).

6.5.6 Statistical analyses

We used descriptive statistics (means and proportions) to summarize the characteristics of initiators of long-acting insulin analogues and NPH at cohort entry, overall and by cohort-entry defining basal insulin. We estimated absolute values of standardized differences to compare the characteristics of each exposure group before and after weighting with inverse probability of treatment weights (IPTW). Crude incidence rates and 95% confidence intervals (CIs) for MACE and our secondary outcomes (MI, ischaemic stroke, cardiovascular death, hospitalization for heart failure, all-cause mortality) were calculated overall and by exposure group based on the Poisson distribution.

We constructed marginal structural models (MSMs) using time-updated stabilized IPTWs (to account for potential time-varying confounding) and inverse probability of censoring weights (IPCW; to account for possible informative censoring) to estimate the association between MACE

and current use of long-acting insulin analogues versus NPH insulin. A more detailed description of this approach is described in **Supplemental Methods 6.17**. Analyses were conducted on the follow-up time axis and using 30-day time intervals. The stabilized weights were included in a Cox proportional hazards model with robust variance estimators[34] and adjusted for baseline covariates[35] to estimate marginal HRs and 95% CIs for each outcome of interest, comparing current use of long-acting insulin analogues to NPH. The proportional hazards assumption was verified using log-log plots and Schoenfeld residuals. Continuous variables (age, duration of treated diabetes, and month of follow-up time) were modelled using restricted cubic splines with 5 knots (3 interior knots) to account for potential non-linear associations and to decrease the variance of the estimator[36]. Multiple imputation was performed for variables with missing information (Index of Multiple Deprivation, ethnicity, BMI, SBP, DBP, HbA1c, and eGFR, more details available in **Supplemental Methods 6.17**)[37].

Secondary analyses

We conducted nine exploratory secondary analyses. First, we compared the risk of MACE for each long-acting insulin separately (glargine, detemir, degludec). In this analysis, multinomial logistic regression was used to compute the numerator and the denominator of the IPTW. Second, we repeated our primary analysis for each of the 5 secondary outcomes (MI, ischaemic stroke, cardiovascular death, hospitalization for heart failure, and all-cause mortality). Third, we assessed potential effect measure modification by stratifying by subgroups of age (≥70 or <70 years), sex, and history of cardiovascular disease. History of cardiovascular disease was defined by a recorded diagnosis of MI, ischaemic stroke, heart failure, or coronary revascularization at any time prior to study cohort entry.

Sensitivity analyses

We conducted five sensitivity analyses to evaluate the robustness of our findings. First, we varied the exposure grace period to 60 and 90 days. Second, we excluded patients with a hospitalization for MI, stroke, or heart failure in the 30 days before study cohort entry. Third, we repeated our primary analysis using a traditional time-dependent Cox proportional hazards model with baseline adjustment only to determine the amount of time-varying confounding that was present. Finally, we stratified our analyses by use of other antidiabetic drugs at baseline. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

6.5.7 Patient and public involvement

Patients were not involved in the study design and were not invited to comment on the development of patient-relevant outcomes or interpret results, or to participate in the writing and editing process. There are no plans to involve patients in the dissemination of the results presented in this study.

6.6 RESULTS

Our cohort included 57,334 patients (**Figure 6.1**), including 31,136 users of long-acting insulin analogues and 26,198 users of NPH at baseline (flow charts describing cohort construction for the secondary analyses are available in **e-Figures 6.1 to 6.6**). A total of 3,494 MACE events occurred over a mean follow-up of 1.6 years (SD: 2.3). The overall incidence rate of MACE was 37.4 (95% CI: 36.2 to 38.7) per 1000 person-years.

Patient characteristics at cohort entry were generally similar between exposure groups (**Table 6.1**). Compared to users of NPH, users of long-acting insulin analogues were less likely to have a history of MI and more likely to have used metformin and statins before weighting. After weighting, baseline characteristics of users of long-acting insulin analogues and NPH were well balanced (standardized differences ≤ 0.10). When comparing patient characteristics by long-acting insulin analogue molecule before weighting (**e-Table 6.2**), users of degludec were more likely to have a history of comorbidities including hypertension, dyslipidemia, retinopathy, and COPD, while users of glargine and detemir were more likely to have a history of chronic kidney disease. Users of degludec were also more likely to have used other antidiabetic drugs than users of glargine and detemir.

Table 6.2 reports the association between the risk of MACE with current use of long-acting insulin analogues versus NPH, overall and by molecule. After weighting and adjustment for baseline confounders, long-acting insulin analogues were associated with a reduced risk of MACE compared to NPH (HR: 0.89, 95% CI: 0.83 to 0.96). In molecule-specific analyses, glargine was associated with a reduced risk of MACE as compared to NPH (HR: 0.88, 95% CI: 0.81 to 0.95). The adjusted HR for MACE was 0.91 (95% CI: 0.81 to 1.02) for detemir and 0.91 (95% CI: 0.47 to 1.76) for degludec.

Table 6.3 and **e-Figures 6.2-6.6** report the association between long-acting insulin analogues versus NPH and the risk of the secondary outcomes. Compared with the use of NPH, use of long-acting insulin analogues was associated with reduced risks of hospitalization for heart failure (HR: 0.82, 95% CI: 0.77 to 0.88), MI (HR: 0.85, 95% CI: 0.74 to 0.99), cardiovascular death (HR: 0.90, 95% CI: 0.82 to 0.99), and all-cause mortality (HR: 0.88, 95% CI: 0.82 to 0.94) but was not associated with the risk of ischaemic stroke (HR: 0.95, 95% CI: 0.81 to 1.13). In subgroup analyses, long-acting insulin analogues were associated with a reduced risk of MACE among patients aged less than 70 years (HR: 0.85, 95% CI: 0.76 to 0.95) but not among patients aged 70+ years (HR: 0.99, 95% CI: 0.91 to 1.08) (**e-Table 6.3**). Long-acting insulin analogues were also associated with a reduced risk of MACE among patients who used other antidiabetic drugs at baseline (HR: 0.86, 95% CI: 0.79 to 0.94) but not among patients who did not use other antidiabetic drugs at baseline (HR: 0.95, 95% CI: 0.84 to 1.08). Results from the sensitivity analyses were similar to those of our primary analysis (**Figure 6.2**, **e-Tables 6.4-6.6**).

6.7 DISCUSSION

In this large retrospective cohort study, we assessed the comparative effectiveness of long-acting insulin analogues and NPH insulin for the prevention of MACE among patients with type 2 diabetes. We found a modestly reduced risk of MACE with long-acting insulin analogues compared to NPH insulin. Glargine and detemir were modestly associated with a reduced risk of MACE compared to NPH insulin while results for degludec were inconclusive due to wide confidence intervals. Long-acting insulins were associated with a reduced risk of hospitalization for heart failure, MI, cardiovascular death and all-cause mortality but were not associated with the risk of ischaemic stroke. Results were consistent across several sensitivity analyses.

Our study has several strengths. First, by using population-based data, it is generalizable to patients seen in routine clinical practice. Second, the large sample size allowed us to generate more precise estimates of the benefits and risks of long-acting insulins compared to NPH and to conduct molecule-specific analyses. Third, we were able to control for severity of diabetes and comorbidities using clinical measures not typically available in claims databases such as HbA1c, BMI, eGFR, and blood pressure measurements. Fourth, the use of time-varying exposure allowed us to reduce the risk of exposure misclassification, while the use of a marginal structural Cox proportional hazards model allowed us to minimize bias due to time-varying confounding. Fifth, our exposure definition was in line with current treatment guidelines: patients with type 2 diabetes using insulin are typically prescribed either a long-acting insulin or NPH insulin, but it is not recommended to prescribe both long-acting insulin and NPH[4,5]. Similarly, patients with type 2 diabetes that use insulin are generally at an advanced stage of their disease, and thus it is unlikely that the treating physician would recommend stopping treatment. Censoring patients upon

combination use or discontinuation allowed us to emulate the clinical equipoise[38] that would be observed in a randomized controlled trial.

Our study also has some limitations. As in most observational studies, our study may be affected by residual confounding. However, we used several approaches to reduce this risk, including using an active comparator and rigorous statistical adjustment. As the CPRD records prescriptions and not dispensings or consumption, exposure misclassification may be possible. However, we have no reason to believe this would be differential between the two exposure groups and would thus likely bias the results toward the null hypothesis. Similarly, outcome misclassification is also possible, although likely not differential. We also have limited data on degludec, as it only entered the UK market in 2013[39]. Due to our exposure definition, which included censoring upon discontinuation, the addition of another insulin treatment, or loss to follow-up, informative censoring may be present in our study. However, the use of two IPCW models helped mitigate this issue.

The effect of different basal insulins on cardiovascular outcomes has only been examined in a small number of trials, as insulin is exempt from the post-marketing cardiovascular outcome trials requirement of the FDA[31]. ORIGIN randomized 12,537 patients at high risk of cardiovascular events to insulin glargine or standard of care, which included lifestyle modification, metformin, sulfonylureas, or non-glargine insulins. After a mean of 6.2 years of follow-up, no difference was observed in the risk of MI between treatment groups (HR: 1.02, 95% CI: 0.94 to 1.11)[17]. We also did not find a reduced risk of MI with the use of glargine as compared to NPH insulin[17], but we did find a reduced risk of MACE. However, ORIGIN included patients with pre-diabetes and included first-line therapies in their comparator group, which may not be clinically relevant. More recently, the Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine

in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) randomized 7,637 patients with type 2 diabetes to degludec or glargine and reported non-inferiority of degludec to glargine for the risk of MACE (HR: 0.91, 95% CI: 0.78 to 1.06)[40]. In addition, the large number of inclusion and exclusion criteria can limit the generalizability of RCTs due to inherent differences between trial populations and populations seen in routine clinical care[22].

Previous observational studies on the risk of cardiovascular outcomes with long-acting insulin analogues and NPH have found inconsistent results. Rhoads et al.[18] reported a reduced risk of MI (HR: 0.65, 95% CI 0.55 to 0.78) for insulin glargine compared to NPH. However, by requiring a minimum of 1 year of insurance coverage during follow-up, the authors may have introduced immortal time bias. A more recent study by Cammarota et al.[20] also reported a reduced risk of macrovascular complications with glargine as compared to NPH (HR: 0.61, 95% CI: 0.44 to 0.84). However, the authors did not exclude prevalent users, which may have induced prevalent user bias[41]. Strandberg et al.[19] reported a reduced risk of all-cause mortality when comparing detemir (HR: 0.42, 95% CI: 0.28 to 0.61) and glargine (HR: 0.65, 95% CI: 0.47 to 0.91) with NPH, but this study also presented immortal time bias. Neugebauer et al. reported that long-acting insulin analogues were not associated with the risk of cardiovascular mortality (HR: 1.26, 95% CI: 0.81 to 1.78), MI (HR: 1.11. 95% CI: 0.77 to 1.45), stroke (HR: 1.30, 95% CI: 0.81 to 1.78), or heart failure hospitalization (HR: 0.93, 95% CI: 0.75 to 1.11) in the United States (US)[21]. However, as the study period ranged from 2000 to 2013, this study did not include degludec (marketed in 2015) and presented wide 95% CIs which limit the interpretability of their findings. In light of the available evidence to date, our study offers a comprehensive and contemporary assessment of the comparative effectiveness of long-acting insulin analogues and NPH among patients with type 2 diabetes.

Several mechanisms may explain the reduced risk of cardiovascular outcomes with long-acting insulin analogues as compared to NPH insulin in our study. NPH is an intermediate-acting insulin; its effect in the bloodstream peaks between 5 to 8 hours and can last up to 18 hours. In contrast, long-acting insulin analogues do not have this peak and have longer time-action profiles (glargine: 24-32 hours, detemir: 24 hours and degludec: up to 42 hours[12,42,43]), which some studies suggest may reduce the risk of adverse events such as hypoglycaemia[44]. Both hyper-[16] and hypoglycaemia[15] have been linked with increased risks of cardiovascular outcomes among patients with type 2 diabetes. It is possible that the tempered insulin action observed with long-acting insulin analogues may help reduce the risk of cardiovascular events in this population through both improved control of hyperglycaemia and a lower hypoglycaemia risk.

With the increase in the prevalence of diabetes[45] and the subsequent increase in users of long-acting insulin analogues and NPH insulin[46], our results add important information to the available evidence regarding the effectiveness profiles of these medications. These results may be relevant to guideline writing committees given the limited high-quality evidence regarding the comparative effectiveness of different insulins and to drug plan managers study to help guide medication reimbursement policies given the stark differences in price between long-acting insulin analogues and NPH[13,47]. Our findings may help guide physicians and patients to make informed decisions regarding the benefits and risks of these treatments.

6.8 CONCLUSION

In this population-based cohort study, we found that use of long-acting insulin analogues was associated with a modest reduction in the risk of MACE compared to use of NPH insulin among patients with type 2 diabetes. Benefits were also observed with long-acting insulin analogues for the risks of MI, cardiovascular death, all-cause mortality, and hospitalization for heart failure. This study provides regulatory agencies, drug plan managers, guideline writers, clinicians, and patients with the information needed to make informed decisions regarding the use of basal insulins for the treatment of type 2 diabetes.

6.9 CONFLICT OF INTEREST STATEMENT

Dr. Platt has received personal fees from Amgen, Analysis Group, Biogen, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser, all outside the submitted work. The other authors have no relationships to disclose.

6.10 COPYRIGHT STATEMENT

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6.12 AUTHOR CONTRIBUTIONS

Ms. Brunetti and Dr. Filion conceived the study idea. Ms. Brunetti drafted the manuscript and performed statistical analyses. All authors contributed to the study design, were involved in the interpretation of the data, and reviewed the manuscript for intellectual content. Dr. Filion is the guarantor of this study.

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6.14 TABLES

Table 6.1: Baseline characteristics of patients with type 2 diabetes who initiated insulin analogues or NPH between 2002 and 2018 in the United Kingdom, before and after inverse probability of treatment weighting.

Characteristics	Before weighting				After weighting			
	Total	Insulin Analogues	NPH	aSD	Total	Insulin Analogues	NPH	aSD
N (%)	57,334	31,136 (54.3)	26,198 (45.7)	-	114,651 (100)	57,373 (50.0)	57,279 (50.0)	-
Female	25,399 (44.3)	13,538 (43.5)	11,861 (45.3)	0.036	50,856 (44.4)	25,449 (44.4)	25,407 (44.4)	0.000
Age, years, mean (SD)	63.8 (14.2)	63.3 (14.3)	64.4 (14.2)	0.078	63.8 (20.1)	63.8 (19.3)	63.8 (21.0)	0.001
<40	3,322 (5.8)	1,747 (5.6)	1,575 (6.0)		7,017 (6.1)	3,421 (6.0)	3,596 (6.3)	
40 – 49.9	6,071 (10.6)	3,663 (11.8)	2,408 (9.2)		12,593 (11.0)	6,463 (11.3)	6,130 (10.7)	
50 – 59.9	11,668 (20.4)	6,732 (21.6)	4,936 (18.8)		23,800 (20.8)	11,787 (20.5)	12,013 (21.0)	
60 – 69.9	14,629 (25.5)	7,793 (25.0)	6,836 (26.1)		29,392 (25.6)	14,790 (25.8)	14,603 (25.5)	
70 – 79.9	13,825 (24.1)	6,984 (22.4)	6,841 (26.1)		27,248 (23.8)	13,561 (23.6)	13,687 (23.9)	
80+	7,819 (13.6)	4,217 (13.5)	3,602 (13.7)		14,601 (12.7)	7,352 (12.8)	7,249 (12.7)	
Year of cohort entry				0.106				0.001
2002	801 (1.4)	122 (0.4)	679 (2.6)		1,743 (1.5)	217 (0.4)	1,527 (2.7)	
2003	3,188 (5.6)	939 (3.0)	2,249 (8.6)		6,828 (6.0)	1,647 (2.9)	5,180 (9.0)	
2004	3,338 (5.8)	1,583 (5.1)	1,755 (6.7)		6,784 (6.0)	2,728 (4.8)	4,056 (7.1)	
2005	2,970 (5.2)	1,770 (5.7)	1,200 (4.6)		5,850 (5.1)	3,065 (5.3)	2,485 (4.3)	
2006	3,195 (5.6)	2,117 (6.8)	1,078 (4.1)		6,093 (5.3)	3,605 (6.3)	2,489 (4.4)	
2007	3,414 (6.0)	2,445 (7.9)	969 (3.7)		6,461 (5.6)	4,199 (7.3)	2,262 (4.0)	
2008	3,002 (5.2)	2,229 (7.2)	773 (3.0)		5,627 (4.9)	3,855 (6.7)	1,772 (3.1)	
2009	3,005 (5.2)	2,320 (7.5)	685 (2.6)		5,647 (4.9)	4,096 (7.1)	1,550 (2.7)	
2010	2,932 (5.1)	2,284 (7.3)	648 (2.5)		5,525 (4.8)	4,087 (7.1)	1,438 (2.5)	
2011	3,225 (5.6)	2,118 (6.8)	1,107 (4.2)		6,403 (5.6)	3,885 (6.8)	2,517 (4.4)	
2012	3,653 (6.4)	1,893 (6.1)	1,760 (6.7)		7,457 (6.5)	3,538 (6.2)	3,918 (6.8)	
2013	3,683 (6.4)	1,737 (5.6)	1,946 (7.4)		7,498 (6.5)	3,270 (5.7)	4,227 (7.4)	

Characteristics	Before weighting				After weighting			
	Total	Insulin Analogues	NPH	aSD	Total	Insulin Analogues	NPH	aSD
2014	3,959 (6.9)	1,737 (5.6)	2,222 (8.5)		8,130 (7.1)	3,333 (5.8)	4,796 (8.4)	
2015	4,492 (7.8)	1,899 (6.1)	2,593 (9.9)		9,186 (8.0)	3,706 (6.5)	5,478 (9.6)	
2016	4,219 (7.4)	1,943 (6.2)	2,276 (8.7)		8,608 (7.5)	3,919 (6.8)	4,688 (8.2)	
2017	4,295 (7.5)	2,067 (6.6)	2,228 (8.5)		8,734 (7.6)	4,221 (7.4)	4,512 (7.9)	
2018	3,963 (6.9)	1,933 (6.2)	2,030 (7.8)		8,072 (7.0)	3,995 (7.0)	4,077 (7.1)	
Duration of treated diabetes, years, mean (SD)	6.3 (5.0)	6.3 (4.8)	6.3 (5.2)	0.014	6.3 (7.0)	6.3 (6.7)	6.3 (7.4)	0.000
Ethnicity				0.037				0.000
Caucasian	46,100 (80.4)	25,075 (80.5)	21,025 (80.3)		96,603 (84.3)	48,327 (84.2)	48,276 (84.3)	
Non-Caucasian	8,604 (15.0)	4,523 (14.5)	4,081 (15.6)		18,048 (15.7)	9,046 (15.)	9,002 (15.7)	
Missing	2,630 (4.6)	1,538 (4.9)	1,092 (4.2)		0 (0.0)	0 (0.0)	0 (0.0)	
Index of Multiple Deprivation				0.010				0.000
1	10,064 (17.6)	5,457 (17.5)	4,607 (17.6)		20,180 (17.6)	10,096 (17.6)	10,084 (17.6)	
2	10,739 (18.7)	5,984 (19.2)	4,755 (18.2)		21,489 (18.7)	10,752 (18.7)	10,737 (18.7)	
3	11,157 (19.5)	6,010 (19.3)	5,147 (19.6)		22,352 (19.5)	11,188 (19.5)	11,164 (19.5)	
4	12,323 (21.5)	6,579 (21.1)	5,744 (21.9)		24,643 (21.5)	12,334 (21.5)	12,309 (21.5)	
5	12,983 (22.6)	7,071 (22.7)	5,912 (22.6)		25,987 (22.7)	13,003 (22.7)	12,984 (22.7)	
Missing	68 (0.1)	35 (0.1)	33 (0.1)		0 (0.0)	0 (0.0)	0 (0.0)	
Smoking	42,484 (74.1)	23,026 (74.0)	19,458 (74.3)	0.007	84,967 (74.1)	42,520 (74.1)	42,447 (74.1)	0.000
BMI, kg/m^2, mean (SD)	30.9 (6.7)	30.9 (6.8)	30.9 (6.7)	0.007	30.8 (9.5)	30.8 (9.2)	30.8 (9.8)	0.000
<25	9,620 (16.8)	5,336 (17.1)	4,284 (16.4)		20,483 (17.9)	10,406 (18.1)	10,078 (17.6)	
25 - 29.9	17,248 (30.1)	9,466 (30.4)	7,782 (29.7)		36,156 (31.5)	18,007 (31.4)	18,150 (31.7)	
30 - 34.9	14,859 (25.9)	8,107 (26.0)	6,752 (25.8)		31,224 (27.2)	15,449 (26.9)	15,775 (27.5)	
35 - 39.9	7,655 (13.4)	4,184 (13.4)	3,471 (13.2)		16,347 (14.3)	8,163 (14.2)	8,184 (14.3)	
40+	5,050 (8.8)	2,787 (9.0)	2,263 (8.6)		10,440 (9.1)	5,348 (9.3)	5,092 (8.9)	
Missing	2,902 (5.1)	1,256 (4.0)	1,646 (6.3)		0 (0.0)	0 (0.0)	0 (0.0)	

Characteristics	Before weighting				After weighting			
	Total	Insulin Analogues	NPH	aSD	Total	Insulin Analogues	NPH	aSD
HbA1c, %, mean (SD)	9.7 (2.2)	9.7 (2.1)	9.7 (2.2)	0.012	9.7 (3.1)	9.7 (2.9)	9.7 (3.2)	0.001
<6.5	2,471 (4.3)	1,131 (3.6)	1,340 (5.1)		5,407 (4.7)	2,451 (4.3)	2,957 (5.2)	
6.5 - 8	8,697 (15.2)	4,698 (15.1)	3,999 (15.3)		18,430 (16.1)	9,121 (15.9)	9,309 (16.3)	
8+	41,781 (72.9)	23,456 (75.3)	18,325 (69.9)		90,814 (79.2)	45,801 (79.8)	45,013 (78.6)	
missing	4,385 (7.6)	1,851 (5.9)	2,534 (9.7)		0 (0.0)	0 (0.0)	0 (0.0)	
eGFR, ml/min/1.73m^2, mean (SD)	68.1 (21.0)	68.2 (20.7)	68.0 (21.3)	0.010	69.6 (28.9)	69.7 (27.6)	69.6 (30.4)	0.000
<60	10,685 (18.6)	5,872 (18.9)	4,813 (18.4)		32,267 (28.1)	15,874 (27.7)	16,394 (28.6)	
60+	24,957 (43.5)	14,317 (46.0)	10,640 (40.6)		82,384 (71.9)	41,499 (72.3)	40,885 (71.4)	
Missing	21,692 (37.8)	10,947 (35.2)	10,745 (41.0)		0 (0.0)	0 (0.0)	0 (0.0)	
SBP, mmHg, mean (SD)	133.4 (17.2)	133.5 (17.0)	133.4 (17.6)	0.008	133.4 (24.4)	133.4 (23.2)	133.4 (25.7)	0.000
DBP, mmHg, mean (SD)	76.1 (10.3)	76.4 (10.2)	75.8 (10.3)	0.058	76.2 (14.5)	76.2 (13.9)	76.2 (15.2)	0.000
Comorbidities								
Acute kidney injury	6,590 (11.5)	3,146 (10.1)	3,444 (13.1)	0.095	13,398 (11.7)	6,713 (11.7)	6,685 (11.7)	0.001
Alcohol-related disease	13,070 (22.8)	6,958 (22.3)	6,112 (23.3)	0.023	26,125 (22.8)	13,083 (22.8)	13,042 (22.8)	0.000
Atrial fibrillation	5,388 (9.4)	2,771 (8.9)	2,617 (10.0)	0.037	10,830 (9.4)	5,419 (9.4)	5,412 (9.4)	0.000
Cancer	8,737 (15.2)	4,438 (14.3)	4,299 (16.4)	0.060	17,555 (15.3)	8,789 (15.3)	8,766 (15.3)	0.000
Chronic kidney disease	13,642 (23.8)	7,283 (23.4)	6,359 (24.3)	0.021	27,378 (23.9)	13,705 (23.9)	13,673 (23.9)	0.000
COPD	8,258 (14.4)	4,268 (13.7)	3,990 (15.2)	0.043	16,531 (14.4)	8,276 (14.4)	8,255 (14.4)	0.000
Coronary artery disease	17,765 (31.0)	9,185 (29.5)	8,580 (32.8)	0.070	35,535 (31.0)	17,770 (31.0)	17,765 (31.0)	0.001

Characteristics	Before weighting				After weighting			
	Total	Insulin Analogues	NPH	aSD	Total	Insulin Analogues	NPH	aSD
Coronary revascularization	4,465 (7.8)	2,256 (7.2)	2,209 (8.4)	0.044	8,964 (7.8)	4,484 (7.8)	4,480 (7.8)	0.000
Dialysis	490 (0.9)	235 (0.8)	255 (1.0)	0.024	990 (0.9)	497 (0.9)	493 (0.9)	0.000
Dyslipidaemia	54,517 (95.1)	29,838 (95.8)	24,679 (94.2)	0.075	109,052 (95.1)	54,574 (95.1)	54,478 (95.1)	0.000
Hypertension	34,587 (60.3)	18,866 (60.6)	15,721 (60.0)	0.012	69,186 (60.3)	34,625 (60.4)	34,561 (60.3)	0.000
Hypoglycaemia	5,944 (10.4)	3,166 (10.2)	2,778 (10.6)	0.014	11,957 (10.4)	5,985 (10.4)	5,972 (10.4)	0.000
Myocardial infarction	3,893 (6.8)	1,696 (5.4)	2,197 (8.4)	0.116	7,778 (6.8)	3,887 (6.8)	3,891 (6.8)	0.001
Neuropathy	3,484 (6.1)	1,951 (6.3)	1,533 (5.9)	0.017	7,015 (6.1)	3,507 (6.1)	3,508 (6.1)	0.000
Peripheral vascular disease	7,417 (12.9)	3,944 (12.7)	3,473 (13.3)	0.037	14,866 (13.0)	7,437 (13.0)	7,429 (13.0)	0.000
Retinopathy	25,051 (43.7)	13,622 (43.8)	11,429 (43.6)	0.003	50,165 (43.8)	25,105 (43.8)	25,060 (43.8)	0.000
Stroke	2,393 (4.2)	1,194 (3.8)	1,199 (4.6)	0.037	4,822 (4.2)	2,413 (4.2)	2,409 (4.2)	0.000
Previous use of antidiabetic drugs								
Metformin	43,419 (75.7)	24,331 (78.1)	19,088 (72.9)	0.123	86,816 (75.7)	43,451 (75.7)	43,365 (75.7)	0.001
Sulfonylureas	39,992 (69.8)	22,079 (70.9)	17,913 (68.4)	0.056	80,068 (69.8)	40,062 (69.8)	40,006 (69.8)	0.000
TZD	26,928 (47.0)	15,318 (49.2)	11,610 (44.3)	0.098	53,998 (47.1)	27,032 (47.1)	26,966 (47.1)	0.001
DPP-4 inhibitors	13,399 (23.4)	7,018 (22.5)	6,381 (24.4)	0.043	26,994 (23.5)	13,503 (23.5)	13,491 (23.6)	0.000
GLP-1 receptor agonists	5,530 (9.6)	3,010 (9.7)	2,520 (9.6)	0.002	11,215 (9.8)	5,608 (9.8)	5,607 (9.8)	0.000
Alpha-glucosidase inhibitors	973 (1.7)	521 (1.7)	452 (1.7)	0.004	2,028 (1.8)	856 (1.5)	1,173 (2.0)	0.042
SGLT-2 inhibitors	2,569 (4.5)	1,286 (4.1)	1,283 (4.9)	0.037	5,211 (4.5)	2,607 (4.5)	2,604 (4.5)	0.000

Characteristics	Before weighting				After weighting			
	Total	Insulin Analogues	NPH	aSD	Total	Insulin Analogues	NPH	aSD
Previous use of other drugs								
ACE inhibitors	29,110 (50.8)	15,941 (51.2)	13,169 (50.3)	0.019	58,134 (50.7)	29,100 (50.7)	29,034 (50.7)	0.001
Antiplatelets	24,523 (42.8)	13,803 (44.3)	10,720 (40.9)	0.069	48,877 (42.6)	24,483 (42.7)	24,394 (42.6)	0.002
ARB	17,200 (30.0)	9,409 (30.2)	7,791 (29.7)	0.010	34,392 (30.0)	17,225 (30.0)	17,168 (30.0)	0.001
Beta-blockers	16,828 (29.4)	8,798 (28.3)	8,030 (30.7)	0.053	33,741 (29.4)	16,876 (29.4)	16,865 (29.4)	0.001
Calcium-channel blockers	17,084 (29.8)	9,152 (29.4)	7,932 (30.3)	0.019	34,168 (29.8)	17,101 (29.8)	17,067 (29.8)	0.000
Diuretics	21,215 (37.0)	11,399 (36.6)	9,816 (37.5)	0.018	42,452 (37.0)	21,236 (37.0)	21,216 (37.0)	0.001
DOACs	870 (1.5)	403 (1.3)	467 (1.8)	0.040	1,767 (1.5)	886 (1.5)	881 (1.5)	0.000
NSAIDs	13,600 (23.7)	7,401 (23.8)	6,199 (23.7)	0.003	27,184 (23.7)	13,598 (23.7)	13,586 (23.7)	0.000
Statins	40,281 (70.3)	22,580 (72.5)	17,701 (67.6)	0.108	80,417 (70.1)	40,265 (70.2)	40,152 (70.1)	0.002

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs.

Table 6.2: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK.

Exposure	Events	Person-years	Crude IR* (95% CI)	Crude HR (95% CI)	Weighted and adjusted HR†‡§ (95% CI)
Overall	3,494	93,436	37.4 (36.2 to 38.7)	-	-
NPH	1,819	40,375	45.1 (43.0 to 47.2)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	1,675	53,061	31.6 (30.0 to 33.1)	0.70 (0.66 to 0.75)	0.89 (0.83 to 0.96)
Glargine	1,193¶	36,811¶	32.4 (30.6 to 34.3)	0.73 (0.68 to 0.79)	0.88 (0.81 to 0.95)
Detemir	411¶	13,767¶	29.9 (27.1 to 32.9)	0.68 (0.61 to 0.75)	0.91 (0.81 to 1.02)
Degludec	10¶	436¶	22.9 (12.3 to 42.6)	0.49 (0.26 to 0.91)	0.91 (0.47 to 1.76)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.

¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

Table 6.3: Risks of myocardial infarction, ischaemic stroke, hospitalization for heart failure, cardiovascular death, and all-cause mortality with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK.

Exposure	Events	Person-years	Crude IR* (95% CI)	Crude HR (95% CI)	Weighted and adjusted HR†‡§ (95% CI)
Myocardial infarction					
Overall	1,201	94,080	12.8 (12.1 to 13.5)	-	-
NPH	632	40,755	15.5 (14.3 to 16.8)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	569	53,325	10.7 (9.8 to 11.6)	0.69 (0.62 to 0.78)	0.85 (0.74 to 0.99)
Ischaemic stroke					
Overall	872	94,477	9.2 (8.6 to 9.9)	-	-
NPH	456	41,000	11.1 (10.1 to 12.2)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	416	53,476	7.8 (7.1 to 8.6)	0.71 (0.62 to 0.81)	0.95 (0.81 to 1.13)
Hospitalization for heart failure					
Overall	3,708	91,208	40.7 (39.4 to 42.0)	-	-
NPH	1,963	39,186	50.1 (47.9 to 52.4)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	1,745	52,021	33.5 (32.0 to 35.2)	0.70 (0.65 to 0.74)	0.82 (0.77 to 0.88)
Cardiovascular death					
Overall	2,231	95,309	23.4 (22.4 to 24.4)	-	-
NPH	1,167	41,465	28.1 (26.6 to 29.8)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	1,064	53,844	19.8 (18.6 to 21.0)	0.72 (0.66 to 0.78)	0.90 (0.82 to 0.99)
All-cause mortality					
Overall	4,076	95,309	42.8 (41.4 to 44.1)	-	-
NPH	2,165	41,465	52.2 (50.1 to 54.5)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogues	1,911	53,844	35.5 (33.9 to 37.1)	0.70 (0.66 to 0.74)	0.88 (0.82 to 0.94)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval
*Per 1000 person-years
†Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).
‡Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.
§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.

6.15 FIGURE LEGENDS

Figure 6.1: Flow chart describing construction of study cohort of people with type 2 diabetes initiating use of basal insulins in the United Kingdom between 2002 and 2018. Abbreviations: HES: Hospital Episodes Statistics, NPH: Neutral Protamine Hagedorn.

Figure 6.2: Forest plot of sensitivity analyses of risk of major adverse cardiovascular events with long-acting insulin analogue versus NPH among patients with type 2 diabetes. Abbreviations: CV: cardiovascular, HR: hazard ratio, PH: proportional hazards.

6.16 FIGURES

Figure 6.1

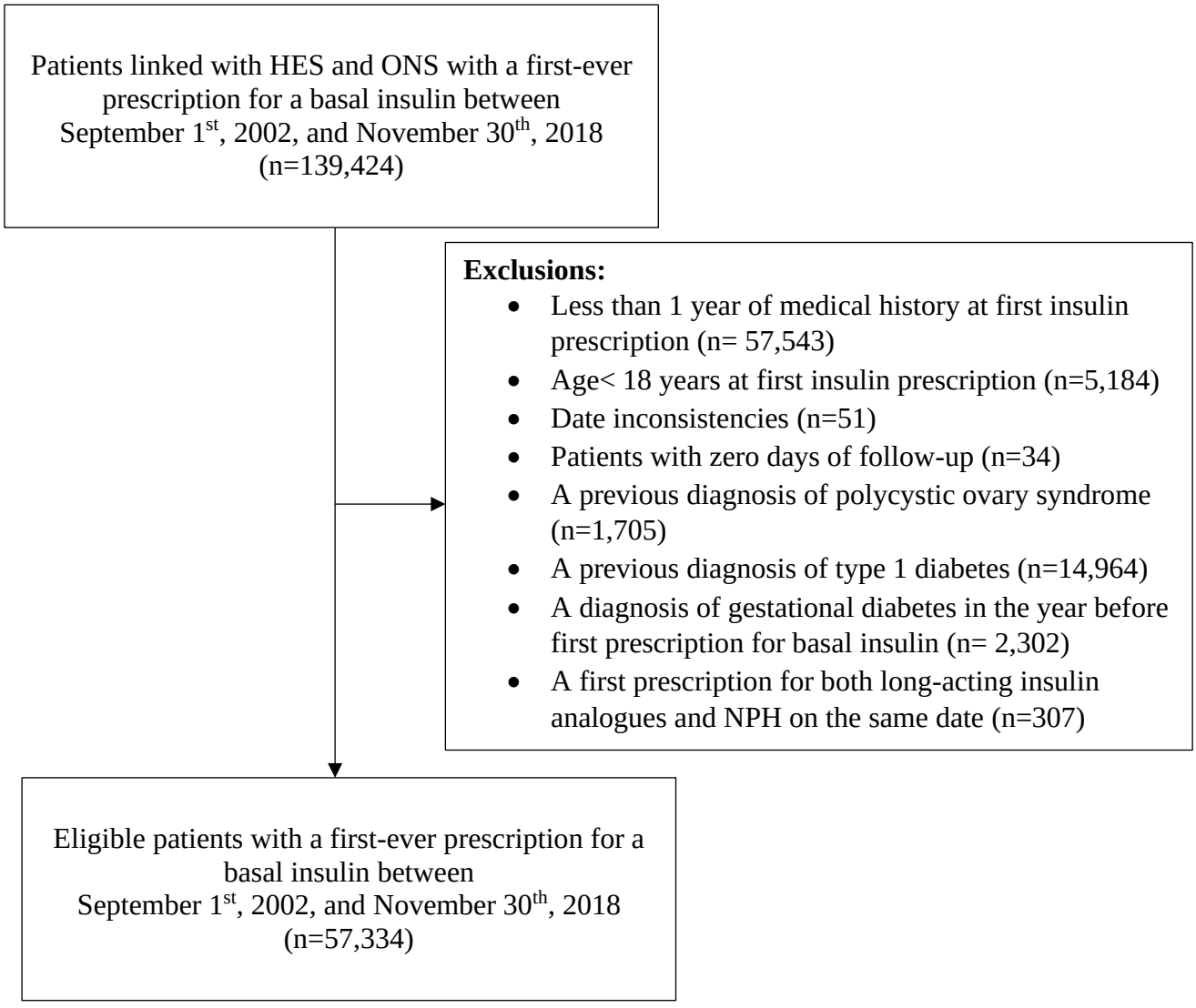
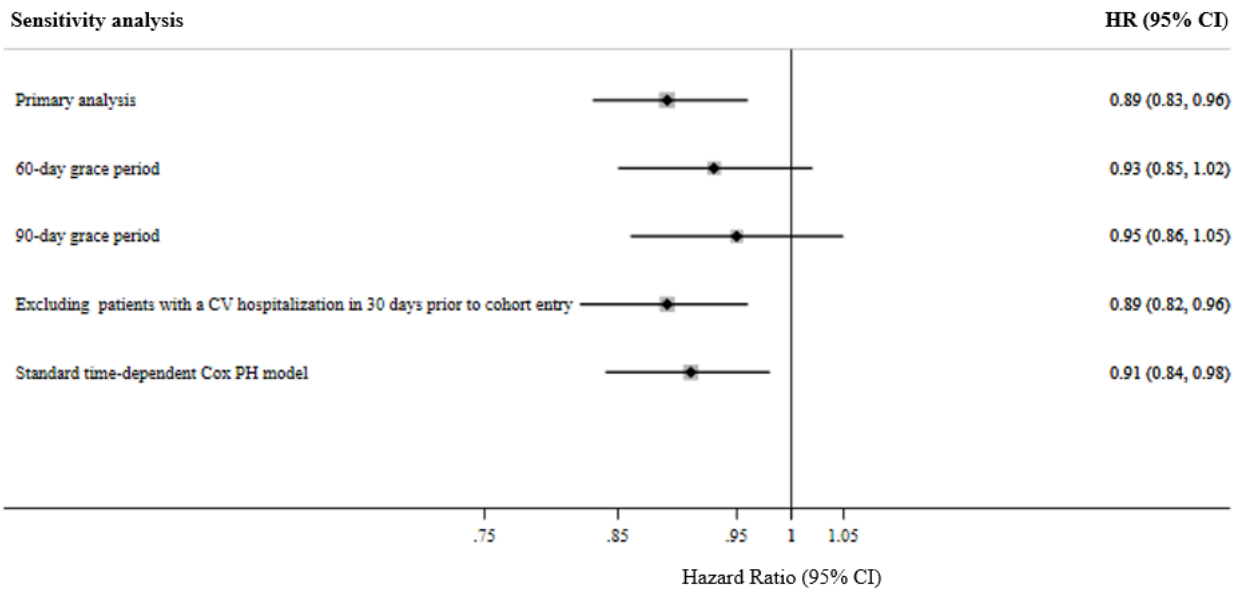


Figure 6.2


Sensitivity analysis
HR (95% CI)
Primary analysis
0.89 (0.83, 0.96)
60-day grace period
0.93 (0.85, 1.02)
90-day grace period
0.95 (0.86, 1.05)
Excluding patients with a CV hospitalization in 30 days prior to cohort entry
0.89 (0.82, 0.96)
Standard time-dependent Cox PH model
0.91 (0.84, 0.98)
.75
.85
.95
1
1.05
Hazard Ratio (95% CI)

6.17 SUPPLEMENTAL METHODS

6.17.1 Inverse probability of treatment weights (IPTW)

For each person-month of follow-up, we generated stabilized weighted using inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs). IPTWs were used to determine the inverse probability of the observed treatment. We used a logistic model to estimate the numerator of the IPTW, estimating the probability of observed treatment (long-acting insulin analogues versus NPH insulin) conditional on baseline covariates (see **e-Table 1**), previous treatment, and month of follow-up duration. The denominator of the IPTW was estimated using a logistic model, conditional on baseline and time-varying covariates, previous treatment, and month of follow-up duration.

6.17.2 Inverse probability of censoring weights (IPCW)

We then constructed two different IPCW models to account for potential differential censoring between exposure groups, according to the reasons for censoring. The first IPCW model ($IPCW_A$) estimated the probability of censoring due to loss to follow-up, end of registration with the CPRD, non-cardiovascular death (except for the outcome of all-cause mortality), or end of the study period (November 30th, 2018). The second IPCW model ($IPCW_B$) estimated the probability of censoring due to either treatment discontinuation or use of both long-acting insulins and NPH. Both IPCWs were estimated using logistic models that were conditioned on baseline covariates, previous treatment, and month of follow-up for the IPCW numerators and baseline and time-varying covariates, previous treatment, and month of follow-up for the IPCW denominators. We used the product of the IPTW, $IPCW_A$, and $IPCW_B$ to obtain standardized weights. Standardized weights below 1st percentile and 99th percentile were truncated to the values of the 1st and 99th percentiles[1,2], respectively.

6.17.3 Multiple imputation

All variables with missing information (Index of Multiple Deprivation, ethnicity, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], glycated haemoglobin A1c [HbA1c], and estimated glomerular filtration rate [eGFR]) were imputed using multiple imputation by chained equations[3] prior to estimating the IPTW and IPCWs to ensure that the positivity assumption[4] was met. We used logistic regression to perform 5 independent imputations using variables that can help predict missingness, including exposure, outcome, and covariates[5]. The resulting datasets were analysed separately. We pooled the estimates and computed standard errors using Rubin's rule [6].

6.18 SUPPLEMENTARY MATERIAL

e-Table 6.1: Description of covariates, their assessment windows, and the models in which they were included.

Characteristic	**Description**	**Baseline lookback**	**Time varying assessment**	**IPTW**	**IPCW$_A$**	**IPCW$_B$**	**Outcome model**
Demographic							
Age		Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sex	women, men	N/A	N/A	yes	yes	yes	yes
Ethnicity	Caucasian, other	N/A	N/A	yes	yes	yes	yes
Index of multiple deprivation quintile	1 (least deprived) to 5 (most deprived)	N/A	N/A	yes	yes	yes	yes
Duration of treated diabetes	Defined as time between the first prescription of	Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Smoking status	ever/never	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Clinical measurements							
Body mass index	continuous, kg/m^2	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only

HbA1c	continuous, %	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
eGFR	continuous, ml/min/1.73m^2	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Systolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Diastolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Comorbidities							
Alcohol related disorders: alcoholism, cirrhosis, hepatitis, and liver failure	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Atrial fibrillation	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Cancer	other than non-melanoma skin cancer yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only

COPD	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Coronary artery disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dyslipidaemia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypertension	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Peripheral vascular disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Stroke	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals, except where stroke or MACE is the outcome	yes*	yes	yes	yes, baseline only
MI	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals (except where MI or MACE is the outcome)	yes*	yes	yes	yes, baseline only
Coronary revascularization	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acute kidney injury	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Chronic kidney disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Retinopathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Neuropathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dialysis	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypoglycaemia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of antidiabetic drugs							

Metformin	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sulfonylureas	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Thiazolidinediones	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
DPP-4 inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
SGLT-2 inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
GLP-1 receptor agonists	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Alpha-glucosidase inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Meglitinides	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Non-basal insulin	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of other drugs							
Angiotensin-converting enzyme inhibitors	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Angiotensin II receptor blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Beta-blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Calcium channel blockers	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Diuretics	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Oral anticoagulants	vitamin K antagonists, direct-acting	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only

	oral anticoagulants yes/no						
Antiplatelets	clopidogrel, ticagrelor, prasugrel yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Statins	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acetylsalicylic acid	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Nonsteroidal anti-inflammatory drugs	yes/no	year prior to cohort entry	updated at 30-day intervals	yes	yes	yes	yes, baseline only

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs

e-Table 6.2: Baseline characteristics of initiators of glargine, detemir, and degludec among patients with type 2 diabetes in the UK.

Characteristic	NPH	Detemir	Glargine	Degludec
N (%) *	26,198 (45.7)	8,368 (14.6)	22,226 (38.8)	437 (0.8)
Female	11,861 (45.3)	3,757 (44.9)	9,538 (42.9)	193 (44.2)
Age, years, mean (SD)	64.4 (14.2)	61.3 (14.5)	64.0 (14.1)	61.5 (13.2)
<40	1,575 (6.0)	643 (7.7)	1,071 (4.8)	26 (5.9)
40 to 49.9	2,408 (9.2)	1,142 (13.6)	2,466 (11.1)	42 (9.6)
50 to 59.9	4,936 (18.8)	1,879 (22.5)	4,700 (21.1)	126 (28.8)
60 to 69.9	6,836 (26.1)	2,079 (24.8)	5,566 (25.0)	123 (28.1)
70 to 79.9	6,841 (26.1)	1,745 (20.9)	5,139 (23.1)	82 (18.8)
80+	3,602 (13.7)	880 (10.5)	3,284 (14.8)	38 (8.7)
Ethnicity				
Caucasian	21,025 (80.3)	6,822 (81.5)	17,803 (80.1)	356 (81.5)
Non-Caucasian	4,081 (15.6)	1,127 (13.5)	3,341 (15.0)	48 (11.0)
Missing	1,092 (4.2)	419 (5.0)	1,082 (4.9)	33 (7.6)
Index of Multiple Deprivation				
1	4,607 (17.6)	1,533 (18.3)	3,812 (17.2)	92 (21.1)
2	4,755 (18.2)	1,703 (20.4)	4,172 (18.8)	88 (20.1)
3	5,147 (19.6)	1,613 (19.3)	4,296 (19.3)	80 (18.3)
4	5,744 (21.9)	1,690 (20.2)	4,776 (21.5)	96 (22.0)
5	5,912 (22.6)	1,821 (21.8)	5,143 (23.1)	81 (18.5)
Missing	33 (0.1)	8 (0.1)	27 (0.1)	0 (0.0)
Smoking	19,458 (74.3)	6,191 (74.0)	16,420 (73.9)	340 (77.8)
BMI, kg/m^2, mean (SD)	30.9 (6.7)	31.4 (7.0)	30.6 (6.6)	33.7 (7.7)
<25	4,284 (16.4)	1,310 (15.7)	3,958 (17.8)	46 (10.5)
25 to 29.9	7,782 (29.7)	2,407 (28.8)	6,930 (31.2)	98 (22.4)
30 to 34.9	6,752 (25.8)	2,278 (27.2)	5,694 (25.6)	112 (25.6)
35 to 39.9	3,471 (13.2)	1,250 (14.9)	2,822 (12.7)	96 (22.0)

40+	2,263 (8.6)	893 (10.7)	1,813 (8.2)	75 (17.2)
Missing	1,646 (6.3)	230 (2.7)	1,009 (4.5)	10 (2.3)
HbA1c, %, mean (SD)	9.7 (2.2)	9.7 (2.1)	9.7 (2.1)	10.1 (2.1)
<6.5	1,340 (5.1)	335 (4.0)	789 (3.5)	6 (1.4)
6.5 to 8	3,999 (15.3)	1,112 (13.3)	3,509 (15.8)	59 (13.5)
8+	18,325 (69.9)	6,414 (76.6)	16,600 (74.7)	363 (83.1)
Missing	2,534 (9.7)	507 (6.1)	1,328 (6.0)	9 (2.1)
eGFR, ml/min/1.73m^2, mean (SD)	68.0 (21.3)	69.3 (20.5)	67.6 (20.8)	73.3 (17.9)
<60	4,813 (18.4)	1,528 (18.3)	4,254 (19.1)	65 (14.9)
≥60	10,640 (40.6)	4,315 (51.6)	9,639 (43.4)	310 (70.9)
Missing	10,745 (41.0)	2,525 (30.2)	8,333 (37.5)	62 (14.2)
SBP, mmHg, mean (SD)	133.4 (17.6)	132.7 (16.5)	133.9 (17.2)	130.2 (13.5)
DBP, mmHg, mean (SD)	75.8 (10.3)	76.3 (10.0)	76.4 (10.3)	74.4 (9.00)
Comorbidities				
Acute kidney injury	3,444 (13.1)	655 (7.8)	2,403 (10.8)	77 (17.6)
Alcohol-related disease	6,112 (23.3)	1,976 (23.6)	4,830 (21.7)	127 (29.1)
Atrial fibrillation	2,617 (10.0)	676 (8.1)	2,039 (9.2)	45 (10.3)
Cancer	4,299 (16.4)	1,143 (13.7)	3,237 (14.6)	46 (10.5)
Chronic kidney disease	6,359 (24.3)	1,999 (23.9)	5,170 (23.3)	84 (19.2)
COPD	3,990 (15.2)	1,151 (13.8)	3,032 (13.6)	71 (16.2)
Coronary artery disease	8,580 (32.8)	2,276 (27.2)	6,759 (30.4)	122 (27.9)
Coronary revascularization	2,209 (8.4)	578 (6.9)	1,642 (7.4)	30 (6.9)
Dialysis	255 (1.0)	S	166 (0.7)	S
Dyslipidaemia	24,679 (94.2)	7,981 (95.4)	21,330 (96.0)	429 (98.2)
Hypertension	15,721 (60.0)	4,958 (59.2)	13,564 (61.0)	287 (65.7)
Hypoglycaemia	2,778 (10.6)	739 (8.8)	2,332 (10.5)	82 (18.8)
Myocardial infarction	2,197 (8.4)	421 (5.0)	1,249 (5.6)	22 (5.0)
Neuropathy	1,533 (5.9)	487 (5.8)	1,428 (6.4)	31 (7.1)
Peripheral vascular disease	3,473 (13.3)	899 (10.7)	2,986 (13.4)	50 (11.4)

Retinopathy	11,429 (43.6)	3,851 (46.0)	9,476 (42.6)	253 (57.9)
Stroke	1,199 (4.6)	253 (3.0)	921 (4.1)	18 (4.1)
Previous use of other antidiabetic drugs				
Metformin	19,088 (72.9)	6,603 (78.9)	17,285 (77.8)	369 (84.4)
Sulfonylureas	17,913 (68.4)	5,793 (69.2)	15,943 (71.7)	271 (62.0)
TZD	11,610 (44.3)	4,253 (50.8)	10,659 (48.0)	359 (82.2)
DPP-4 inhibitors	6,381 (24.4)	1,955 (23.4)	4,871 (21.9)	174 (39.8)
GLP-1 receptor agonists	2,520 (9.6)	1,062 (12.7)	1,673 (7.5)	261 (59.7)
Alpha-glucosidase inhibitors	452 (1.7)	S	391 (1.8)	S
SGLT-2 inhibitors	1,283 (4.9)	234 (2.8)	925 (4.2)	125 (28.6)
Previous use of other drugs				
ACE inhibitors	13,169 (50.3)	4,304 (51.4)	11,358 (51.1)	229 (52.4)
Antiplatelets	10,720 (40.9)	3,611 (43.2)	10,019 (45.1)	133 (30.4)
ARB	7,791 (29.7)	2,536 (30.3)	6,701 (30.1)	139 (31.8)
Beta-blockers	8,030 (30.7)	2,328 (27.8)	6,328 (28.5)	113 (25.9)
Calcium-channel blockers	7,932 (30.3)	2,408 (28.8)	6,599 (29.7)	117 (26.8)
Diuretics	9,816 (37.5)	2,936 (35.1)	8,303 (37.4)	121 (27.7)
DOAC	467 (1.8)	90 (1.1)	289 (1.3)	23 (5.3)
NSAID	6,199 (23.7)	1,971 (23.6)	5,287 (23.8)	115 (26.3)
Statins	17,701 (67.6)	6,164 (73.7)	16,007 (72.0)	332 (76.0)

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs

Smoking status and comorbidities were measured at any time prior to cohort entry. Medication use was measured in the year prior to cohort entry. The most recent measurement in the 5 years prior to cohort entry was used for HbA1c, eGFR, BMI, SBP and DBP. * Percentages represent proportion of the total cohort.

e-Table 6.3: Secondary analyses of risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, stratified by baseline age categories, sex, history of cardiovascular disease, and concomitant use of antidiabetic drugs at baseline.

Exposure	Events	Person-years	Crude IR* (95% CI)	Weighted HR† (95% CI)	Weighted and adjusted HR†‡§ (95% CI)
Age					
< 70					
Overall	1,361	65,747	20.7 (19.6 to 21.8)	-	-
NPH	661	26,380	25.1 (23.2 to 27.0)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	700	39,366	17.8 (16.5 to 19.1)	0.71 (0.63 to 0.79)	0.85 (0.76 to 0.95)
≥70					
Overall	2,133	27,690	77.0 (73.8 to 80.4)	-	-
NPH	1,158	13,995	82.7 (78.1 to 87.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	975	13,696	71.2 (66.9 to 75.8)	0.86 (0.79 to 0.94)	0.99 (0.91 to 1.08)
Sex					
Women					
Overall	1,356	40,445	33.5 (31.8 to 35.4)	-	-
NPH	709	18,303	38.7 (36.0 to 41.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	647	22,142	29.2 (27.1 to 31.6)	0.77 (0.69 to 0.85)	0.99 (0.89 to 1.11)
Male					
Overall	2,138	52,991	40.3 (38.7 to 42.1)	-	-
NPH	1,110	22,071	50.3 (47.4 to 53.3)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	1,028	30,920	33.2 (31.3 to 35.3)	0.67 (0.62 to 0.73)	0.91 (0.83 to 0.99)
History of CVD					
No history of CVD					
Overall	1,403	64,984	21.6 (20.4 to 22.7)	-	-
NPH	665	26,715	24.9 (23.1 to 26.9)	1.00 (Reference)	1.00 (Reference)

Long-acting insulin	738	38,269	19.3 (17.9 to 20.7)	0.78 (0.70 to 0.87)	1.01 (0.90 to 1.13)
History of CVD					
Overall	2,091	28,453	73.5 (70.4 to 76.7)	-	-
NPH	1,154	14,793	84.5 (79.7 to 89.5)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	937	13,660	63.3 (59.4 to 67.5)	0.75 (0.69 to 0.82)	0.91 (0.83 to 0.99)
Concomitant use of antidiabetic drugs					
No use of antidiabetic drugs					
Overall	1,135	22,590	50.2 (47.4 to 53.3)	-	-
NPH	655	11,277	58.1 (53.8 to 62.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	480	11,314	42.4 (38.8 to 46.4)	0.74 (0.66 to 0.84)	0.95 (0.84 to 1.08)
Use of antidiabetic drugs					
Overall	2,359	70,846	33.3 (32.0 to 34.7)	-	-
NPH	1,164	29,098	40.0 (37.8 to 42.4)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	1,195	41,748	28.6 (27.0 to 30.3)	0.74 (0.68 to 0.81)	0.86 (0.79 to 0.94)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

[*] Per 1000 person-years

[†] Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

[‡] Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

[§] The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/never smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.

¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 6.4: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, varying from the grace period to 60 and 90 days.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Weighted and adjusted HR†‡§ (95% CI) §
60-day grace period					
Overall	4,726	123,866	38.2	-	-
NPH	2,380	51,600	46.1 (44.3 to 48.0)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	2,346	72,267	32.5 (31.2 to 33.8)	0.72 (0.68 to 0.76)	0.93 (0.85 to 1.02)
90-day grace period					
Overall	5,632	142,850	39.4 (38.4 to 40.5)	-	-
NPH	2,766	58,446	47.3 (45.6 to 49.1)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	2,866	84,403	34.0 (32.7 to 35.2)	0.73 (0.69 to 0.77)	0.95 (0.86 to 1.05)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.

¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 6.5: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, excluding patients with a hospitalization for heart failure, stroke, or myocardial infarction in the 30 days prior to cohort entry.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI) §
Overall	3,141	91,323	34.4 (33.2 to 35.6)	-	-
NPH	1,583	38,768	40.8 (38.9 to 42.9)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	1,558	52,554	29.6 (28.2 to 31.2)	0.74 (0.69 to 0.79)	0.89 (0.82 to 0.96)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smokers), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.

¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

e-Table 6.6: Risk of major adverse cardiovascular events (MACE) with the current use of long-acting insulin analogues and NPH among patients with type 2 diabetes in the UK, assessed using a standard time-dependent Cox proportional hazards model with adjustment for baseline covariates.

Exposure	Events	Person-Years	Incidence Rate (95% CI) *	Crude HR (95% CI)	Adjusted HR (95% CI) †‡
Overall	11,735	274,664	42.7 (42.0 to 43.5)	-	-
NPH	2,974	65,404	45.5 (43.9 to 47.1)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	3,232	101,490	31.8 (30.7 to 33.0)	0.72 (0.68 to 0.75)	0.91 (0.84 to 0.98)
Glargine	2,344	71,622	32.5 (31.2 to 33.9)	0.73 (0.69 to 0.77)	0.90 (0.83 to 0.98)
Detemir	847	28,318	29.3 (27.4 to 31.4)	0.67 (0.62 to 0.73)	0.92 (0.82 to 1.02)
Degludec	36	1,550	19.2 (13.0 to 28.2)	0.59 (0.43 to 0.82)	0.90 (0.60 to 1.35)
No use or combination	5,529	107,926	51.2 (49.9 to 52.6)	1.21 (1.16 to 1.27)	1.40 (1.30 to 1.49)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

* Per 1000 person-years

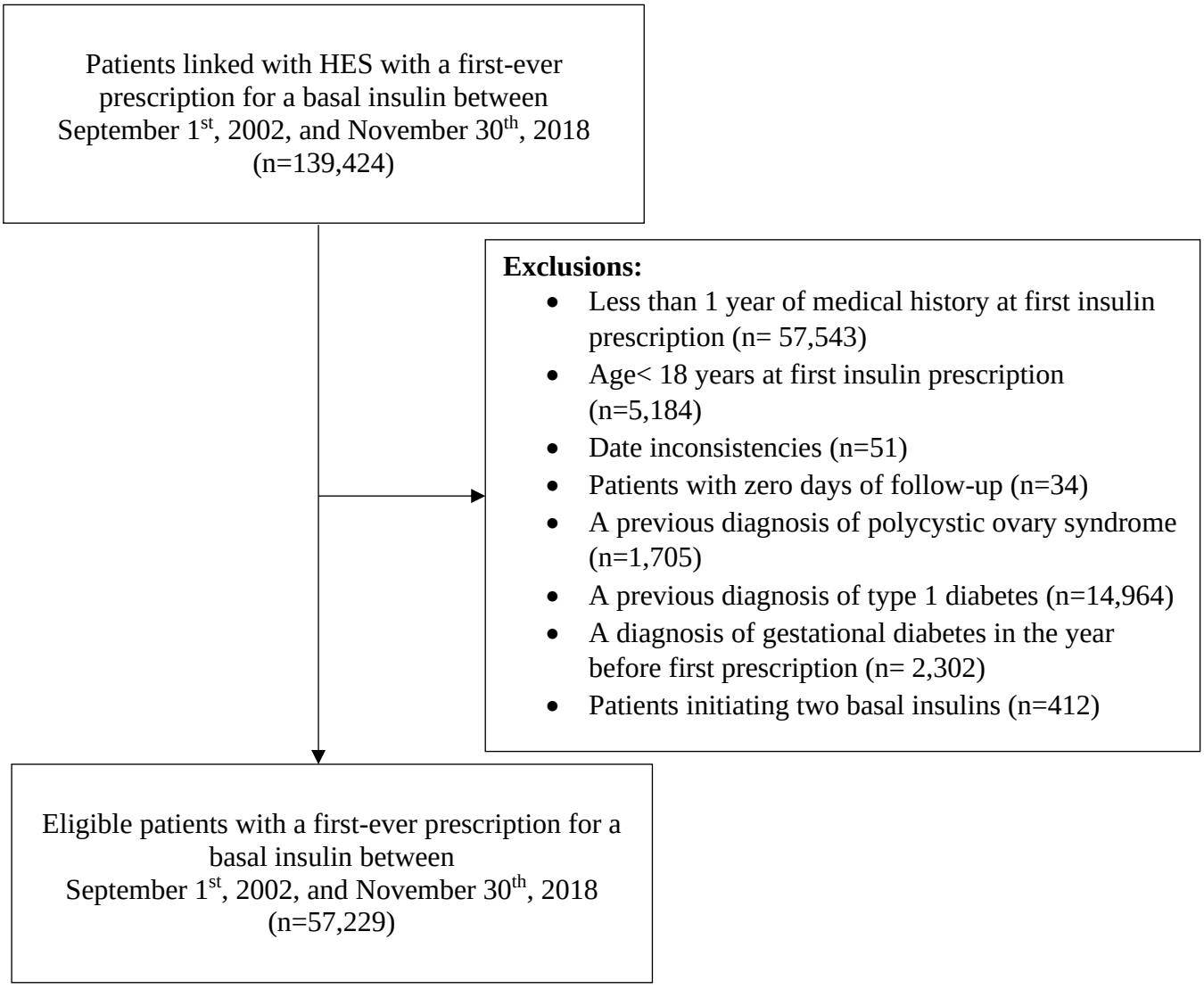
† Marginal structural model weighted with standardized weights using inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCWs).

‡ Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots.

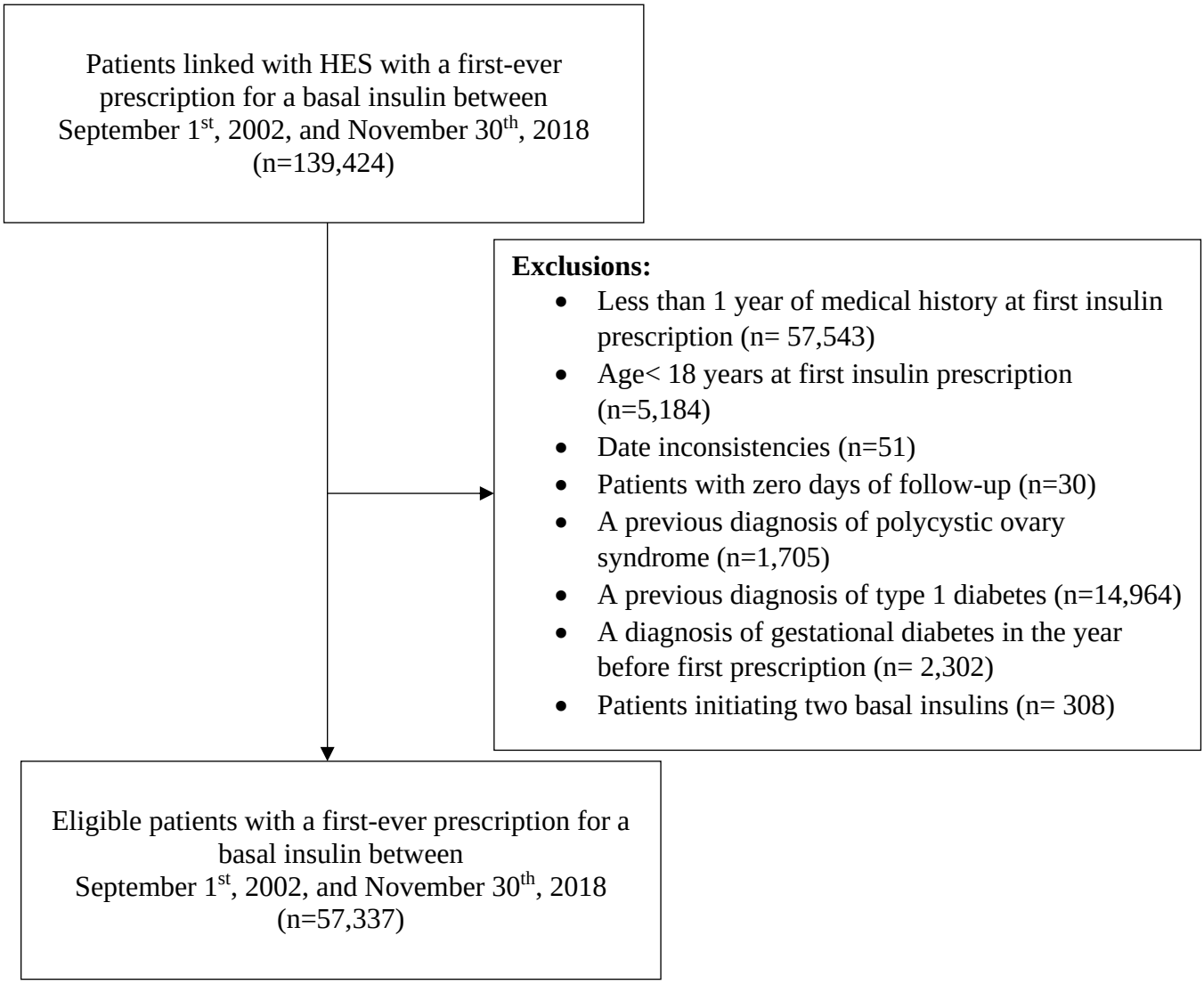
§ The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (ever/ never smokers), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-

steroidal anti-inflammatory drugs. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated haemoglobin A1c, systolic blood pressure, diastolic blood pressure.
¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogues due to censoring upon combination use.

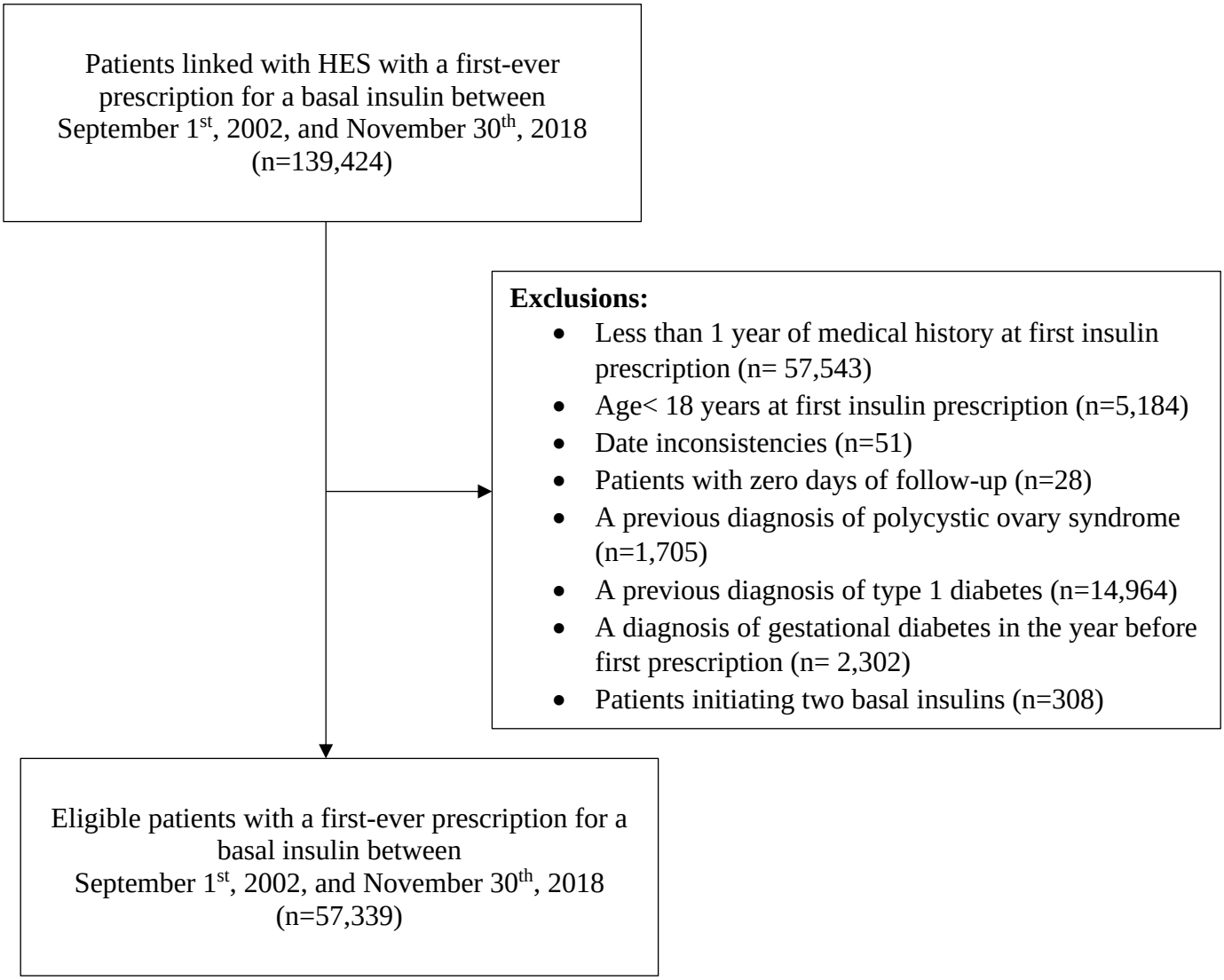
e-Figure 6.1: Study flow-chart for primary analysis on the association between current use of individual long-acting insulin analogs (glargine, detemir, degludec) and NPH and the risk of major adverse cardiovascular events (MACE)



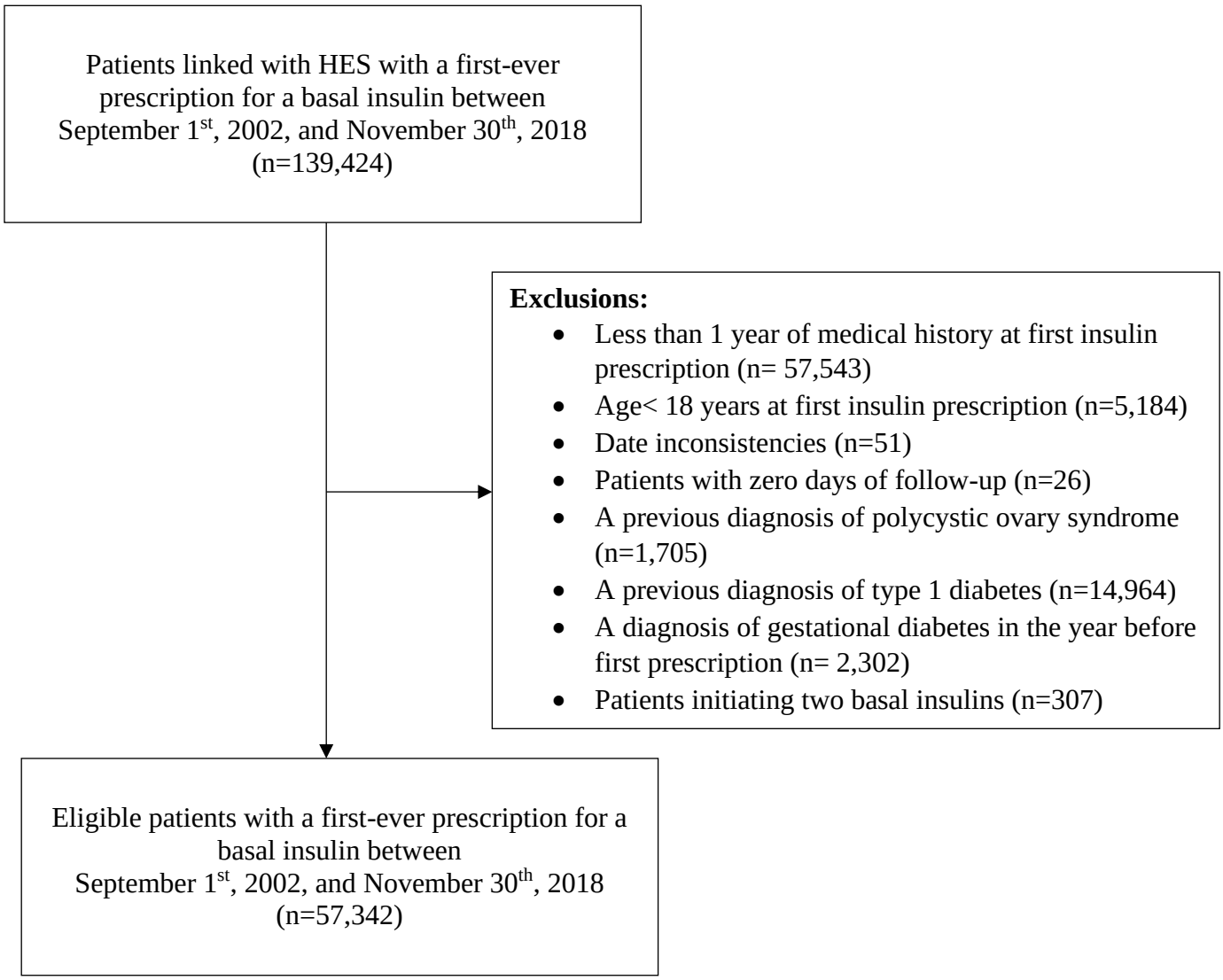
e-Figure 6.2: Flow chart for secondary analysis of the association between current use of long-acting insulin analogues and the risk of myocardial infarction (MI).



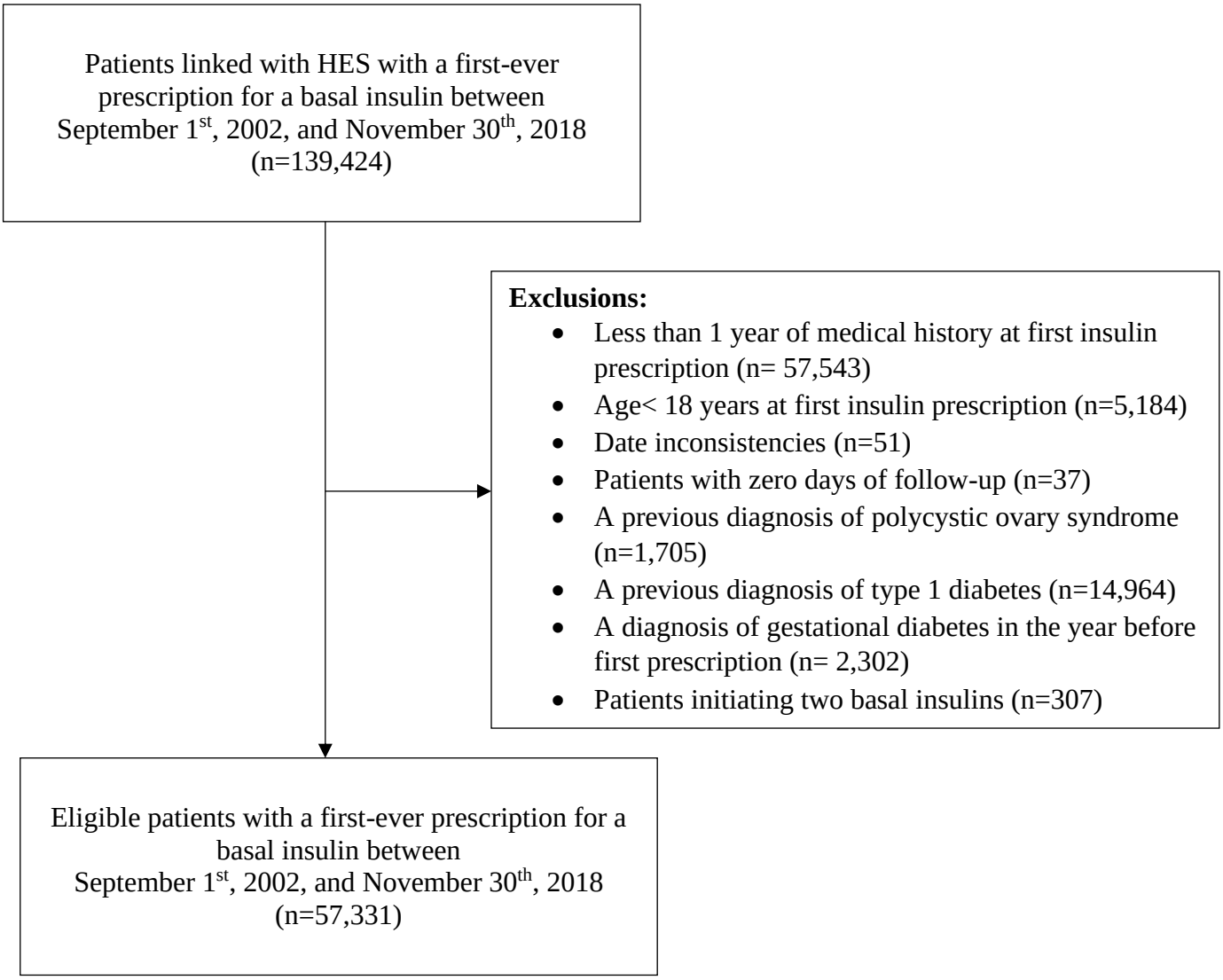
e-Figure 6.3: Flow chart for secondary analysis of the association between current use of long-acting insulin analogues and the risk of ischaemic stroke.



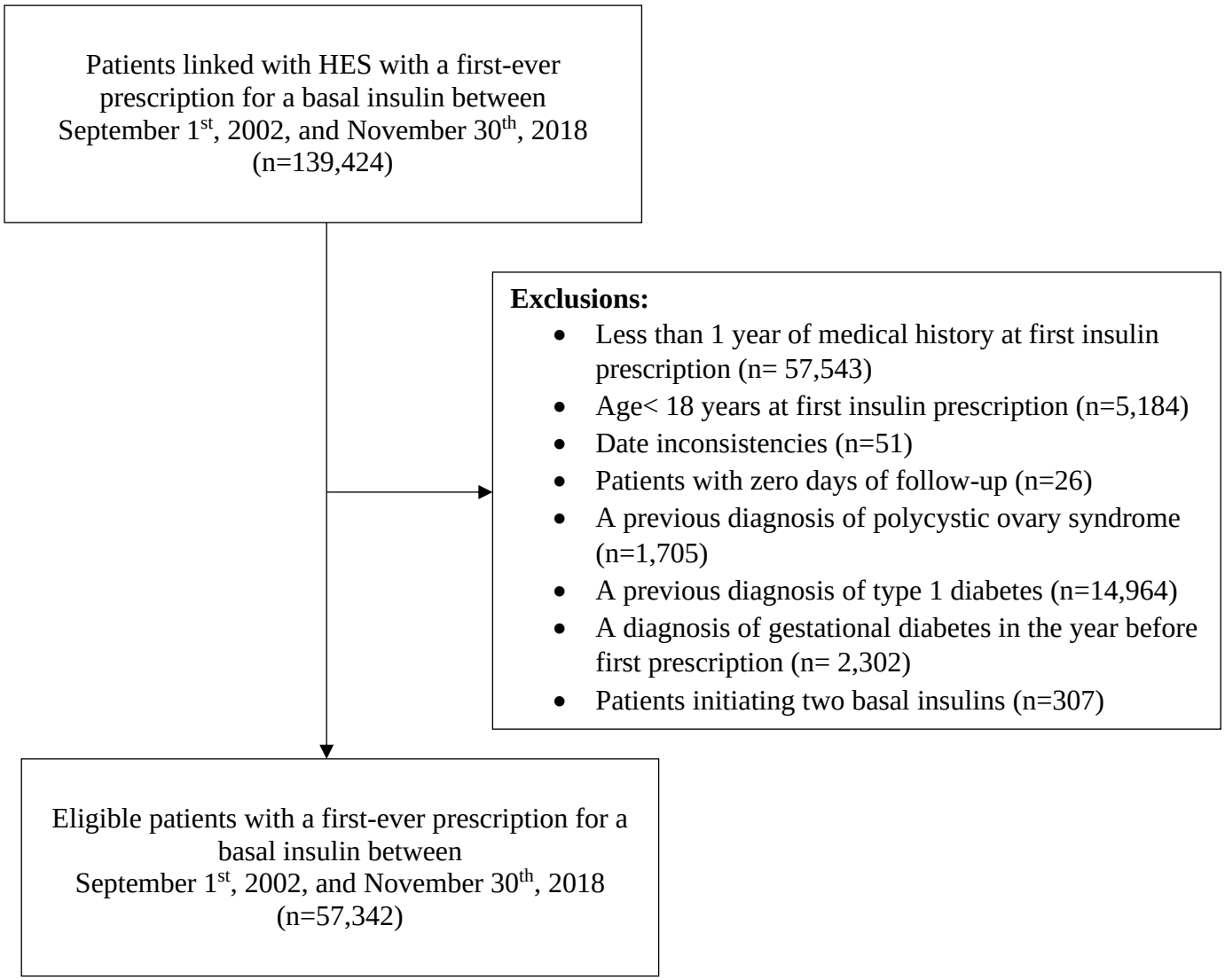
e-Figure 6.4: Flow chart for secondary analysis of the association between current use of long-acting insulin analogues and the risk of cardiovascular death.



e-Figure 6.5: Flow chart for secondary analysis of the association between current use of long-acting insulin analogues and the risk of hospitalization for heart failure.



e-Figure 6.6: Flow chart for secondary analysis of the association between current use of long-acting insulin analogues and the risk of all-cause mortality.



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7. Chapter 7: Manuscript 3- Long-Acting Insulin Analogs versus Neutral Protamine Hagedorn Insulin and the Risk of Severe Hypoglycemia among Patients in Type 2 Diabetes in the United Kingdom

7.1 Preface

In Chapter 6, we found that long-acting insulin analogues were associated with a reduced risk of MACE as compared to NPH insulin. We also found that long-acting insulin analogues were associated with a reduced risk of MI, cardiovascular death, all-cause mortality, and hospitalization for heart failure, but were not associated with a reduced risk of stroke. These results helped us better understand the effectiveness of long-acting insulin analogues and NPH, but additional studies are needed to better evaluate their safety, especially with respect to their risk of severe hypoglycaemia. Nine previous studies evaluated the risk of severe hypoglycaemia with the use of long-acting insulin analogues and NPH, but these studies were also affected by potentially conclusion-altering biases such as immortal-time bias[23,24], differential exposure definition between cases and non-cases[29], no statistical adjustment[30,31], or no comparator group[32]. They also did not include degludec[23,24,29-31,176] . Thus, methodologically rigorous, and contemporary studies were needed to assess the risk of severe hypoglycaemia in patients with type 2 diabetes. Therefore, the objective of this manuscript was to assess the risk of hospitalization for hypoglycaemia associated with the use of long-acting insulin analogues and NPH in patients with type 2 diabetes in the UK.

7.2 Title Page

Long-Acting Insulin Analogs versus Neutral Protamine Hagedorn Insulin and the Risk of Severe Hypoglycemia among Patients with Type 2 Diabetes in the United Kingdom

Running title: Basal Insulins and Risk of Hypoglycemia in Type 2 Diabetes

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7.3 ABSTRACT

Objective: To compare the risk of severe hypoglycemia with long-acting insulin analogs versus NPH insulin among patients with type 2 diabetes in the United Kingdom.

Research Design and Methods: We used the United Kingdom's Clinical Practice Research Datalink Aurum, linked with hospital and vital statistics data, to conduct a retrospective cohort study of patients with type 2 diabetes initiating basal insulin treatment between 2002 and 2018. We used a marginal structural Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of hospitalization for hypoglycemia with current use of long-acting insulin analogs versus NPH insulin, overall and by long-acting insulin molecule, adjusting for time-varying confounders.

Results: Our cohort (n = 57,336 patients) experienced 1,842 severe hypoglycemic events over a mean follow-up duration of 1.7 years (incidence rate: 19.6, 95% CI: 18.8, 20.6 per 1000 person-years). After adjusting for potential confounders, long-acting insulin analogs were associated with a decreased risk of severe hypoglycemia compared to NPH (HR: 0.87, 95% CI: 0.79, 0.95). Secondary analyses by molecule revealed a reduced risk of severe hypoglycemia with glargine compared to NPH (HR: 0.83, 95% CI: 0.74, 0.94). The HRs were 0.93 (95% CI: 0.79, 1.11) for detemir and 1.22 (95% CI: 0.62, 2.37) for degludec.

Conclusions: Current use of long-acting insulin analogs is associated with a reduced risk of severe hypoglycemia compared to current use of NPH insulin among patients with type 2 diabetes.

Key words: type 2 diabetes, insulin, severe hypoglycemia, glargine, detemir, degludec, NPH insulin.

7.4 INTRODUCTION

Basal insulins are currently recommended by guidelines for the treatment of patients with type 2 diabetes with advanced disease or with poorly controlled glycemia[1,2]. Basal insulins include long-acting insulin analogs, namely glargine, determir, and degludec, and intermediate-acting neutral protamine Hagedorn (NPH) human insulin. Randomized controlled trials (RCTs) have shown similar efficacy for long-acting insulin analogs and NPH insulin in terms of glycemic control among patients with types 2 diabetes. However, differences exist in the peak and duration of their action in the bloodstream. NPH insulin peaks after 5-8 hours, and its action in the bloodstream can last up to 18 hours. Conversely, long-acting insulin analogs do not produce this peak, and their action can last between 24 (glargine, detemir) to 42 hours (degludec)[3].

Severe hypoglycemia, characterized by an abnormally low serum glucose level[4], is a well-established safety concern with basal insulins. If left untreated, it can result in complications such as seizures, coma, and death[5]. RCTs have reported a decreased risk of nocturnal hypoglcaemia[6,7] but not symptomatic hypoglaecemia[6] with the use of long-acting insulin analogs compared to NPH. However, RCTs generally include highly-selected patient populations that do not reflect the patients seen in routine clinical practice[8]. Previous observational studies of the risk of hypoglycemia with long-acting insulin analogs and NPH provided mixed results and had important limitations such as immortal-time bias[9,10], differential exposure definitions between cases and non-cases[11], no statistical adjustment[12,13], or had no comparator group[16]. Furthermore, most did not include degludec[9-15], the most recently marketed insulin analog. Due to these important limitations, the risk of hypoglycemia with long-acting insulin analogs versus NPH insulin remains unclear. Therefore, the objective of our study was to compare the risk of severe hypoglycemia with long-acting insulin analogs versus NPH insulin among patients with type 2 diabetes.

7.5 METHODS

7.5.1 Data source

We used the Clinical Practice Research Datalink (CPRD) Aurum to conduct a population-based retrospective cohort study. This database contains the primary care medical records of >19 million patients in the United Kingdom (UK)[17]. It includes information on prescriptions and diagnoses made by general practitioners as well as laboratory test information such as glycated hemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR), anthropometric information such as body mass index (BMI), and blood pressure measurements and lifestyle information such as smoking status. Prescriptions are attributed a ProdCode based on the Dictionary of Medicines and Devices, which is classified following the British National Formulary, and diagnoses are recorded using Read Version 2 codes and Snomed Clinical Terms[18,19] (UK edition) codes[17]. CPRD data were linked to Hospital Episodes Statistics (HES) hospitalization data and the Office for National Statistics (ONS) vital statistics data. In-hospital diagnoses in HES and causes of death in ONS are recorded using the International Classification of Diseases 10th edition (ICD-10), and in-hospital procedures are classified using OPCS Classification of Interventions and Procedures version 4 (OPCS-4) codes[17]. CPRD Aurum data have been extensively validated[20,21]. The CPRD is suitable for the study of diabetes as long-term management of type 2 diabetes is primarily handled by the general practitioners in the UK. In addition, the CPRD Aurum presents 94-98% completeness and 99% correctness for diagnoses related to type 2 diabetes[20].

The Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital have approved this study (protocol number: 19_217RA). This protocol was made available to journal reviewers.

7.5.2 Study population

All patients with type 2 diabetes with a first-ever prescription for a basal insulin between September 1st, 2002 and November 30th, 2018 and linkable with HES and ONS were included in our study. Cohort entry was defined by the date of their first basal insulin prescription, which included long-acting insulin analogs (glargine, detemir, and degludec) and NPH insulin. Patients were excluded from this cohort if they met any of the following criteria at the time of basal insulin initiation: 1) less than 365 days of medical history in the CPRD; 2) age less than 18 years; 3) a previous diagnosis of polycystic ovary syndrome; 4) a previous diagnosis of type 1 diabetes; 5) a diagnosis of gestational diabetes in the year before cohort entry; 6) concomittant initiation of long-acting insulin analogs and NPH at cohort entry; and 7) patients with an outcome on the date of cohort entry (resulting in a follow-up duration of 0 days). Patients were followed from cohort entry until the occurrence of the outcome (defined below) or censoring due to death, end of registration with the CPRD, or November 30th 2018, whichever occurred first.

7.5.3 Exposure

Exposure was defined in a time-varying manner, where each person-month (30 days) of follow-up was classified as either: 1) current use of long-acting insulin analogs (glargine, detemir, or degludec) or 2) current use of NPH insulin. We defined current use using the recorded days of supply of each prescription, which is typically 28 days for insulin in the CPRD. To account for non-adherence, we applied a 30-day grace period to the end of the prescription duration, during which the patient was considered to be exposed. Patients were censored if they received two prescriptions of different types of basal insulin in the same monthly interval (combination use) or if they had no new prescriptions for insulin by the end of the grace period (discontinuation). In the primary analyses, combation use included patients with a long-acting insulin analogue and an NPH

insulin prescription in the same monthly interval. For secondary analyses by molecule, combination use included patients with a prescription for either at least two different long-acting insulin analogues (glargine, detemir, or degludec) or at least one of these molecules and NPH in the same monthy interval.

7.5.4 Outcome

Our primary outcome was severe hypoglycemia, defined as a hospitalization with hypoglycemia (ICD-10: E16.2) in any diagnostic position in HES data. The event date was defined by the date of hospital admission.

7.5.5 Covariates

We assessed 53 time-fixed and time-varying covariates using both the CPRD and HES (**e-Table 7.1** presents the details regarding the measurement and assessment of covariates). These covariates included information on demographics (age, sex, ethnicity, Index of Multiple Deprivation quintile), comorbidities (duration of treated diabetes [defined as the time between the first prescription for an antidiabetic drug and cohort entry date], smoking status, previous history of alcohol-related disorders [alcoholism, cirrhosis, hepatitis, and liver failure], atrial fibrillation, a previous diagnosis of cancer [other than non-melanoma skin cancer], chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, stroke, myocardial infarction, coronary revascularization, acute kidney injury, chronic kidney disease, retinopathy, neuropathy, dialysis and dementia), clinical measurements (BMI, HbA1c, systolic blood pressure [SBP], diastolic blood pressure [DBP], eGFR), use of other antidiabetic drugs (thiazolidinediones, glucagon-like peptide-1 [GLP-1] receptor agonists, alpha-glucosidase inhibitors, meglitinides, sodium-glucose co-transporter 2 [SGLT-2] inhibitors, dipeptidyl-peptidase 4 [DPP-4] inhibitors, other insulin) and use of other drugs (glucagon,

angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, statins, direct oral anticoagulants, antiplatelets, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], use of oral anticoagulants [vitamin K antagonists, direct-acting oral anticoagulants], antiplatelets [clopidogrel, ticagrelor, prasugrel]), glucagon, paracetamol, digoxin, fibrates, and opioids.

7.5.6 Statistical analyses

Means (standard deviations) and proportions were used to summarize the characteristics between users of long-acting insulin analogs and NPH insulin at cohort entry. We also assessed pre- and post-weighting differences between exposure groups at cohort entry using absolute values of standardized differences. We estimated crude incidence rates and 95% confidence intervals (CI) for severe hypoglycemia overall and by exposure group based on the Poisson distribution.

We used marginal structural models (MSM) with time-updated stabilized weights to estimate the association between long-acting insulin analogs and NPH insulin, using follow-up time in 30-day intervals as the underlying time-axis. For each patient, we estimated three time-varying standardized weights at each 30-day intervals. The standardized weights were composed of an inverse probability of treatment weight (IPTW) and two inverse probability of censoring weights (IPCWs). First, we used logistic regression to estimate the numerator and the denominator of the IPTWs. In the numerator, we estimated the probability of the observed treatment given baseline covariates, previous treatment, and month of follow-up duration. In the denominator of the IPTW, we estimated the probability of the observed treatment based on baseline and time-varying covariates, previous treatment, and month of follow-up duration. Second, we estimated two IPCWs to account for potential informative censoring. The first censoring weight ($IPCW_A$) was to account for administrative censoring (end of registration with the CPRD, death, or end of the study period

[November 30, 2018]). The second censoring weight ($IPCW_B$) was to account for censoring related to changes in exposure status (censoring due to combination use or discontinuation). As with the IPTW, the numerator of the $IPCW_A$ and $IPCW_B$ were computed using logistic regression and included baseline covariates, history of treatment, and month of follow-up, and the models used for denominators included baseline and time-varying covariates, history of treatment, and month of follow-up. The three weights (IPTW, $IPCW_A$, $IPCW_B$) were then multiplied to obtain the stabilized weights that were used in our outcome models. The marginal hazard ratio (HR) and 95% CIs for the risk of severe hypoglycemia with the use of long-acting insulin analogs and NPH was estimated using a Cox proportional hazards model, including the stabilized weights with robust variance estimators[22] and adjusted for the baseline covariates described above. The proportional hazards assumption was verified using log-log plots and Schoenfeld residuals. We modelled continuous variables, including age, duration of treated diabetes, and month of follow-up, using restricted cubic splines with 5 knots (3 interior knots) to account for potential non-linear associations and to decrease the variance of the estimator. Variables with missing information were imputed using multiple imputation by chained equations (MICE), with 5 imputed datasets that were analysed separately and pooled using Rubin's rules[23].

We performed six exploratory secondary analyses. We compared the risk of hospitalization for hypoglycemia for each long-acting insulin analog molecule (glargine, detemir, degludec) seperately versus NPH insulin. We used multinomial logistic regression to compute the numerator and denominator of the IPTW in this analysis. In addition, the presence of effect measure modification was evaluated by stratifying our primary analyses by subgroups defined by age (≥70 or <70 years), sex, and history of hospitalization for hypoglycemia at cohort entry.

Six sensitivity analyses were conducted to test the robustness of our findings. First, we augmented the duration of the grace period to 60 and 90 days. Second, we excluded patients with a hospitalization for hypoglycemia in the 30 days prior to cohort entry. Third, we repeated our primary analysis with outcomes restricted to events recorded in the primary or secondary diagnostic positions only and to outcomes with diagnostic codes recorded in the first two days of hospitalization. Fourth, we repeated our primary analysis using a traditional time-dependent Cox proportional hazards model adjusted for baseline covariates to assess how much time-varying confounding had been removed by our use of time-varying inverse probability weights. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

7.6 RESULTS

A total of 57,336 patients were included in our cohort (**Figure 7.1**), including 31,135 patients who used long-acting insulin analogs and 26,201 patients who used NPH insulin at baseline. The mean duration of follow-up was 1.7 years (standard deviation: 2.3), and the median duration was 0.7 years (interquartile range: 0.3, 2.0). During this time, a total of 1,842 hospitalizations for hypoglycemia occurred. The overall incidence rate of hospitalization with hypoglycemia was 19.6 (95% CI: 18.8, 20.6) per 1000 person-years.

Patient characteristics at cohort entry are described in **Table 7.1**. Mean age was 63.8 (SD: 14.2) years, and 44.3% of included patients were women. Before weighting, users of long-acting insulin analogs were less likely to have a history of myocardial infarction and more likely to have used metformin and statins in the year before cohort entry. Characteristics of long-acting insulin analog users and NPH insulin users were well balanced after weighting, with all characteristics having standardized differences < 0.01. Patient characteristics of long-acting insulin analogs varied by molecule subgroups (**e-Table 7.2**). Users of glargine and detemir were more likely to have a history of chronic kidney disease than degludec users, and users of degludec were more likely to have a history of hypertension, dyslipidemia, retinopathy, and COPD and more likely to have used other antidiabetic drugs in the year prior to cohort entry than users of glargine or detemir.

Results from our primary analyses and molecule-specific secondary analyses are reported in **Table 7.2**. After weighting and adjusting for baseline covariates, current use of long-acting insulin analogs was associated with a decreased risk of hospitalization for hypoglycaecemia compared to current use of NPH insulin(HR: 0.87, 95% CI: 0.79, 0.95). In molecule-specific secondary analyses, compared to NPH insulin, insulin glargine was associated with a reduced risk of hospitalization for hypoglycemia (HR: 0.83, 95% CI: 0.74, 0.94) but not detemir (HR: 0.93, 95%

CI: 0.79, 1.11), while results were inconclusive for degludec due to wide confidence intervals (HR: 1.22, 95% CI: 0.62, 2.37).

In subgroup analyses, long-acting insulin analogs were associated with a reduced risk of hospitalization for hypoglycemia among men (HR: 0.85, 95% CI: 0.73 to 0.98) but not among women (HR: 0.93, 95% CI: 0.81, 1.08) (**e-Table 7.3**). Long-acting insulin analogs were associated with a greater reduction in the risk of hospitalization for hypoglycemia among patients with a history of hospitalization for hypoglycemia at cohort entry (HR: 0.73, 95% CI: 0.57, 0.93) than among patients without a history of hospitalization for hypoglycemia at cohort entry (HR: 0.90, 95% CI: 0.80, 1.01). Long-acting insulin analogs were associated with a reduced risk of hospitalization for hypoglycemia in patients with (HR: 0.87, 95% CI: 0.77, 0.99) and without concomitant use of other antidiabetic drugs at baseline (HR: 0.83, 95% CI: 0.69, 1.00).

Results of sensitivity analyses were similar to those of our primary analyses (**Figure 7.2, e-Tables 7.4-7.9**).

7.7 DISCUSSION

The objective of this large, population-based cohort study was to evaluate the risk of severe hypoglycemia with long-acting insulin analogs versus NPH insulin among patients with type 2 diabetes. We found a reduced risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs compared to NPH insulin. Glargine was modestly associated with a reduced risk of hospitalization for hypoglycemia compared to NPH insulin, while detemir was not, and results for degludec were inconclusive. Results were consistent across sensitivity analyses.

The reduced risk of hospitalization for hypoglycemia observed with long-acting insulin analogs compared to NPH insulin is consistent with the pharmacokinetics of these drugs. The peak-less time-action profile of long-acting insulin analogs has been shown to induce gradual glucose absorption, which may reduce the risk of hypoglycemia[24]. In contrast, NPH insulin exerts its peak action in the bloodstream around 5-8 hours after injection, during which there is a greater level of glucose uptake by glucose-sensitive tissues. The increased uptake of glucose during this period could cause hypoglycemia if the glucose uptake is greater than the available glucose (i.e., if the insulin action is greater than what is needed)[4].

Severe hypoglycemia can greatly impact quality of life of patients with type 2 diabetes. In addition to severe negative health outcomes such as coma and death[25], hospitalization for hypoglycemia is associated with substantial economic costs, with the cost of hospital admissions for hypoglycemia estimated to be $17,564 per patient in the United States[26]. With the rise in the use of basal insulin[27], it becomes increasingly important to better understand the safety profiles of these medications to ensure that patients receive optimal treatment. Our results provide important information to help guideline writing committees and physicians advise their patients on treatment options that minimize the risk of hypoglycemic events while ensuring adequate glycemic control.

The risk of severe hypoglycemia with the use of long-acting insulin analogs and NPH insulin has been examined previously, with studies reporting conflicting results. Previous RCTs have reported decreased risks of hypoglycemia with long-acting insulin analogs compared to NPH[6,24,28-32]; similar results were reported in a Cochrane review[33] and other meta-analyses[7,34]. However, most of these RCTs were not designed to assess safety outcomes. In addition, the highly selected patient populations of these trials limit their generalizability to a real-world setting[8].

Observational studies on the risk of hypoglycemia of long-acting insulin analogs and NPH insulin among patients with type 2 diabetes have provided conflicting results. A study using US MarketScan data from 2003-2009 compared glargine to NPH insulin and found similar rates of hypoglycemia between the two groups after one year of follow-up (both 4.4%)[12], a finding confirmed by a subsequent study[35]. In contrast, Rhoads et. al[9] and Cammarota et al.[10] both reported a lower rate of hypoglycemia with insulin glargine than with NPH insulin[36,37]. However Cammarota et al. required users in the glargine group to use it throughout the entire follow-up, and Rhoads et al. imposed a minimum duration of insurance coverage of 1 year during follow-up, both of which may have introduced immortal time bias. Solomon et al. reported an increased risk of severe hypoglycemia with NPH insulin vs glargine (HR: 2.02, 95% CI: 1.25, 3.26), but not detemir (HR: 1.20, 95% CI: 0.43, 3.34)[11]. However, these findings are difficult to interpret given the different exposure definitions used for patients with and without hypoglycemic events: patients who experienced a hypoglycemic event were classified into the exposure category of the insulin type they used most recently, while patients who did not experience a hypoglycemic event were classified in the exposure group corresponding to the insulin they received for the longest duration. In contrast, Strandberg et al. did not find a reduced risk of severe hypoglycemia with glargine compared to NPH insulin (HR: 0.92, 95% CI: 0.74, 1.15) but found a reduced risk with detemir

compared to NPH (HR 0.70, 95% CI: 0.51, 0.94) and detemir compared to glargine (HR 0.76, 95% CI: 0.58, 0.99)[38]. Lipska et al. found no difference in hypoglycemia risk between long-acting insulins and NPH insulin (HR 1.16, 95% CI: 0.71, 1.78)[14], although this study did not include degludec.

Our study has several strengths. First, our exposure definition was in line with current treatment guidelines, which recommend treating patients with type 2 diabetes with either long-acting insulin analogs or NPH, but not both[2]. In addition, as patients with type 2 diabetes using insulin are at an advanced stage of their disease, physician-recommended discontinuation of insulin is unlikely. Censoring patients upon discontinuation or combination use allowed us to reproduce clinical equipoise that would be examined in an RCT. In addition, the use of a time-varying exposure definition was well suited to study acute events such as hospitalization for hypoglycemia. Second, we were able to adjust for potential confounders using patient anthropometric measures (e.g., BMI) and laboratory test results (e.g., HbA1c, eGFR). Third, the population-based nature of this study makes it generalizable to patients seen in everyday practice. Fourth, our contemporary data allowed us to study the use of degludec, which has seldom been included as an exposure in other observational studies in this area.

Our study also has some limitations. First, the CPRD does not capture prescriptions issued in hospital or issued by specialists. However, we were likely able to capture most of the eligible patient population as type 2 diabetes is generally managed by general practitioners in the UK. Second, our study may be affected by residual confounding, as in most observational studies. However, the use of an active comparator and rigorous statistical adjustment reduced this risk. Third, exposure misclassification is possible as the CPRD only records prescriptions and not dispensings or consumption, although we have no reason to believe that this would be differential

between exposure groups. Outcome misclassification may be possible, as the outcome of hypoglycemia has not been formally validated in this data source. However, it has been used in prior studies[39,40], and we do not think this misclassification would differ between groups. Fourth, informative censoring may be present in our study due to our exposure definition where we censored patients upon concomitant basal insulin therapy, discontinuation, or loss to follow-up. However, we used two IPCW models to address this limitation. Fifth, patients must seek medical attendance to be captured in the HES, and thus we only included cases of severe hypoglycemia. It is possible that patients experienced hypoglycemia at home and did not seek help or sought help of non-medical peers. Although we were unable to capture these events, we captured the more clinically and economically relevant events.

7.8 CONCLUSION

We found that the use of long-acting insulin analogs was associated with a modest reduction in the risk of hospitalization for hypoglycemia compared to the use of NPH insulin among patients with type 2 diabetes, and that this risk differs between types of long-acting insulin analogs. This study fills an important gap in the literature on the risk of hypoglycemia associated with basal insulin use. Its results may guide physicians and patients on treatment options that reduce the risk of hospitalization for hypoglycemia among patients with type 2 diabetes using long-acting insulin analogs and NPH.

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7.10 DISCLOSURES

Dr. Platt has received personal fees from Amgen, Analysis Group, Biogen, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser, all outside the submitted work. The other authors have no relationships to disclose. Ms. Brunetti is currently an employee of Analysis Group; this work was completed during her doctoral training at McGill University, prior to her employment at Analysis Group.

7.11 AUTHOR CONTRIBUTIONS

Ms. Brunetti and Dr. Filion conceived the study idea. Ms. Brunetti drafted the manuscript and performed statistical analyses. Ms. Reynier provided programming support. All authors contributed to the study design, were involved in the interpretation of the data, and reviewed the manuscript for intellectual content. Dr. Filion is the guarantor of this study.

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7.13 TABLES

Table 7.1: Characteristics at cohort entry of patients with type 2 diabetes who initiated insulin analogs or NPH between 2002 and 2018 in the United Kingdom, before and after inverse probability of treatment weighting.

	Before weighting				After weighting*			
Characteristics	**Total**	**Analog**	**NPH**	**aSD**	**Total**	**Analog**	**NPH**	**aSD**
N (%)	57,336	31,135	26,201	-	114,661	57,390	57,271	-
Female	25,397 (44.3)	13,537 (43.5)	11,860 (45.3)	0.036	50,892 (44.4)	25,472 (44.4)	25,420 (44.4)	0.000
Age, years, mean (SD)	63.8 (14.2)	63.3 (14.2)	64.4 (14.1)	0.078	63.8 (20.1)	63.8 (19.6)	63.9 (20.7)	0.001
<40	3,506 (6.1)	1,854 (6.0)	1,652 (6.3)		7,008 (6.1)	3,375 (5.9)	3,634 (6.3)	
40 – 49.9	6,333 (11.0)	3,821 (12.3)	2,512 (9.6)		23,699 (20.7)	12,117 (21.1)	11,583 (20.2)	
50 – 59.9	11,898 (20.8)	6,842 (22.0)	5,056 (19.3)		29,509 (25.7)	14,253 (24.8)	15,257 (26.6)	
60 – 69.9	14,725 (25.7)	7,824 (25.1)	6,901 (26.3)		27,328 (23.8)	13,027 (22.7)	14,302 (25.0)	
70 – 79.9	13,610 (23.7)	6,877 (22.1)	6,733 (25.7)		12,497 (10.9)	6,684 (11.6)	5,813 (10.2)	
80+	7,264 (12.7)	3,917 (12.6)	3,347 (12.8)		14,619 (12.7)	7,935 (13.8)	6,684 (11.7)	
Year of cohort entry, N (%)				0.106				0.001
2002	801 (1.4)	122 (0.4)	679 (2.6)		1,756 (1.5)	217 (0.4)	1,539 (2.7)	
2003	3,189 (5.6)	939 (3.0)	2,250 (8.6)		6,847 (6.0)	1,659 (2.9)	5,188 (9.1)	
2004	3,338 (5.8)	1,583 (5.1)	1,755 (6.7)		6,809 (5.9)	2,738 (4.8)	4,071 (7.1)	
2005	2,971 (5.2)	1,770 (5.7)	1,201 (4.6)		5,852 (5.1)	3,070 (5.4)	2,782 (4.9)	
2006	3,195 (5.6)	2,117 (6.8)	1,078 (4.1)		6,112 (5.3)	3,620 (6.3)	2,492 (4.4)	
2007	3,416 (6.0)	2,446 (7.9)	970 (3.7)		6,482 (5.7)	4,214 (7.3)	2,268 (4.0)	
2008	3,002 (5.2)	2,229 (7.2)	773 (3.0)		5,641 (4.9)	3,859 (6.7)	1,781 (3.1)	
2009	3,005 (5.2)	2,320 (7.5)	685 (2.6)		5,648 (4.9)	4,096 (7.1)	1,552 (2.7)	
2010	2,932 (5.1)	2,284 (7.3)	648 (2.5)		5,531 (4.8)	4,086 (7.1)	1,445 (2.5)	
2011	3,225 (5.6)	2,118 (6.8)	1,107 (4.2)		6,382 (5.6)	3,883 (6.8)	2,499 (4.4)	
2012	3,653 (6.4)	1,892 (6.1)	1,761 (6.7)		7,455 (6.5)	3,540 (6.2)	3,915 (6.8)	
2013	3,685 (6.4)	1,738 (5.6)	1,947 (7.4)		7,509 (6.6)	3,278 (5.7)	4,231 (7.4)	
2014	3,959 (6.9)	1,737 (5.6)	2,222 (8.5)		8,108 (7.1)	3,323 (5.8)	4,785 (8.4)	
2015	4,448 (7.8)	1,897 (6.1)	2,591 (9.9)		9,163 (8.0)	3,705 (6.5)	5,458 (9.5)	

2016	4,219 (7.4)	1,943 (6.2)	2,276 (8.7)		8,587 (7.5)	3,902 (6.8)	4,685 (8.2)	
2017	4,294 (7.5)	2,066 (6.6)	2,228 (8.5)		8,714 (7.6)	4,204 (7.3)	4,510 (7.9)	
2018	3,964 (6.9)	1,934 (6.2)	2,030 (7.8)		8,063 (7.0)	3,994 (7.0)	4,068 (7.1)	
Duration of treated diabetes, years, mean (SD)	6.3 (5.0)	6.3 (4.8)	6.3 (5.2)	0.014	6.3 (7.0)	6.3 (6.6)	6.3 (7.5)	0.001
Ethnicity				0.037				0.000
Caucasian	46,103 (80.4)	25,075 (80.5)	21,028 (80.3)		96,728 (84.4)	48,398 (84.3)	48,330 (84.4)	
Non-Caucasian	8,603 (15.0)	4,522 (14.5)	4,081 (15.6)		17,933 (15.6)	8,992 (15.7)	8,941 (15.6)	
Missing	2,630 (4.6)	1,538 (4.9)	1,092 (4.2)		-	-	-	
Index of multiple deprivation				0.010				0.000
1	10,065 (17.6)	5,456 (17.5)	4,609 (17.6)		20,171 (17.6)	10,090 (17.6)	10,081 (17.6)	
2	10,738 (18.7)	5,983 (19.2)	4,755 (18.1)		21,493 (18.7)	10,755 (18.7)	10,737 (18.7)	
3	11,157 (19.5)	6,011 (19.3)	5,146 (19.6)		22,354 (19.5)	11,191 (19.5)	11,163 (19.5)	
4	12,322 (21.5)	6,578 (21.1)	5,744 (21.9)		24,657 (21.5)	12,343 (21.5)	12,315 (21.5)	
5	12,986 (22.6)	7,072 (22.7)	5,914 (22.6)		25,986 (22.7)	13,011 (22.7)	12,975 (22.7)	
Missing	68 (0.1)	35 (0.1)	33 (0.1)		-	-	-	
Smoking	42,483 (74.1)	23,025 (74.0)	19,458 (74.3)	0.007	49,431 (77.6)	24,776 (77.6)	24,655 (77.6)	0.000
BMI, kg/m^2, mean (SD)	30.9 (6.7)	30.9 (6.8)	30.9 (6.7)	0.007	30.8 (9.5)	30.8 (9.2)	30.8 (9.8)	0.000
<25	9,620 (16.8)	5,334 (17.1)	4,286 (16.4)		20,503 (17.9)	10,439 (18.2)	10,064 (17.6)	
25 – 29.9	17,250 (30.1)	9,467 (30.4)	7,783 (29.7)		36,146 (31.5)	18,004 (31.4)	18,142 (31.7)	
30 – 34.9	14,858 (25.9)	8,107 (26.0)	6,751 (25.8)		31,242 (27.2)	15,452 (26.9)	15,790 (27.6)	
35 - 39.9	7,657 (13.4)	4,185 (13.4)	3,472 (13.3)		16,327 (14.2)	8,130 (14.2)	8,198 (14.3)	
40+	5,050 (8.8)	2,787 (9.0)	2,263 (8.6)		10,443 (9.1)	5,366 (9.3)	5,078 (8.9)	
Missing	2,901 (5.1)	1,255 (4.0)	1,646 (6.3)		-	-	-	
HbA1c				0.013				0.001
%, mean (SD)	9.7 (2.2)	9.7 (2.1)	9.7 (2.2)		9.7 (3.1)	9.7 (2.9)	9.7 (3.2)	
mmol/mol	83	83	83		83	83	83	
<6.5 [<48]	2,471 (4.3)	1,131 (3.6)	1,340 (5.1)		5,424 (4.7)	2,422 (4.2)	3,003 (5.2)	
6.5 – 8 [48 – 63]	8,699 (15.2)	4,698 (15.1)	4,001 (15.3)		18,464 (16.1)	9,154 (15.9)	9,310 (16.3)	

8+ [64+]	41,780 (72.9)	23,455 (75.3)	18,325 (69.9)		90,773 (79.2)	45,814 (79.8)	44,958 (78.5)	
Missing	4,386 (7.6)	1,851 (3.2)	2,535 (9.7)		-	-	-	
eGFR, ml/min/1.73m^2, mean (SD)	69.8 (20.5)	69.9 (20.3)	69.7 (20.7)	0.010	69.8 (29.0)	69.8 (27.8)	69.8 (30.4)	0.000
<60	10,684 (30.0)	5,872 (18.9)	4,812 (18.4)		32,091 (28.0)	15,796 (27.5)	16,295 (28.5)	
60+	24,957 (43.5)	14,315 (46.0)	10,642 (40.6)		82,570 (72.0)	41,594 (72.5)	40,976 (71.5)	
Missing	21,695 (37.8)	10,948 (35.2)	10,747 (41.0)		-	-	-	
SBP, mmHg, mean (SD)	133.4 (17.2)	133.4 (17.0)	133.3 (17.5)	0.009	133.4 (24.4)	133.4 (23.2)	133.4 (25.8)	0.001
DBP, mmHg, mean (SD)	76.1 (10.3)	76.4 (10.2)	75.8 (10.3)	0.058	76.2 (14.5)	76.1 (13.9)	76.2 (15.2)	0.000
Comorbidities								
Acute kidney injury	6,589 (11.5)	3,146 (10.1)	3,443 (13.1)	0.095	13,404 (11.7)	6,715 (11.7)	6,689 (11.7)	0.001
Alcohol-related disease	13,071 (22.8)	6,958 (22.3)	6,113 (23.3)	0.023	26,136 (22.8)	13,086 (22.8)	13,049 (22.0)	0.000
Atrial fibrillation	5,388 (9.4)	2,773 (8.9)	2,615 (10.0)	0.037	10,865 (9.5)	5,436 (9.5)	5,428 (9.5)	0.000
Cancer	8,737 (15.2)	4,439 (14.3)	4,298 (16.4)	0.06	17,575 (15.3)	8,801 (15.3)	8,773 (15.3)	0.000
Chronic kidney disease	13,641 (23.8)	7,283 (23.4)	6,358 (24.3)	0.021	27,448 (23.9)	13,736 (23.9)	13,712 (23.9)	0.000
COPD	8,257 (14.4)	4,268 (13.7)	3,989 (15.2)	0.043	16,544 (14.4)	8,283 (14.4)	8,261 (14.4)	0.000
Coronary artery disease	17,766 (31.0)	9,186 (29.5)	8,580 (32.7)	0.07	35,585 (31.0)	17,801 (31.0)	17,784 (31.1)	0.001
Coronary revascularization	4,465 (7.8)	2,256 (7.2)	2,209 (8.4)	0.044	8,979 (7.8)	4,493 (7.8)	4,486 (7.8)	0.000
Dementia	1,015 (1.8)	579 (1.9)	436 (1.7)	0.015	2,080 (1.8)	1,036 (1.8)	1,044 (1.8)	0.001
Dialysis	489 (0.9)	234 (0.8)	255 (1.0)	0.024	992 (0.9)	497 (0.9)	495 (0.9)	0.000
Dyslipidemia	54,519 (95.1)	29,837 (95.8)	24,682 (94.2)	0.075	109,053(95.1)	54,584 (95.1)	54,469 (95.1)	0.000
Hypertension	34,592 (60.3)	18,868 (60.6)	15,724 (60.0)	0.012	69,269 (60.4)	34,664 (60.4)	34,605 (60.4)	0.000

Hypoglycemia	5,944 (10.4)	3,164 (10.2)	2,777 (10.6)	0.014	11,950 (10.4)	5,983 (10.4)	5,967 (10.4)	0.000
Myocardial infarction	3,897 (6.8)	1,698 (5.5)	2,199 (8.4)	0.116	7,817 (6.8)	3,913 (6.8)	3,904 (6.8)	0.000
Neuropathy	3,484 (6.1)	1,951 (6.3)	1,533 (5.9)	0.017	7,030 (6.1)	3,512 (6.1)	3,518 (6.1)	0.001
Peripheral vascular disease	7,417 (12.9)	3,943 (12.7)	3,474 (13.3)	0.018	14,879 (13.0)	7,443 (13.0)	7,436 (13.0)	0.000
Retinopathy	25,052 (43.7)	13,623 (43.8)	11,429 (43.6)	0.003	50,222 (43.8)	25,134 (43.8)	25,088 (43.8)	0.000
Stroke	2,397 (4.2)	1,196 (3.8)	1,201 (4.6)	0.037	4,838 (4.2)	2,423 (4.2)	2,416 (4.2)	0.000
Thyroid disorders	2,952 (5.1)	1,544 (5.0)	1,408 (5.4)	0.019	5,926 (5.2)	2,963 (5.2)	2,963 (5.2)	0.001
Previous use of antidiabetic drugs								
Metformin	43,422 (75.7)	24,332 (78.1)	19,090 (72.9)	0.123	86,750 (75.7)	43,424 (75.7)	43,326 (75.7)	0.000
Sulfonylureas	39,994 (69.8)	22,079 (70.9)	17,915 (68.4)	0.055	80,067 (69.8)	40,064 (69.8)	40,002 (69.8)	0.001
TZD	26,931 (47.0)	15,318 (49.2)	11,613 (44.3)	0.098	53,931 (47.0)	27,004 (47.1)	26,927 (47.0)	0.001
DPP-4 inhibitors	13,399 (23.4)	7,017 (22.5)	6,382 (24.4)	0.043	26,955 (23.5)	13,489 (23.5)	13,466 (23.5)	0.000
GLP-1 receptor agonists	5,530 (9.6)	3,010 (9.7)	2,520 (9.6)	0.002	11,197 (9.8)	5,598 (9.8)	5,599 (9.8)	0.001
Alpha-glucosidase inhibitors	973 (1.7)	521 (1.7)	452 (1.7)	0.004	2,043 (1.8)	850 (1.5)	1,192 (2.1)	0.045
SGLT-2 inhibitors	2,569 (4.5)	1,286 (4.1)	1,283 (4.9)	0.037	5,211 (4.5)	2,607 (4.5)	2,604 (4.5)	0.000
Previous use of other drugs								
ACE inhibitors	29,113 (50.8)	15,942 (51.2)	13,171 (50.3)	0.019	58,205 (50.8)	29,133 (50.8)	29,072 (50.8)	0.000
Antiplatelets	24,523 (42.8)	13,802 (44.3)	10,721 (40.9)	0.069	48,950 (42.7)	24,514 (42.7)	24,436 (42.7)	0.001
ARB	17,203 (30.0)	9,409 (30.2)	7,794 (29.7)	0.01	34,421 (30.0)	17,235 (30.0)	17,186 (30.0)	0.000
Beta-blockers	16,825 (29.3)	8,797 (28.3)	8,028 (30.6)	0.052	33,787 (29.5)	16,903 (29.5)	16,885 (29.5)	0.001

Calcium-channel blockers	17,084 (29.8)	9,152 (29.4)	7,932 (30.3)	0.019	34,202 (29.8)	17,115 (29.8)	17,087 (29.8)	0.000
Digoxin	3,031 (5.3)	1,645 (5.3)	1,386 (5.3)	0.000	6,094 (5.3)	3,045 (5.3)	3,048 (5.3)	0.001
Diuretics	21,213 (37.0)	11,399 (36.6)	9,814 (37.5)	0.018	42,516 (37.1)	21,266 (37.1)	21,249 (37.1)	0.001
DOAC	870 (1.5)	404 (1.3)	466 (1.8)	0.039	1,773 (1.5)	889 (1.5)	883 (1.5)	0.001
Fibrate	1,667 (2.9)	989 (3.2)	678 (2.6)	0.035	3,331 (2.9)	1,668 (2.9)	1,664 (2.9)	0.000
Glucagon	196 (0.3)	120 (0.4)	76 (0.3)	0.016	396 (0.3)	197 (0.3)	199 (0.3)	0.001
NSAIDs	13,601 (23.7)	7,400 (23.8)	6,201 (23.7)	0.002	27,205 (23.7)	13,613 (23.7)	13,592 (23.7)	0.000
Opioids	22,648 (39.5)	12,166 (39.1)	10,482 (40.0)	0.019	45,456 (39.6)	22,744 (39.6)	22,711 (39.6)	0.000
Paracetamol	23,857 (41.6)	12,799 (41.1)	11,058 (42.2)	0.022	47,867 (41.7)	23,954 (41.7)	23,913 (41.8)	0.000
Statins	40,280 (70.3)	22,580 (72.5)	17,700 (67.6)	0.109	80,445 (70.2)	40,280 (70.2)	40,165 (70.1)	0.001

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs.

Table 7.2: Risk of severe hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK.

Exposure	Events	Person-years	Crude IR (95% CI) *	Crude HR (95% CI)	Adjusted HR (95% CI) †‡§
Overall	1,842	93,749	19.6 (18.8, 20.6)	-	-
NPH	934	40,685	23.0 (21.5, 24.5)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	908	53,065	17.1 (16.0, 18.3)	0.74 (0.67, 0.81)	0.87 (0.79, 0.95)
Glargine	630¶	36,844¶	17.1 (15.8, 18.5)	0.73 (0.66, 0.81)	0.83 (0.74, 0.94)
Detemir	231¶	13,755¶	16.8 (14.8, 19.1)	0.73 (0.64, 0.85)	0.93 (0.79, 1.11)
Degludec	9¶	427¶	21.1 (11.0, 40.5)	0.95 (0.49, 1.82)	1.22 (0.62, 2.37)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval

*Per 1000 person-years

†Models using standardized weights generated for the marginal structural model. See appendix for detailed list of included variables.

‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.

§The model was adjusted for the following covariates at baseline: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status, history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, opioids . Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

¶ Sum of events and person-time in molecule specific analyses do not add up to the totals for long-acting insulin analogs due to censoring upon combination use.

7.14 FIGURE LEGENDS

Figure 7.1: Study cohort flow chart including people with type 2 diabetes initiating use of basal insulins in the United Kingdom between 2002 and 2018. Abbreviations: HES: Hospital Episodes Statistics, NPH: neutral protamine Hagedorn.

Figure 7.2: Forest plot of sensitivity analyses of risk of hospitalization for hypoglycemia with long-acting insulin analogs versus NPH among patients with type 2 diabetes. Abbreviations: HH: Hospitalization for hypoglycemia, HR: hazard ratio.

7.15 FIGURES

Figure 7.1

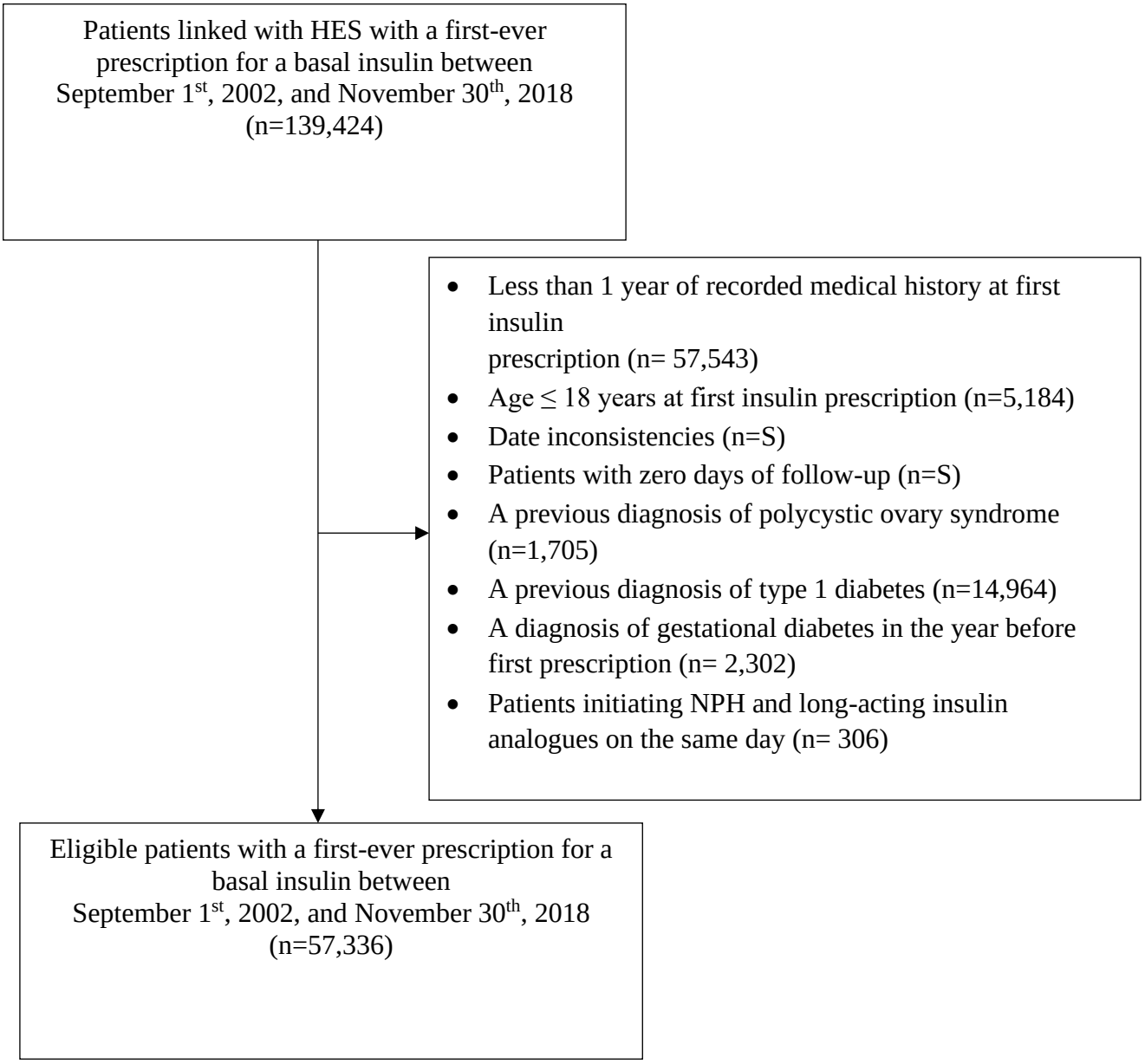
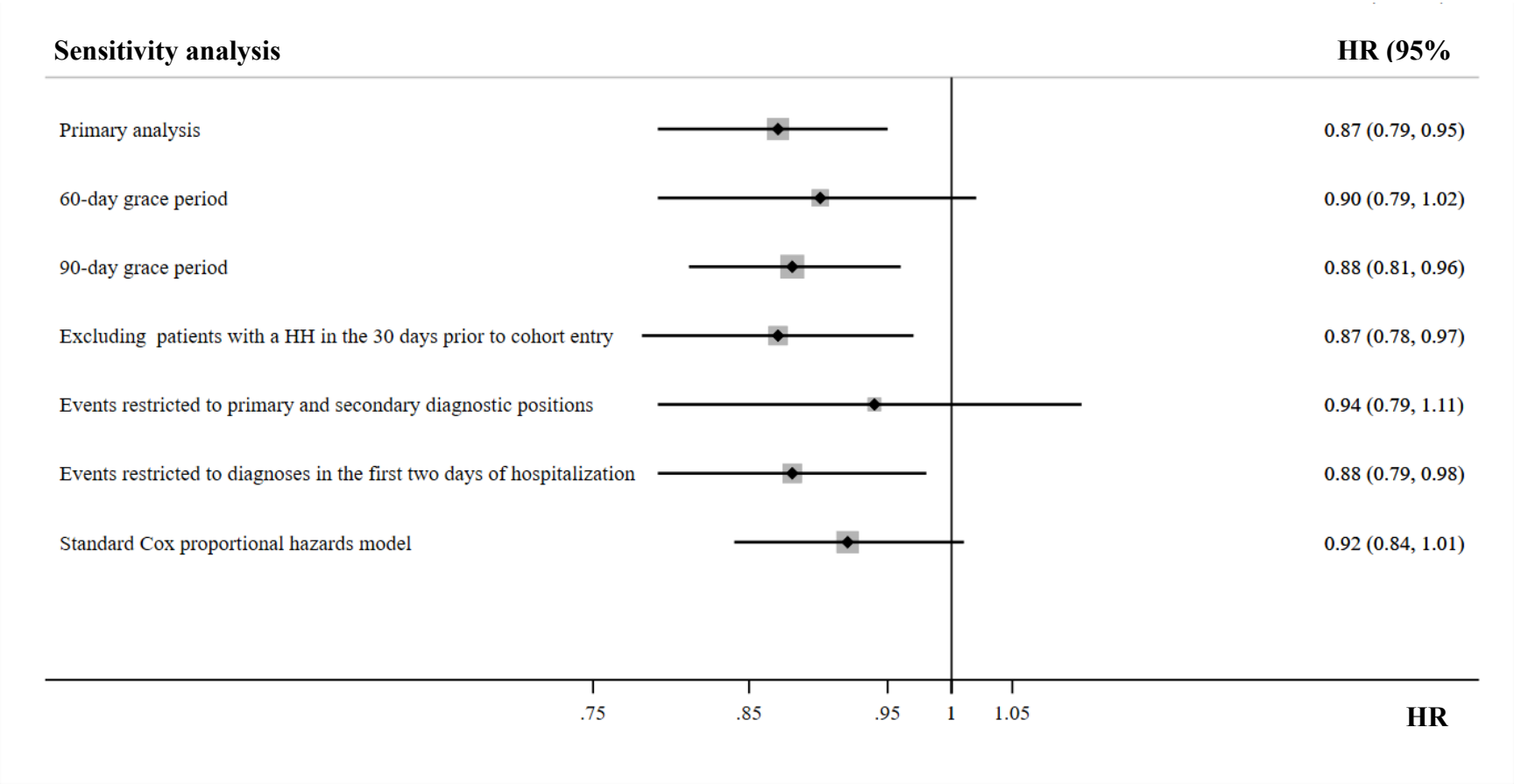


Figure 7.2


Sensitivity analysis
HR (95%
Primary analysis
0.87 (0.79, 0.95)
60-day grace period
0.90 (0.79, 1.02)
90-day grace period
0.88 (0.81, 0.96)
Excluding patients with a HH in the 30 days prior to cohort entry
0.87 (0.78, 0.97)
Events restricted to primary and secondary diagnostic positions
0.94 (0.79, 1.11)
Events restricted to diagnoses in the first two days of hospitalization
0.88 (0.79, 0.98)
Standard Cox proportional hazards model
0.92 (0.84, 1.01)
.75
.85
.95
1
1.05
HR

7.16 SUPPLEMENTARY MATERIAL

e-Table 7.1: Description of covariates, their assessment windows, and the models in which they were included.

Characteristic	**Description**	**Baseline lookback**	**Time varying assessment**	**IPTW**	**IPCW$_A$**	**IPCW$_B$**	**Outcome model**
Demographic							
Age		Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Sex	women, men	N/A	N/A	yes	yes	yes	yes
Ethnicity	Caucasian, other	N/A	N/A	yes	yes	yes	yes
Income quintile	1 (least deprived) to 5 (most deprived)	N/A	N/A	yes	yes	yes	yes
Duration of treated diabetes	Defined as time between the first prescription of antidiabetic drugs and cohort entry	Defined at cohort entry date	updated at 30-day intervals	yes	yes	yes	yes, baseline only
Smoking status	ever/never	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Clinical measurements							
Body mass index (BMI)	continuous, kg/m^2	latest measurement in	updated every 365 days	yes	yes	yes	yes, baseline only

		the year prior to cohort entry					
Glycated hemoglobin A1c (HbA1c)	continuous, %	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Estimated glomerular filtration rate (eGFR)	continuous, ml/min/1.73m^2	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Systolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Diastolic blood pressure	continuous, mmHg	latest measurement in the year prior to cohort entry	updated every 365 days	yes	yes	yes	yes, baseline only
Comorbidities							
Alcohol related disorders (alcoholism, cirrhosis, hepatitis, and liver failure)	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Atrial fibrillation	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Cancer	other than non-melanoma skin cancer yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
COPD	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only

Coronary artery disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dyslipidemia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Hypertension	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Peripheral vascular disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Myocardial infarction	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Stroke	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Peripheral vascular disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Thyroid disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Acute kidney injury	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Chronic kidney disease	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Retinopathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Neuropathy	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dialysis	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Dementia	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Glucagon use	yes/no	any time prior to cohort entry	ever/never, updated at 30-day intervals	yes	yes	yes	yes, baseline only
Use of antidiabetic drugs							
Metformin	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only

Sulfonylureas	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Thiazolidinediones	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
DPP-4 inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
SGLT-2 inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
GLP-1 receptor agonists	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Alpha-glucosidase inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Meglitinides	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
non-basal insulin	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Use of other drugs							
Angiotensin-converting enzyme inhibitors	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Angiotensin II receptor blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Beta-blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Calcium channel blockers	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Diuretics	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Direct oral anticoagulants	vitamin K antagonists, direct-acting oral	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only

	anticoagulants yes/no						
Antiplatelets	clopidogrel, ticagrelor, prasugrel yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Statins	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Acetylsalicylic acid	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Nonsteroidal anti-inflammatory drugs	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Paracetamol	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Digoxin	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Fibrates	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only
Opioids	yes/no	year prior to cohort entry	updated every 30 days	yes	yes	yes	yes, baseline only

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs

e-Table 7.2: Characteristics at cohort entry of initiators of detemir, glargine, and degludec among patients with type 2 diabetes in the UK.

Characteristic	NPH	Detemir	Glargine	Degludec
N (%) *	26,201 (45.8)	8,370 (14.6)	22,224 (38.8)	437 (0.8)
Female	11,860 (45.3)	3,758 (44.9)	9,537 (42.9)	193 (44.2)
Age, years, mean (SD)	64.4 (14.1)	64.4 (14.1)	64.0 (14.1)	61.5 (13.2)
<40	1,652 (6.3)	677 (8.1)	1,144 (5.1)	26 (5.9)
40 – 49.9	2,512 (9.6)	1,183 (14.1)	2,579 (11.6)	46 (10.5)
50 – 59.9	5,056 (19.3)	1,900 (22.7)	4,784 (21.5)	130 (29.7)
60 – 69.9	6,901 (26.3)	2,087 (24.9)	5,590 (25.2)	123 (28.1)
70 – 79.9	6,733 (25.7)	1,714 (20.5)	5,069 (22.8)	77 (17.6)
80+	3,347 (12.8)	809 (9.7)	3,058 (13.8)	35 (8.0)
Duration of treated diabetes, years, mean (SD)	6.3 (5.2)	6.3 (5.2)	6.3 (4.8)	8.0 (5.4)
Ethnicity				
Caucasian	21,028 (80.3)	6,824 (81.5)	17,802 (80.1)	356 (81.5)
Non-Caucasian	4,081 (15.6)	1,127 (13.5)	3,340 (15.0)	48 (11.0)
Missing	1,092 (4.2)	419 (5.0)	1,082 (4.9)	33 (7.6)
Index of Multiple Deprivation				
1	4,609 (17.6)	1,533 (18.3)	3,812 (17.2)	92 (21.1)
2	4,755 (18.1)	1,703 (20.3)	4,171 (18.8)	88 (20.1)
3	5,146 (19.6)	1,613 (19.3)	4,297 (19.3)	80 (18.3)
4	5,744 (21.9)	1,690 (20.2)	4,775 (21.5)	96 (22.0)
5	5,914 (22.6)	1,823 (21.8)	5,142 (23.1)	81 (18.5)
Missing	33 (0.1)	8 (0.1)	27 (0.1)	0 (0.0)
Smoking	19,458 (74.3)	6,192 (74.0)	16,419 (73.9)	340 (77.8)
BMI, kg/m^2, mean (SD)	30.9 (6.7)	30.9 (6.7)	30.6 (6.6)	33.7 (7.7)
<25	4,286 (16.4)	1,310 (15.7)	3,956 (17.8)	46 (10.5)
25 – 29.9	7,783 (29.7)	2,407 (28.8)	6,931 (31.2)	98 (22.4)
30 – 34.9	6,751 (25.8)	2,279 (27.2)	5,693 (25.6)	112 (25.6)
35 – 39.9	3,472 (13.3)	1,251 (14.9)	2,822 (12.7)	96 (22.0)
40+	2,263 (8.6)	893 (10.7)	1,813 (8.2)	75 (17.2)
Missing	1,646 (6.3)	230 (2.7)	1,009 (4.5)	10 (2.3)

HbA1c				
%, mean (SD)	9.7 (2.2)	9.7 (2.2)	9.7 (2.1)	10.1 (2.1)
mmol/mol, mean	83	83	83	87
<6.5 [<48]	1,340 (5.1)	335 (4.0)	789 (3.6)	6 (1.4)
6.5 – 7.9 [48 – 63]	4,001 (15.3)	1,112 (13.3)	3,509 (15.8)	59 (13.5)
8+ [64+]	18,325 (69.9)	6,416 (76.7)	16,598 (74.7)	363 (83.1)
Missing	2.535 (9.7)	507 (6.1)	1,328 (6.0)	9 (2.1)
eGFR, ml/min/1.73m^2, mean (SD)	69.7 (20.7)	68.0 (21.3)	67.6 (20.8)	73.3 (17.9)
<60	4,812 (18.4)	1,529 (18.3)	4,235 (19.1)	65 (14.9)
60+	10,642 (40.6)	4,315 (51.6)	9,638 (43.4)	310 (70.9)
Missing	10,747 (41.0)	2,526 (30.2)	8,333 (37.5)	62 (14.2)
SBP, mmHg, mean (SD)	133.3 (17.5)	132.7 (16.5)	133.9 (17.2)	130.3 (13.3)
DBP, mmHg, mean (SD)	75.8 (10.3)	76.3 (10.0)	76.4 (10.2)	75.4 (8.9)
Comorbidities				
Acute kidney injury	3,443 (13.1)	657 (7.8)	2,401 (10.8)	77 (17.6)
Alcohol-related disease	6,113 (23.3)	1,977 (23.6)	4,829 (21.7)	127 (29.1)
Atrial fibrillation	2,615 (10.0)	677 (8.1)	2,040 (9.2)	45 (10.3)
Cancer	4,298 (16.4)	1,145 (13.7)	3,236 (14.6)	46 (10.5)
Chronic kidney disease	6,358 (24.3)	2,001 (23.9)	5,168 (23.3)	84 (19.2)
COPD	3,989 (15.2)	1,152 (13.8)	3,031 (13.6)	71 (16.2)
Coronary artery disease	8,580 (32.7)	2,277 (27.2)	6,759 (30.4)	122 (27.9)
Coronary revascularization	2,209 (8.4)	578 (6.9)	1,642 (7.4)	30 (6.9)
Dementia	436 (1.7)	S	165 (0.7)	S
Dialysis	255 (1.0)	66 (0.8)	165 (0.7)	3 (0.7)
Dyslipidemia	24,682 (94.2)	7,983 (95.4)	21,328 (96.0)	429 (98.2)
Hypertension	15,724 (60.0)	4,960 (59.3)	13,564 (61.0)	287 (65.7)
Hypoglycemia	2,777 (10.6)	739 (8.8)	2,332 (10.5)	82 (18.8)
Myocardial infarction	2,199 (8.4)	422 (5.0)	1,250 (5.6)	22 (5.0)
Neuropathy	1,533 (5.9)	487 (5.8)	1,428 (6.4)	31 (7.1)
Peripheral vascular disease	3,474 (13.3)	899 (10.7)	2,985 (13.4)	50 (11.4)
Retinopathy	11,429 (43.6)	3,851 (46.0)	9,477 (42.6)	253 (57.9)
Stroke	1,201 (4.6)	254 (3.0)	922 (4.1)	18 (4.1)

Thyroid disorders	1,408 (5.4)	426 (5.1)	1,097 (4.9)	18 (4.1)
Previous use of other antidiabetic drugs				
Metformin	19,090 (72.9)	6,604 (78.9)	17,286 (77.8)	369 (84.4)
Sulfonylureas	17,915 (68.4)	5,795 (69.2)	15,941 (71.7)	271 (62.0)
TZD	11,613 (44.3)	4,253 (50.8)	10,659 (48.0)	359 (82.2)
DPP-4 inhibitors	6,382 (24.4)	1,955 (23.4)	4,870 (21.9)	174 (39.8)
GLP-1 receptor agonists	2,520 (9.6)	1,062 (12.7)	1,673 (7.5)	261 (59.7)
Alpha-glucosidase inhibitors	452 (1.7)	S	391 (1.8)	S
SGLT-2 inhibitors	1,283 (4.9)	234 (2.8)	925 (4.2)	125 (28.6)
Previous use of other drugs				
ACE inhibitors	13,171 (50.3)	4,304 (51.4)	11,360 (51.1)	229 (52.4)
Antiplatelets	10,721 (40.9)	3,611 (43.1)	10,018 (45.1)	133 (30.4)
ARB	7,794 (29.7)	2,538 (30.3)	6,699 (30.1)	139 (31.8)
Beta-blockers	8,028 (30.6)	2,329 (27.8)	6,326 (28.5)	113 (25.9)
Calcium-channel blockers	7,932 (30.3)	2,408 (28.8)	6,599 (29.7)	117 (26.8)
Digoxin	1,386 (5.3)	405 (4.8)	1,212 (5.5)	21 (4.8)
Diuretics	9,814 (37.5)	2,937 (35.1)	8,303 (37.4)	121 (27.7)
DOAC	466 (1.8)	91 (1.1)	289 (1.3)	23 (5.3)
Fibrates	678 (2.6)	265 (3.2)	714 (3.2)	8 (1.8)
Glucagon	76 (0.3)	S	85 (0.4)	S
NSAID	6,201 (23.7)	1,972 (23.6)	5,285 (23.8)	115 (26.3)
Opioids	10,482 (40.0)	3,228 (38.6)	8,716 (39.2)	178 (40.7)
Paracetamol	11,058 (42.2)	3,311 (39.6)	9,283 (41.8)	159 (36.4)
Statins	17,700 (67.6)	6,165 (73.7)	16,006 (72.0)	332 (76.0)

Abbreviations: NPH: neutral protamine Hagedorn, aSD: absolute standardized difference, SD: standard deviation. BMI: body mass index, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, COPD: chronic obstructive pulmonary disorder, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1, SGLT-2: sodium-glucose co-transporter 2, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, DOAC: direct oral anticoagulants, NSAID: non-steroidal anti-inflammatory drugs; S: suppressed data due to small cells and the CPRD's privacy policies.

e-Table 7.3: Secondary analyses of risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK, stratified by age categories, sex, history of hospitalization for hypoglycemia, and concomitant use of antidiabetic drugs at cohort entry.

Exposure	Events	Person-years	Crude IR* (95% CI)	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI)
Age					
< 70					
Overall	764	66,108	11.6 (10.8, 12.4)	-	-
NPH	355	26,628	13.3 (12.0, 14.8)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	409	39,480	10.4 (9.4, 11.4)	0.76 (0.66, 0.87)	0.90 (0.76, 1.06)
≥70					
Overall	1,078	27,642	39.0 (36.7, 41.4)	-	-
NPH	579	14,057	41.2 (38.0, 44.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	499	13,585	36.7 (33.6, 40.1)	0.88 (0.78, 0.99)	0.87 (0.77, 1.00)
Sex					
Women					
Overall	833	40,382	20.6 (19.2, 22.1)	-	-
NPH	424	18,350	23.1 (21.0, 25.4)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	409	22,032		0.80 (0.70, 0.91)	0.93 (0.81, 1.08)
Male					
Overall	1,009	53,368	18.9 (17.8, 20.1)	-	-
NPH	510	22,335	22.8 (20.9, 24.9)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	499	31,033	16.1 (14.7, 17.6)	0.69 (0.61, 0.78)	0.85 (0.73, 0.98)
History of hypoglycemia					
No history of hypoglycemia					
Overall	1,536	86,174	17.8 (17.0, 18.7)	-	-
NPH	760	37,114	20.5 (19.1, 22.0)	1.00 (Reference)	1.00 (Reference)

Long-acting insulin	776	49,060	15.8 (14.7, 17.0)	0.76 (0.68, 0.84)	0.90 (0.80, 1.01)
History of hypoglycemia					
Overall	306	5,941	40.4 (36.1, 45.2)	-	-
NPH	174	3,571	48.7 (42.0, 56.5)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin	132	4,005	33.0 (27.8, 39.1)	0.67 (0.53, 0.84)	0.73 (0.57, 0.93)
Concomitant use of antidiabetic drugs					
No use of antidiabetic drugs					
Overall	553	22,651	24.4 (22.4, 26.5)	-	-
NPH	322	11,333	28.4 (25.4, 31.7)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	231	11,318	20.4 (17.9, 23.2)	0.72 (0.61, 0.85)	0.83 (0.69, 1.00)
Use of antidiabetic drugs					
Overall	1,289	71,099	18.1 (17.2, 19.1)	-	-
NPH	612	29,352	20.9 (19.3, 22.6)	1.00 (Reference)	1.00 (Reference)
Long-acting insulin analogs	677	41,747	16.2 (15.0, 17.5)	0.76 (0.68, 0.85)	0.87 (0.77, 0.99)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease

*Per 1000 person-years

†Models using time-varying standardized weights

‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.

§ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

e-Table 7.4: Risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK, varying the grace period to 60 and 90 days.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI) §
60-day grace period					
Overall	2,496	124,392	20.1 (19.3, 20.9)	-	-
NPH	1,222	52,057	23.5 (22.2, 24.8)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	1,274	72,335	17.6 (16.7, 18.6)	0.74 (0.68, 0.80)	0.90 (0.79, 1.02)
90-day grace period					
Overall	2,922	143,583	20.4 (19.6, 21.1)	-	-
NPH	1,402	58,936	23.8 (22.6, 25.1)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	1,520	84,647	18.0 (17.1, 18.9)	0.74 (0.69, 0.80)	0.88 (0.81, 0.96)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease
*Per 1000 person-years
†Models using time-varying standardized weights
‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.
§ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

e-Table 7.5: Risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK, excluding patients with a hospitalization for hypoglycemia in the 30 days prior to cohort entry.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI) §
Overall	1,806	93,415	19.3 (18.5, 20.2)	-	-
NPH	914	40,513	22.6 (21.1, 24.1)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	892	52,902	16.9 (15.8, 18.0)	0.74 (0.67, 0.81)	0.87 (0.78, 0.97)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease
*Per 1000 person-years
†Models using time-varying standardized weights
‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.
§ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

e-Table 7.6: Diagnostic positions of hospitalization for hypoglycemia.

Diagnostic position	Frequency	Percent
1	595	32.3
2	261	14.2
3	232	12.6
4	202	11.0
5	128	7.0
6	130	7.1
7	69	3.8
8	65	3.5
9	47	2.6
10	32	1.7
11	22	1.2
12	17	0.9
13	15	0.8
14	8	0.4
15	6	0.3
16	S*	S*
17	S*	S*
18	S*	S*
19	S*	S*
20	S*	S*

* S denotes value suppressed due to CPRD's privacy policy.

e-Table 7.7: Risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH in patients with type 2 diabetes in the UK, restricting the outcome definition to a hospitalization for hypoglycemia in the primary or secondary diagnostic positions only.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI) §
Overall	856	94,494	9.1 (8.5, 9.7)	-	-
NPH	439	41,008	10.7 (9.7, 11.8)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	417	53,487	7.8 (7.1, 8.6)	0.72 (0.63, 0.83)	0.94 (0.79, 1.11)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease
*Per 1000 person-years
†Models using time-varying standardized weights
‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.§ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

e-Table 7.8: Risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK, restricting the outcome definition to a diagnosis of severe hypoglycemia within the first two days of hospital admission.

Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡§ (95% CI) §
Overall	1,703	93,824	18.2 (17.3, 19.0)	-	-
NPH	856	40,727	21.0 (19.7, 22.5)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	847	53,097	16.0 (14.9, 17.1)	0.75 (0.68, 0.82)	0.88 (0.79, 0.98)

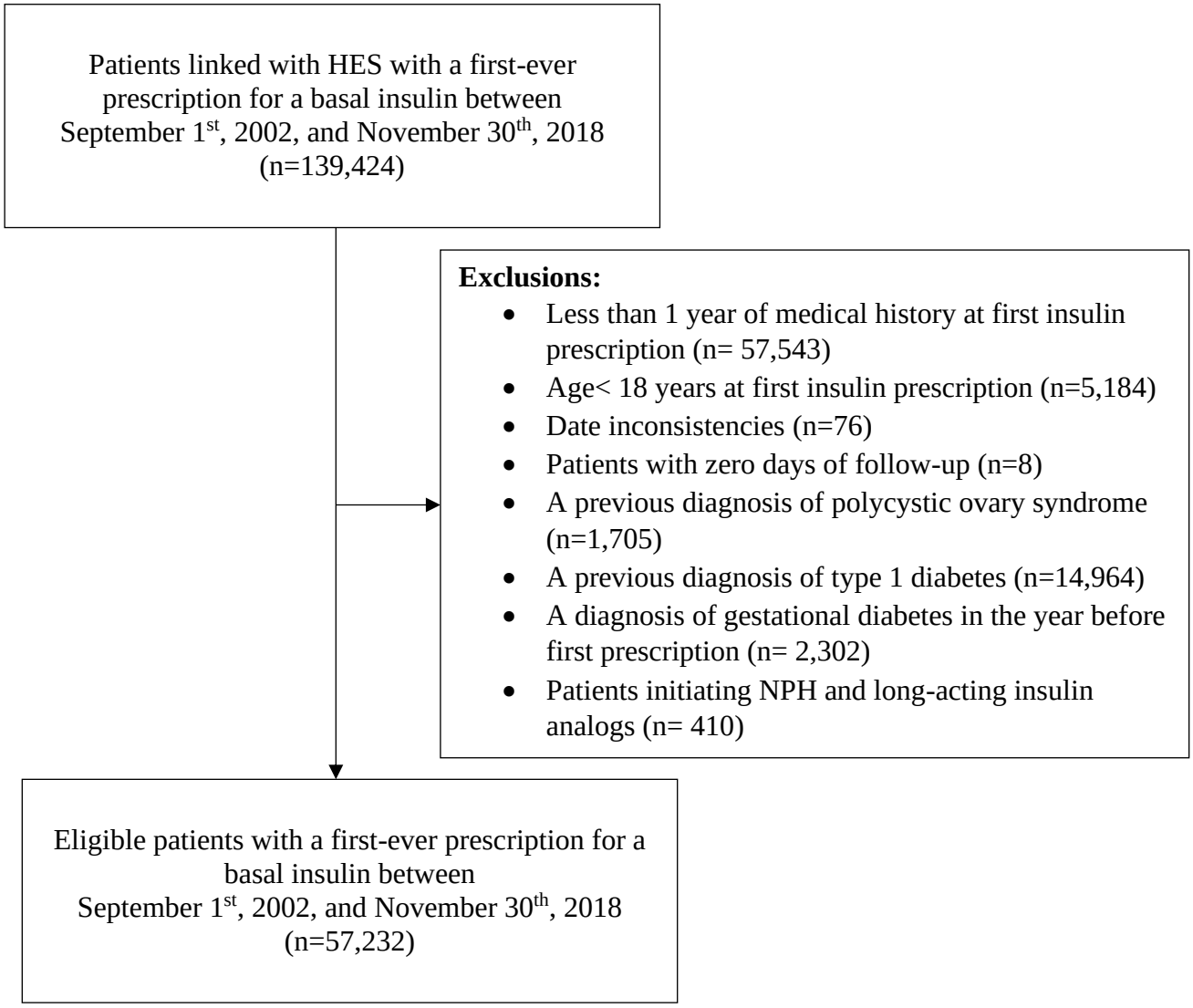
Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease
*Per 1000 person-years
†Models using time-varying standardized weights
‡Age and duration of treated diabetes were modeled as cubic b splines with 5 knots.
§ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

e-Table 7.9: Risk of hospitalization for hypoglycemia with the current use of long-acting insulin analogs and NPH among patients with type 2 diabetes in the UK, using a standard time-dependent Cox proportional hazards model.

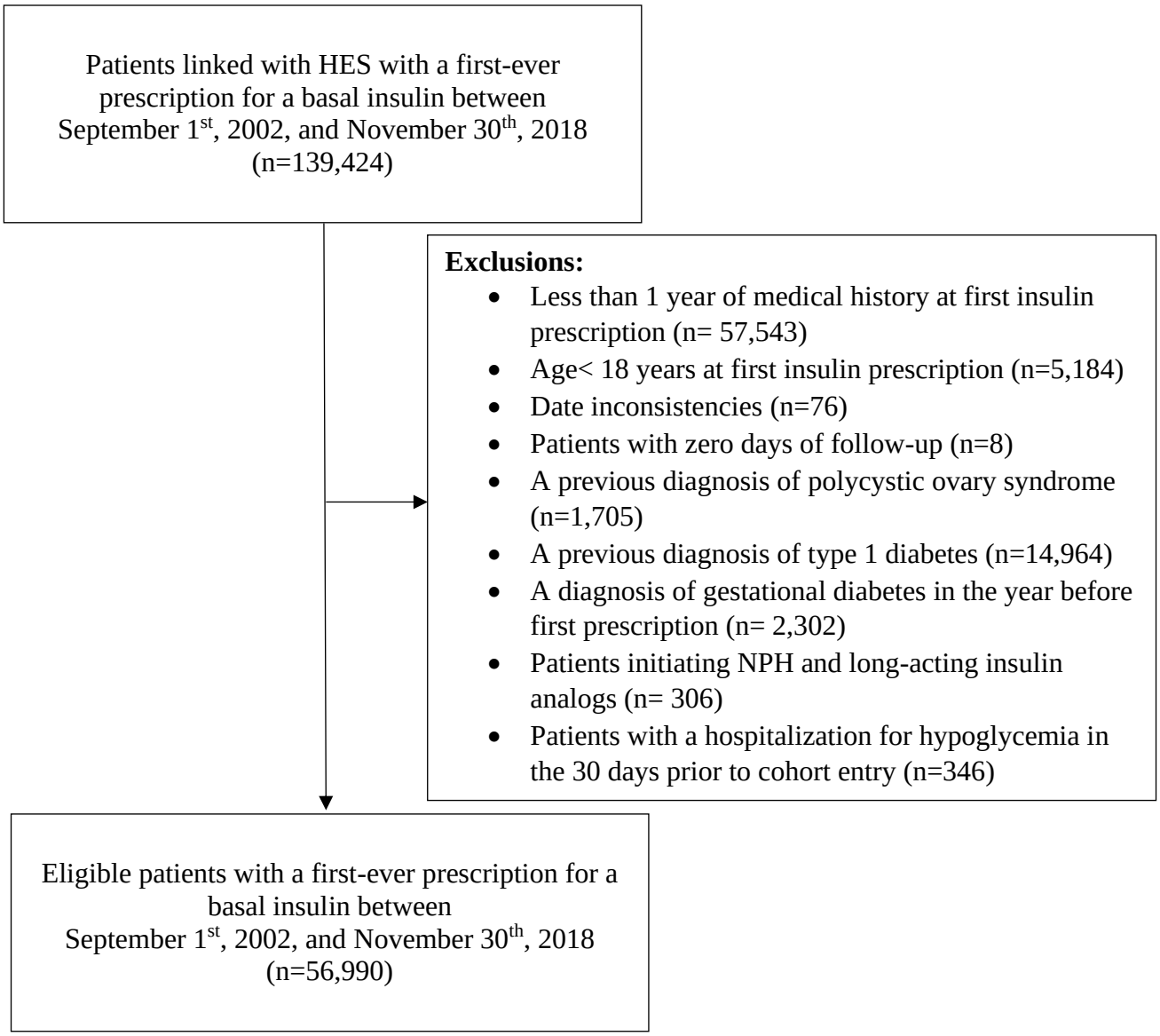
Exposure	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR†‡ (95% CI)
Overall	6,013	275,723	21.8 (21.3, 22.4)	-	-
NPH	1,727	56,305	30.7 (29.3, 32.2)	1.00 (reference)	1.00 (reference)
Long-acting insulin analogs	1,994	89,450	22.3 (21.3, 23.3)	0.73 (0.69, 0.78)	0.92 (0.84, 1.01)
Combination use	32	599	53.5 (37.8, 76.0)	1.85 (1.30, 2.62)	2.17 (1.37, 3.42)
No use	2,260	129,369	17.5 (16.8, 18.2)	0.81 (0.76, 0.87)	0.98 (0.89, 1.07)

Abbreviations: HR: Hazard ratio; IR: incidence rate; CI: confidence interval**,** CVD: cardiovascular disease
*Per 1000 person-years
† Age and duration of treated diabetes were modeled as restricted cubic splines with 5 knots
‡ The model was adjusted for the following covariates at cohort entry: age, sex, ethnicity, year of cohort entry, index of multiple deprivation quintile, duration of treated diabetes, smoking status (past or current smoker/ non-smoker), history of alcohol-related disorders, coronary artery disease, myocardial infarction, stroke, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, neuropathy, retinopathy, peripheral vascular disease, atrial fibrillation, dementia. History of prescription drug use in the year prior to cohort entry included the following: metformin, sulfonylureas, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 inhibitors, other antidiabetic drugs, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, direct oral anticoagulants, antiplatelets, statins, non-steroidal anti-inflammatory drugs, paracetamol, digoxin, glucagon, fibrates, and opioids. Clinical measurements were assessed in the year prior to cohort entry and included the following: body mass index, estimated glomerular filtration rate, glycated hemoglobin A1c, systolic blood pressure, diastolic blood pressure.

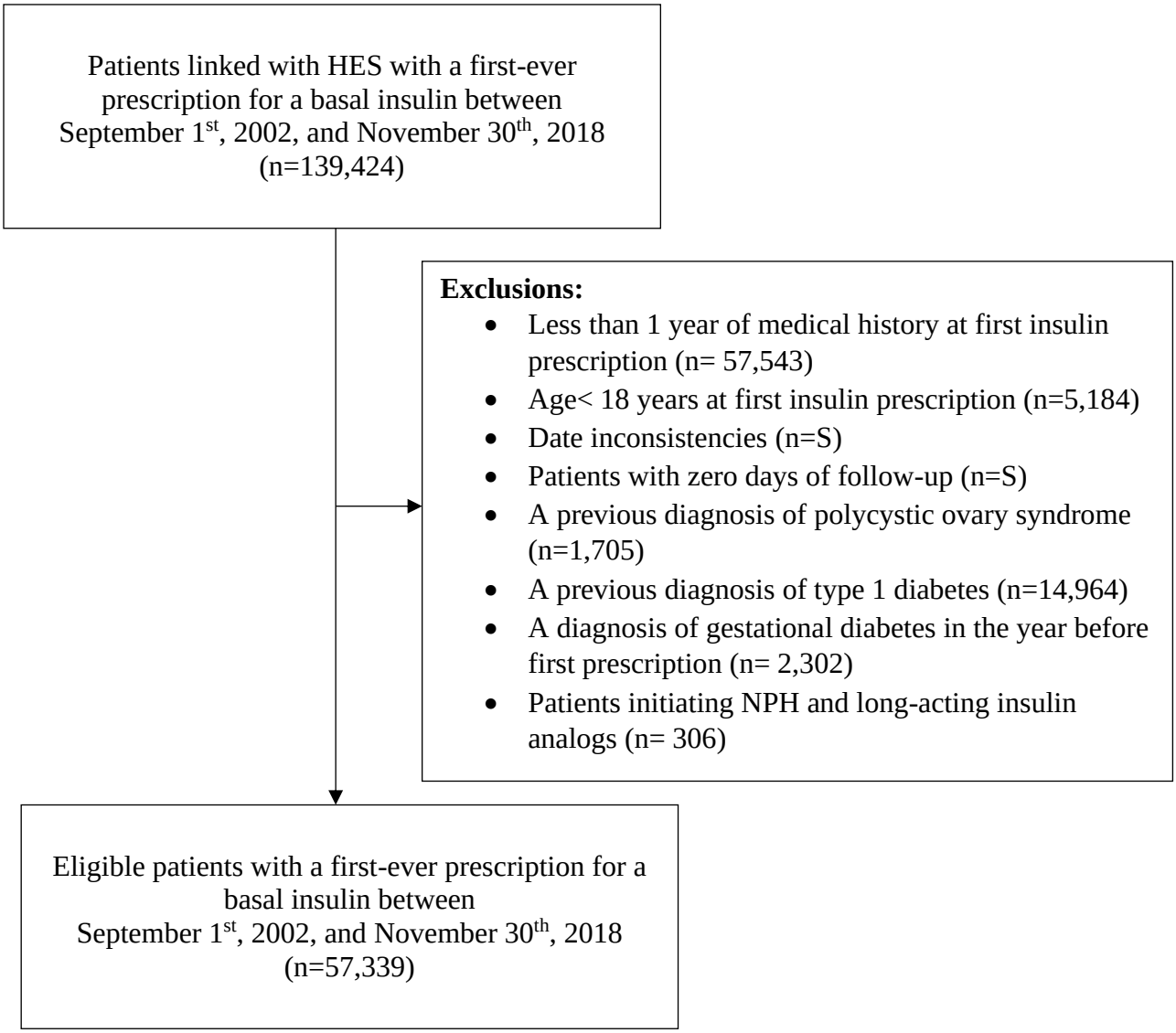
e-Figure 7.1: Flow-chart for the secondary analysis on the association between current use of individual long-acting insulin analogs (glargine, detemir, degludec) and NPH and the risk of hospitalization for hypoglycemia.



e-Figure 7.2: Flow-chart for the sensitivity analysis on the association between current use of long-acting insulins analogs and NPH and the risk of hospitalization for hypoglycemia, excluding patients with a history of hospitalization hypoglycemia in 30 days prior.

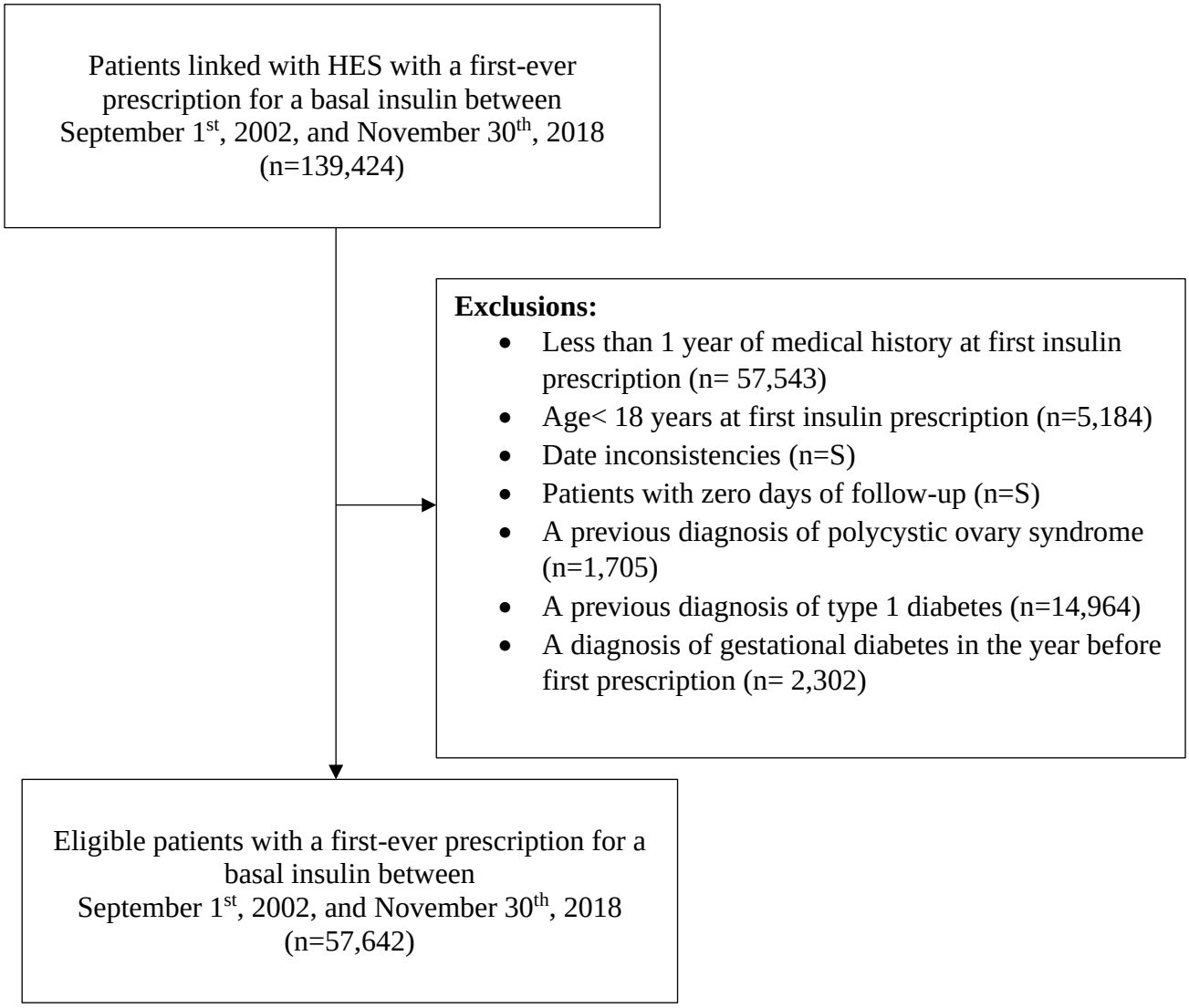


e-Figure 7.3: Flow-chart for the sensitivity analysis on the association between current use of long-acting insulins analogs and NPH and the risk of hospitalization for hypoglycemia, restricting to events of hypoglycemia within the first two days of hospital admission.



S denotes value suppressed due to CPRD's privacy policy.

e-Figure 7.4: Flow-chart for the sensitivity analysis on the association between current use of long-acting insulins analogs and NPH and the risk of hospitalization for hypoglycemia, using a standard time-dependent Cox proportional hazards model.



S denotes value suppressed due to CPRD's privacy policy.

8. Chapter 8: Discussion

8.1 Summary and interpretation of findings

The overarching aim of my thesis was to evaluate the utilization, comparative effectiveness, and safety of long-acting insulin analogues and NPH among patients with type 2 diabetes. Findings from previous utilization studies revealed an increasing use of basal insulins in patients with type 2 diabetes. However, sparse data were available on the use of different basal insulin types, such as long-acting insulin analogues and NPH, and few studies have evaluated treatment switching and discontinuation among patients with type 2 diabetes. Previous studies on the comparative effectiveness of long-acting insulin analogues and NPH for the reduction in the risk of MACE provided mixed results and were affected by important biases (e.g., immortal time bias[23-25], prevalent-user bias[24]) or were outdated[26]. Previous studies on the risk of severe hypoglycaemia with the use of long-acting insulin analogues and NPH also had important limitations (e.g., crude analyses only[30,31], were outdated, had no comparator group[32], or had limited generalizability[33]). Given these limitations, I conducted contemporary, methodologically rigorous studies to better understand the use, effectiveness, and safety profile of these drugs.

The aim of the first manuscript was to assess the utilization of long-acting insulin analogues and NPH insulin between 2003 and 2018 among patients with type 2 diabetes in the UK. We found that initiators of degludec were more likely to have a history of CVD and to have used other antidiabetic drugs prior to initiating insulin than initiators of NPH, glargine, or detemir. We also found that prescription rates of long-acting insulin analogues increased over time, while rates of NPH insulin decreased during the study period. In addition, we found that initiators of detemir were more likely to switch insulin treatments than initiators of NPH, and initiators of glargine were less likely to switch treatments than initiators of NPH.

Differential use of long-acting insulin analogues and NPH may be explained by patient preference related to their relative convenience. For instance, long-acting insulin analogues typically require fewer injections to attain glycaemic control, which may make them more appealing, particularly in vulnerable populations[212]. This may explain the increased use of long-acting insulin analogues in recent years, despite their elevated costs[114,115]. Practical considerations such as the frequency of injection may also explain the increased rates of treatment switching observed with detemir. Indeed, recent reports suggest that the duration of detemir in the blood stream might be shorter and contain a greater insulin peak compared to degludec and glargine[110]. This in turn may cause individuals using detemir to require multiple injections to achieve optimal glycaemic control. Consequently, physicians may prefer switching patients on detemir to glargine or degludec.

Understanding the use of basal insulin in different sub-populations of patients with type 2 diabetes is important, particularly in the context of the availability of newer glycaemic-lowering drugs and newer basal insulins. Indeed, the marketing of newer antidiabetic drugs, which expanded available treatment options, may delay the initiation of basal insulin in some patients[213,214]. The delay in insulin treatment initiation, referred to as insulin clinical inertia, may affect the characteristics of patients who initiate insulin (e.g., with patients initiating insulin at older ages and with potentially more comorbidities).

The aim of the second manuscript was to compare the effectiveness of long-acting insulin analogues and NPH insulin at preventing MACE among patients with type 2 diabetes. In a cohort of 57,334 patients with type 2 diabetes, we found that the use of long-acting insulin analogues was associated with a decreased risk of MACE compared to the use of NPH insulin. When assessing the risk by long-acting insulin molecule, we found that glargine was associated with a decreased

risk of MACE compared to NPH insulin. We also found that, compared to NPH insulin, long-acting insulin analogues were associated with a reduced risk of MI, cardiovascular death, all-cause mortality, and hospitalization for heart failure, but not with ischaemic stroke.

The aim of the third manuscript was to compare the risk of hospitalization for hypoglycaemia with the use of long-acting insulin analogues versus NPH insulin among patients with type 2 diabetes. A total of 31,135 initiators of long-acting insulin analogues and 26,201 initiators of NPH insulin were included in our study. We found that long-acting insulin analogues were associated with a decreased risk of hospitalization for hypoglycaemia as compared to NPH insulin. In addition, we found that glargine was associated with a modestly reduced risk of hospitalization for hypoglycaemia, while detemir was not associated. Results for degludec were inconclusive due to wide confidence intervals. Results were similar across several sensitivity analyses, including where we restricted events to hypoglycaemia recorded in the first two days of hospitalization.

It is possible that the modest decreased risk in severe hypoglycaemia that we observed with long-acting insulin analogues compared to NPH may partly explain the decreased risk of MACE observed with these drugs. Indeed, post-hoc analyses in both ORIGIN and the DEVOTE trial both reported increased risks of cardiovascular outcomes in patients who experienced severe hypoglycaemia[129,130]. Observational studies have also reported increased risks of cardiovascular events in patients who experienced severe hypoglycaemia[215], with the risk doubled in some cases[131]. Several potential mechanisms have been proposed to explain the association between hypoglycaemia and cardiovascular outcomes. Severe hypoglycaemia is thought to increase the risk of MACE among patients with type 2 diabetes through increased levels of oxidative stress and endothelial dysfunction[216]. In addition, hypoglycaemia activates the sympathetic system through activation of adrenal glands, which induces the release of catecholamines[217]. This release, along

with neural stimulation and the diminished supply of energy due to reduced glucose, appears to have important effects on the cardiovascular system. Indeed, levels of epinephrine have been reported to be 12 times greater among patients with hypoglycaemia that among those without hypoglycaemia, and elevated epinephrine levels can result in an increased heart rate[218]. The release of catecholamines and other hormones also promotes platelet aggregation, which can cause thrombosis[219]. Hypoglycaemia may also induce important hemodynamic responses[220] and can cause myocardial ischaemia[221] and arrythmia[222] through QT prolongation. Thus, the choice of glucose lowering therapy is important to attain adequate glycaemic control to avoid the increased risk of CVD events associated with hyperglycaemia while ensuring that hypoglycaemia is avoided, given its potential deleterious effects on the CVD system.

Although we used MSMs for Objectives 2 and 3, limited time-varying confounding was observed in these studies. In both studies, sensitivity analyses that used time-dependent Cox proportional hazards models with baseline adjustment only yielded similar results as those of our MSM analyses. Our a priori decision to use MSMs was based on the hypothesis that treatment choice and the risks of the outcomes of interest were likely influenced by current and previous level of glycaemic control (see simplified DAG in Section 4.2.6). While physicians use markers of glycaemic control and disease severity, cardiovascular risk factor levels, and other patient characteristics to guide treatment recommendations, minimal time-varying confounding was observed. Possible explanations for this observation are residual confounding due to unobserved or poorly measured confounders or that we were unable to observe the expected time-varying confounding due to modest follow-up duration of our study.

8.2 Strengths and limitations

This thesis has several strengths. The major overall strength of this thesis is that we generated new evidence and addressed important gaps in the literature on the utilization, comparative effectiveness, and safety of long-acting insulin analogues and NPH. This included generating new evidence on the utilization of long-acting insulin analogues and NPH in a contemporary context and providing new information on the insulin treatment switching in this patient population. In addition, we addressed the methodological limitations of previous studies of comparative effectiveness and safety, while also investigating degludec, which had not been studied previously in this literature.

The data source used for this thesis also represents an important strength. The CPRD Aurum allowed us to include a sufficient sample of initiators of basal insulin to comprehensively assess the use of these drugs in a representative sample of the general population. It also provided a sufficiently large sample to derive precise estimates of associations with rare but important outcomes, both overall and in clinically important subgroups. This data source also includes information on important confounders and treatment predictors (e.g., HbA1c, eGFR, SBP, DBP, BMI, and smoking status), which increased the precision of the estimates generated by our IPTW and IPCW models and allowed for tighter confounder control in our outcome models. Finally, our results may be generalizable to the population of patients seen in routine clinical practice in the UK, as the CPRD Aurum is representative of the broader UK population[178].

This thesis also has several potential limitations. We were unable to assess prescriptions issued by specialists or issued in hospital as the CPRD Aurum only captures prescriptions issued by general practitioners. However, type 2 diabetes is primarily managed by general practitioners in the UK[223], and the CPRD has been found to be well suited for the study of diabetes[184]. We also

could not ascertain patient adherence or consumption, which may lead to exposure misclassification. However, there is no reason to believe that such misclassification would be different between users of long-acting insulin analogues and NPH insulin.

As in any observational study, residual confounding is also possible. However, we included more than 40 different confounders in our outcome models in each of the enclosed studies, as well as in our IPTW and IPCW models used in second and third studies, to account for confounding between exposure and outcome, probability of treatment assignment, and informative censoring, respectively. The variables included demographic characteristics, lifestyle characteristics, anthropometric measures, comorbidities, and concomitant medication use. In addition, the use of time-updated stabilized weights at 30-day intervals allowed us to minimize time-varying confounding by rigorously controlling for confounders affected by prior exposure.

In the comparative effectiveness and safety analyses, we censored patients upon combination use of long-acting insulin analogues and NPH or upon treatment discontinuation. While this allowed us to better mimic the treatment guidelines for type 2 diabetes[6], this exposure definition substantially reduced the duration of follow-up. However, as MACE and severe hypoglycemia are acute outcomes, longer follow-up may not have changed our results substantially.

In our assessment of hypoglycaemic risk, patients had to seek medical attention at the hospital to have their events captured in the HES. Consequently, included events consisted of cases of severe hypoglycaemia only. It is possible that patients experienced hypoglycaemia at home and did not seek help or sought help from non-medical peers. Although we were unable to capture these events, we captured the more clinically relevant outcome, as these are the ones that may more substantially impact patients' wellbeing.

In addition, we had limited statistical power for some molecule-specific analyses in the second and third manuscripts, especially when evaluating the risk of MACE and hospitalization for hypoglycaemia with degludec.

8.3 Implication of findings

Our study adds important information to the utilization, effectiveness, and safety profiles of long-acting insulin analogues and NPH. Previous RCTs had shown similar efficacy profiles for long-acting insulin analogues and NPH in terms of glycaemic control, but the lack of comparative studies made these treatments difficult to compare in terms of effectiveness and safety outcomes. As cardiovascular disease is the leading cause of mortality in patients with type 2 diabetes[224], differential risks of long-acting insulin analogues and NPH with respect to MACE is an essential consideration. As well, the FDA requires post-marketing CVOTs for other antidiabetic drugs[91], but insulin is exempt from this requirement, which underscores the importance of assessing the cardiovascular effects of treatments for type 2 diabetes in a real-world setting. In addition, severe hypoglycaemia can have severe consequences in patients with type 2 diabetes, especially in those patients with a heavy comorbidity burden or with limited autonomy[206]. Our study can help physicians recommend treatments that minimize the risks of these adverse events in their patients.

This study can have important implications for drug plan managers and guideline writing committees, especially given the prevalence of type 2 diabetes, the high cost of drugs used to treat it, and its economic burden.[42] Long-acting insulin analogues can cost close to double the price of NPH insulin[225], which may make them inaccessible for certain populations. For example, until recently, the *Regime d'Assurance Maladie du Québec* (RAMQ; Quebec's provincial drug plan manager) only covered the cost of long-acting insulin analogues for patients who had previously failed to attain target glycaemic levels with NPH insulin[226]. However, cardiovascular disease is

also responsible for a substantial economic burden, costing close to $21.2 billion (CAD) in direct and indirect costs in Canada in 2009, which makes it the most costly disease in the country[227]. In 2015, the cost of hypoglycaemia in patients with type 2 diabetes using insulin or sulfonylureas was estimated at $65 million (CAD)[228]. These important costs are an important consideration for drug plan managers when determining the cost-effectiveness of these treatments. In addition, guideline writing committee may recommend treatments aimed at reducing the risk of cardiovascular outcomes and hypoglycaemia in patients with type 2 diabetes. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE), a framework for developing and presenting evidence for making clinical practice recommendations[229], helps guideline writing committees evaluate the quality and robustness of evidence to make clinical practice recommendations. According to this framework, guideline writing committees are encouraged to evaluate the strength of a recommendation according to 4 major factors: 1) quality of evidence, 2) balance between desirable and undesirable effects, 3) variability in values and preferences, and 4) uncertainty about whether the intervention represents a wise use of resources [229]. With advanced statistical methods, rigorous control for confounding and a population representative sample, our study can help inform discussions on future treatment guidelines, as it can be used by guideline writing committees, including within the GRADE framework.

8.4 Future directions

While this thesis addressed the utilization, effectiveness, and safety of long-acting insulin analogues, several issues remain unsolved. In the drug utilization study, we found that patients using detemir were more likely to switch treatments compared to patients using NPH, and patients using glargine were less likely to switch treatments than patients using NPH. While this may be due to the frequency of injection of these drugs, additional studies that examine the risk factors for

switching are needed to better understand this phenomenon. In addition, more research is needed to understand the greater rates of switching found with detemir, and if this switching is being driven by the occurrence of adverse events.

In the assessments of comparative effectiveness and safety, some molecule-specific analyses produced estimates were accompanied by wide 95% CIs. This is particularly true for those of degludec, the most recently marketed long-acting insulin analogue. Larger multi-database observational studies may be needed to examine the cardiovascular and hypoglycaemia risk of the different long-acting insulin analogues. Similarly, additional studies with longer follow-up duration are needed to better understand the long-term cardiovascular effects of these drugs, as well as the microvascular complications of type 2 diabetes, particularly given the long-term use of insulin among patients with type 2 diabetes. In addition, cost-effectiveness studies that consider the real-world comparative effectiveness and safety of long-acting insulin analogues and NPH are needed to better understand the relative cost-effectiveness of these treatments. In addition, while we stratified our results by age, sex, renal function, and history of cardiovascular disease (for Objective 2) and history of severe hypoglycaemia (for Objective 3), additional studies assessing the risk of cardiovascular outcomes and severe hypoglycaemia in patients with different risk profiles are needed. For instance, as the risk of hypoglycaemia is greater in patients with dementia[206], additional studies looking into the risk of severe hypoglycaemia in patients with cognitive impairments may be helpful to better tailor treatment for these patients. Future adaptive treatment strategies may be helpful to develop tailored treatment strategies for patients with type 2 diabetes as we move towards an era of more personalized medicine.

9.0 Chapter 9: Conclusions

This thesis is an important original contribution to the evidence regarding the utilization, the comparative effectiveness, and the safety of long-acting insulin analogues and NPH. We found that the use of long-acting insulin analogues increased during the last two decades in the UK, while the use of NPH insulin decreased during this period. In addition, we found that users of detemir were more likely to switch insulin treatments than users of NPH, and users of glargine were less likely to switch treatments than users of NPH. We also found that long-acting insulin analogues were associated with a reduced risk of MACE compared to NPH. Specifically, long-acting insulin analogues were associated with decreased risks of MI, cardiovascular death, hospitalization for heart failure, and all-cause mortality but not of ischaemic stroke. Finally, we found that long-acting insulin analogues were associated with a reduced risk of hospitalization for hypoglycaemia as compared to NPH, and findings were consistent in several sensitivity analyses. The evidence generated by this thesis may help drug plan managers, guideline writing committees, physicians, and patients make informed decisions regarding the benefits and risks of basal insulin treatments among patients with type 2 diabetes.

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